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European Journal of Cancer

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Aims and Scope

The *European Journal of Cancer* (*including EJC Supplements*) is an international multidisciplinary oncology journal that publishes original research, editorial comments, review articles and news on basic and preclinical research, clinical oncology (medical, paediatric, radiation, surgical), translational oncology and on cancer epidemiology and prevention.

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27 SEPTEMBER
FRIDAY

HEMATOLOGIC MALIGNANCIES * 11.00 - 13.00 * Hall G106
- Refining Therapeutic Strategies in CD30-Positive Lymphomas

Chair: Timothy Illidge, MD, PhD

BREAST CANCER * 14.00 - 15.30 * Hall G102
- Strategic Options in Hard-to-Treat Advanced Breast Cancer: Triple-Negative and Other HER2-Negative Cases

Co-Chairs: Angelo Di Leo, MD, PhD, and Vivianne Tjan-Heijnen, MD, PhD

GASTROINTESTINAL MALIGNANCIES * 17.00 - 18.30 * Hall 3-1
- Sharpening the Focus on Pancreatic Adenocarcinoma

Co-Chairs: Volker Heinemann, MD, and Dirk Richel, MD

GASTROINTESTINAL MALIGNANCIES * 17.00 - 19.00 * Hall G104
- How I Treat Metastatic Colorectal Cancer in 2013

Chair: Aimery de Gramont, MD, PhD

28 SEPTEMBER
SATURDAY

BREAST CANCER * 18.30 - 20.00 * Hall G104
- Contemporary Management of Breast Cancer: A Focus on Innovator and Biosimilar Therapeutic Antibodies

Chair: Javier Cortés, MD, PhD

29 SEPTEMBER
SUNDAY

GENITOURINARY MALIGNANCIES * 18.30 - 20.00 * Hall G104
- Treating Castration-Resistant Prostate Cancer: A Work in Progress

Chair: Bertrand Tombal, MD, PhD

30 SEPTEMBER
MONDAY

GLIOBLASTOMA * 18.30 - 20.00 * Elicium 1
- Therapeutic Trends in Newly Diagnosed Glioblastoma: In Pursuit of Improved Patient Outcomes

Chair: Michael Weller, MD

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Typically the manuscript will be reviewed within 2-8 weeks. Should the reviewers' reports contradict one another or a report is unnecessarily delayed a further expert opinion will be sought. Revised manuscripts are usually returned to the Editors within 3 weeks and the Editors may request further advice from the reviewers at this time. The Editors may request more than one revision of a manuscript.

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Table of Contents

Scientific Programme

ECCO

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Mission: ECCO's role

- To transcend the various interests in the oncology community ***network***
- To act as a coherent, impartial, inclusive and ***collaborative*** force at its centre
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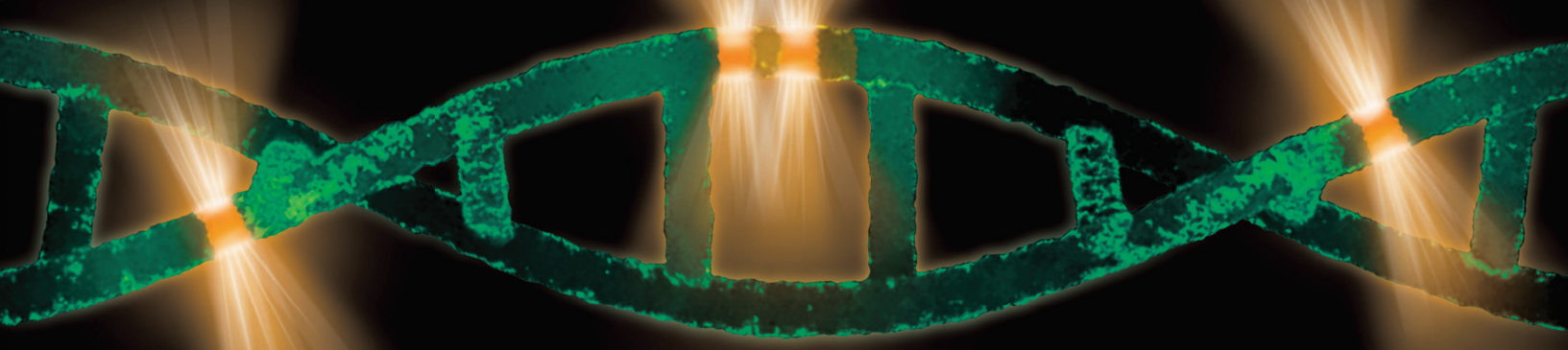
AstraZeneca Sponsored Symposium at the 2013 European Cancer Congress

The revolution in personalised healthcare: towards improved outcomes in oncology

Friday 27 September 2013, 11.00 – 13.00 Hall G102,
Amsterdam RAI Convention Centre, Amsterdam, The Netherlands



P R O G R A M M E

Chair's welcome and introduction	*Frances Shepherd (Canada)*
Choosing the right treatment for each patient: the emergence of personalised healthcare in non-small cell lung cancer	*Frances Shepherd (Canada)*
Traditional and personalised models of therapy in gastrointestinal and endocrine tumours: the role of histological and clinical markers	*Jaume Capdevila (Spain)*
The role of molecular pathways in therapeutic response and outcomes in breast cancer	*Fabrice Andre (France)*
Future perspectives: realising the potential of personalised healthcare in gynaecological cancer	*Jonathan Ledermann (UK)*
Panel discussion	*All*
Summary and close	*Frances Shepherd (Canada)*

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References:

1. Scagliotti G. et al. Oncologist. 2009; 14: 253-263.
2. Paz-Ares L. et al. Lancet Oncol. 2012; 13: 247-255

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Scientific Programme
Invited Abstracts

Saturday 28 September 2013

Special Lecture (Sat, 28 Sep, 08:00–08:45)
Limitation and Indication of Minimally Invasive Surgery for Gastric Cancer

1 INVITED

Limitation and indication of minimally invasive surgery for gastric cancer

K. Maruyama[1]. [1]*University of Health and Welfare Sanno Hospital, Department of Surgical Oncology, Tokyo, Japan*

Early stage gastric cancer is remarkably increasing by development of diagnostic methods and mass-screening system. Proportion of Stage-I cancer increased from 22.5% (1963–66) to 57.3% (2008) in Japanese Nationwide Registry.
According to the increase of early stage cancer and demand for high quality of life, the surgical treatment was shifted from "high radicality" to "minimally invasive surgery with enough curability, high safety, and high quality of life". Such attitude leads to wide variation of the surgical treatments as follows. Intention of "endoscopic mucosal resection" and "endoscopic submucosal dissection" is to avoid disadvantages and risks of gastric resection and to get quick recovery. The indication is for a cancer with definitely no node metastasis. The requirements are a) mucosal cancer, b) no ulcer scar and elevated or flat lesion, c) 2.0 cm or less in diameter, c) well or moderately differentiated carcinoma. Accurate preoperative diagnosis is essential. And we never hesitate to shift gastric resection if the requirements are not met. Intention of "laparoscopic resection" is to avoid disadvantages and risks of open gastric resection and to get quick recovery and cosmetic advantage. This procedure includes "laparoscopic wedge resection", "laparoscopic resection", and "robotic surgery". The indication was for an early stage cancer, but it is now expanded to advanced cancer according to development of the instruments and surgical skills. In the Japanese Nationwide Survey, more than 7,000 patients were treated every year in 2009, 2010, and 2011. Proportion of distal gastrectomy with D2 standard lymphadenectomy was 51.8%, distal gastrectomy with D3 extended lymphadenectomy was 20.6%, and total gastrectomy was 16.5% in 7400 cases (2011). Robotic surgery showed high accuracy and radicality in surgical procedures, and is now remarkably increasing in Korea and Japan.
"D2 systematic lymphadenectomy" was the gold standard for Japanese and most world leading surgeons, but the attitude was changed to "lymphadenectomy with limited or reasonable extent". The Intention is to reduce postoperative complications and nutritional disadvantages. Intention of "sentinel node navigation" is to detect metastatic nodes and to avoid disadvantages by unnecessary node dissection. This technique is indicated for potentially curatively resectable cancer, and most trials are now for early cancer during laparoscopic resection. The tracers are blue dye, fine carbon particle emulsion, oil contrast media, radioactive mm99 Tin colloid, and CEA antibody. The high detectability was reported; 96% of metastatic nodes were found in the hot nodes. The essential progress are to "develop cancer specific tracer" and to "improve accuracy of frozen histological examination".
We have to know that the most important patient's demand is "cure from cancer". We have to understand the scientific base of minimally invasive surgery and should avoid increase of recurrence caused by the indication expansion.
No conflict of interest.

Opening Session (Sat, 28 Sep, 09:00–11:00)
Biological Basis of Personalised Cancer Therapy

2 INVITED

Lgr5 stem cells in self-renewal and cancer

H. Clevers[1]. [1]*Hubrecht Institute, Royal Netherlands Academy of Arts and Sciences & University Medical Centre Utrecht, Utrecht, Netherlands*

The intestinal epithelium is the most rapidly self-renewing tissue in adult mammals. We originally defined *Lgr5* as a Wnt target gene, transcribed in colon cancer cells. Two knock-in alleles revealed exclusive expression of *Lgr5* in cycling, columnar cells at the crypt base. Using an inducible Cre knock-in allele and the Rosa26-*LacZ* reporter strain, lineage tracing experiments were performed in adult mice. The *Lgr5*$^{+ve}$ crypt base columnar cells (CBC) generated all epithelial lineages throughout life, implying that it represents the stem cell of the small intestine and colon. Similar obserations were made in hair follicles and stomach epithelium.
Single sorted *Lgr5*$^{+ve}$ stem cells can initiate ever-expanding crypt-villus organoids in 3D culture. Tracing experiments indicate that the *Lgr5*$^{+ve}$ stem cell hierarchy is maintained in these organoids. We conclude that intestinal crypt-villus units are self-organizing structures, which can be built from a single stem cell in the absence of a non-epithelial cellular niche. The same technology has now been developed for the *Lgr5*$^{+ve}$ stomach stem cells.
Intestinal cancer is initiated by Wnt pathway-activating mutations in genes such as APC. As in most cancers, the cell of origin has remained elusive. Deletion of APC in stem cells, but not in other crypt cells results in progressively growing neoplasia, identifying the stem cell as the cell-of-origin of adenomas. Moreover, a stem cell/progenitor cell hierarchy is maintained in early stem cell-derived adenomas, lending support to the "cancer stem cell"-concept.
Fate mapping of individual crypt stem cells using a multicolor Cre-reporter revealed that, as a population, Lgr5 stem cells persist life-long, yet crypts drift toward clonality within a period of 1–6 months. Lgr5 cell divisions occur symmetrically. The cellular dynamics are consistent with a model in which the resident stem cells double their numbers each day and stochastically adopt stem or TA fates after cell division. Lgr5 stem cells are interspersed between terminally differentiated Paneth cells that are known to produce bactericidal products. We find that Paneth cells are CD24+ and express EGF, TGF-a, Wnt3 and the Notch ligand Dll4, all essential signals for stem-cell maintenance in culture. Co-culturing of sorted stem cells with Paneth cells dramatically improves organoid formation. This Paneth cell requirement can be substituted by a pulse of exogenous Wnt. Genetic removal of Paneth cells in vivo results in the concomitant loss of Lgr5 stem cells. In colon crypts, CD24+ cells residing between Lgr5 stem cells may represent the Paneth cell equivalents. We conclude that Lgr5 stem cells compete for essential niche signals provided by a specialized daughter cell, the Paneth cell.
No conflict of interest.

3 INVITED

The genetic basis for cancer therapy – the opportunity and the challenges

W.R. Sellers[1]. [1]*Novartis Institutes for BioMedical Research, VP/Global Head of Oncology, Cambridge, USA*

Cancer is fundamentally a disease driven by the acquisition and clonal selection of genomic alterations. These genetic changes result in the gain- and loss-of-function of oncogenes and tumor suppressor genes that together cooperate to induce and maintain the transformed state. Therapeutics directly targeting these underlying perturbations have now shown marked single-agent clinical activity in a diverse set of solid and hematologic malignancies well beyond the initial genetically targeted therapy paradigm established by imatinib in CML. Indeed, the efficacy of inhibitors of BRAF, MEK, ALK, EGFR, PDGFR, KIT and ABL mark the emergence of a new generation of highly active cancer therapeutics all taking advantage of the link to the underlying genetic drivers. There is now a significant opportunity to see greater clinical benefit by the utilization of targeted therapeutics in combination both within this space and with chemotherapy and immunotherapy.
Nonetheless, there are significant challenges to more fully realizing this paradigm broadly across all cancers. First, we remain hampered by an incomplete understanding of the genetic alterations characteristic of human cancer. Here, the advent of Next Gen Sequencing promises to allow us to probe the cancer genome at sufficient depth to understand the genetic combinations that enact each cancer type, to understand disease progression from benign to highly refractory states and to understand disease heterogeneity. Second, there have been significant hurdles in developing therapeutics that reverse the activity of non-kinase oncogenes (e.g. RAS and MYC) or reverse the activity of tumor suppressor mutations (e.g. p53, RB1). Third, the development of resistance to targeted therapy remains a problem for the field and this is related to the fourth issue, specifically the need to rapidly identify highly active novel combination therapy regimens and test these early in clinical development. Finally, there has been a chronic lack of a robust pre-clinical translational infrastructure that would allow for the more accurate prediction of human clinical trial results and hence improve the overall clinical trial success rate while shortening the time to maximizing patient benefit.
The aforementioned challenges to this promising field can be met, however, by an increasingly sophisticated set of experimental and therapeutic approaches. Examples of these approaches will be highlighted in the presentation.
Conflict of interest: *Ownership: Novartis Pharmaceuticals. Other substantive relationships: Employee of Novartis Pharmaceuticals*

4 INVITED

Intratumour heterogeneity and cancer evolution

C. Swanton[1]. [1]*London Research Institute, Translational Cancer Therapeutics Laboratory, London, United Kingdom*

Despite advances in genomic technologies, most advanced solid tumors remain incurable and drug resistance is almost inevitable with limited biomarkers available to personalize therapy. Two important lessons have emerged from the comprehensive genomic analyses of cancers, which may provide an explanation for difficulties that have been encountered in biomarker development. First, each tumor contains an individual assortment of multiple genomic aberrations, few of which are shared between patients with the same histopathological tumor subtype. Second, emerging evidence suggests that these anomalies appear to vary both spatially and temporally within the tumor, indicating substantial intratumor heterogeneity. Increasingly, molecular evidence suggests that intratumor heterogeneity may contribute to tumor growth through a branched (polytypic) rather than a linear pattern of tumor evolution. Branched evolutionary growth and intratumor heterogeneity results in coexisting cancer cell subclones with variegated genotypes and associated functional phenotypes that may be regionally separated within the same tumor or distinct within one biopsy. Furthermore, the dynamics of tumour subclonal architectures are seen to alter in dominance over time.
Variegated phenotypes, resulting from intratumoral genetic heterogeneity and the emergence of new subclones at relapse, are likely to have important implications for developing novel targeted therapies and for preventing the emergence of drug resistance. Intratumor heterogeneity and tumour sampling bias, resulting from single biopsy-driven biomarker discovery and validation approaches, may also contribute to the recently reported failures in implementation of robust biomarkers in the clinical setting.
In this talk, evidence for intratumour heterogeneity, impacting upon signal transduction pathway heterogeneity will be reviewed. Darwinian models for biomarker discovery will be discussed based on trunk and branched tumor growth models that may improve drug discovery and clinical outcome prediction. Initiation of longitudinal clinical cohort studies to define the dynamics of tumour subclonal architectures during the disease course and defining drivers of tumour branched evolution and genomic instability are discussed as priority areas for development.
Conflict of interest: *Other substantive relationships: Novartis and Illumina: Research funding support.*

Opening Session (Sat, 28 Sep, 09:30−11:00)
Oncology Nursing Opening and Award Session

5 INVITED

Diversity in cancer care − the importance of transcultural nursing

M. Johnson[1]. [1]*De Montfort University, Leicester, United Kingdom*

Professor Johnson will discuss the importance of recognising ‘diversity’ in the design and provision of cancer services, with special reference to issues related to nursing care. He will examine the evidence base relating to ethnicity and the experiences of migrant/minority people in health care, focussing on the epidemiology and experience of cancer as mediated through culture, religion, language and family, and the implications for service provision.
Based largely on a review of the literature and ‘good practice’ examples, drawing on the experiences of colleagues in UK and EU and USA, he will make recommendations for the training and management of cancer nurses and other health professionals, and the implications for hospitals and clinics delivering services to multicultural and diverse populations. Other aspects of ‘diversity’ may be included as benefitting from the same sort of attention to the user’s identity, needs and experiences.
The approach needs to acknowledge that the ‘cancer journey’ begins with prevention, and recognition of symptoms, through diagnosis and ‘breaking bad news’, to end of life care and rituals associated with death. A whole-of-life approach enhances life and improves care but needs to be approached in a positive manner that recognises ethnic, religious and cultural diversity and the realities of life for migrants and their descendants.
In the absence of best practice evidence, there is a need to develop better practice, drawing on experience in other clinical fields, and to embed these in cancer care, including improved record keeping of salient characteristics, or ‘ethnic monitoring’, to enable better research and audit that will contribute in future to such evidence becoming available.
No conflict of interest.

Scientific Symposium (Sat, 28 Sep, 11:15−13:15)
The Impact of Cancer − Exploring Complexity and Special Needs in Specific Cancers

6 INVITED

Life beyond cervical cancer

C. Hughes[1]. [1]*London Cancer Alliance, Middx, United Kingdom*

More people are living for longer following a cancer diagnosis. Currently, in the UK this equates to about 2 million people. However, this figure is increasing at a rate of 3.2% per year, which means that by 2030 this number will have doubled. We also know that cancer survivors have significant unmet needs and suffer worse health than those who have never had the disease. Current methods of cancer follow-up were developed when the concepts of long term follow-up and chronic disease management were not generally associated with cancer.
The Cancer Reform Strategy (2007) in England saw the creation of the National Cancer Survivorship Initiative (NCSI) with the aim of increasing our understanding of the issues facing cancer survivors, and developing and testing solutions to improve care and support, in a changing healthcare environment. The vision for survivorship involved a cultural shift to focus on recovery, health and wellbeing; the provision of individual and personalised holistic assessment; care based on a model of self-management; follow-up and support tailored to individual need; and patient reported outcome measures.
There are about 19,000 women in the UK who are alive 10 years following a diagnosis of cervical cancer; 66% of women diagnosed with the disease will be alive 5 years following diagnosis and three quarters of these will be younger women aged 25−64 years. The first peak incidence is in women aged 30−34 years. Improvements in cervical screening have resulted in a reduction in the number of women diagnosed with the disease. Although initiatives to promote screening and earlier diagnosis remain important, current models of care following diagnosis and treatment do not meet the needs of patients for living beyond cancer and the effects of what is often radical treatment, and are not sustainable given the changes in the way the disease is managed.
The recent NSCI publication (Living With and Beyond Cancer: Taking Action to Improve Outcomes) brings together the evidence for the improvements tested as part of the initiative. This session will examine the changes recommended in the NCSI document in relation to the care of women with cervical cancer. This will include the use of formalised models of assessment and care planning to encompass holistic needs that include considerations such as access to work and childcare; templates for treatment summaries that support primary care in the management of women post treatment; the provision of a health and well being event to facilitate the transition from treatment to living with and beyond cancer, including the role of physical activity and a healthy lifestyle; risk stratification of follow-up to ensure women with low risk disease have information about the effects of treatment, what to look for in the event of recurrence and access to services but who are encouraged to self-manage, and women with complex needs get more intensive and appropriate support.
No conflict of interest.

7 INVITED

Life beyond head and neck cancer

M. Wells[1]. [1]*University of Dundee, School of Nursing and Midwifery, Dundee, United Kingdom*

Head and neck cancer is the 6th most common cancer worldwide. In the European Union more than 90,000 people are diagnosed with head and neck cancer every year and about 40,000 die from the disease. Rates are highest in Western, Southern and Eastern Europe and the incidence of oral and oropharyngeal cancer, in particular, is rising due to a significant increase in HPV related disease. Although still relatively ‘rare’, head and neck cancers have a profound impact on all aspects of life. Patients are increasingly treated with combined modality therapy which is associated with significant treatment morbidity. During and after cancer treatment, patients experience major challenges with eating and drinking, body image, psychological wellbeing, social and work life. However, public awareness about head and neck cancer and its impact has, until recently, been limited. This paper will draw on evidence from a recent systematic review of qualitative research on living with head and neck cancer, and on focus groups with patients and carers which highlight the ways in which treatment and care experiences can affect their ability to get on with life. Findings from a cross-sectional survey conducted in Scotland will be used to illustrate the most prominent concerns, quality of life issues and unmet needs expressed by survivors in the first five years after treatment. Finally, data from a record-linkage study will highlight those who are at highest risk of poor outcomes.

Nurses and multidisciplinary colleagues face enormous challenges in meeting the complex needs of an increasing number of people who live with the after effects of head and neck cancer, including the emergence of two distinct groups of patients − those who are socially disadvantaged and have poor health behaviours including smoking and drinking, and those with HPV related cancers who tend to be younger and more affluent. This paper will draw attention to some neglected issues in research and practice, and will summarize current initiatives and interventions to support people who live with this highly challenging cancer.
No conflict of interest.

8 INVITED

Beyond lung cancer

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Background: Lung cancer is the most frequent cancer affecting both men and women in the world. Lung cancer patients experience significant physical and psychosocial distress and have many unmet supportive care needs impacting quality of life for patients with lung cancer.
Method: Review of innovative models of care and emerging trends for nurses as members of a multidisciplinary team caring for lung cancer patients and their families. Current evidence related to use of non-pharmacologic interventions aimed at improving quality of life in lung cancer patients is provided.
Results: Given the often-short disease trajectory of lung cancer and the fact that patients are typically symptomatic at the time of diagnosis, early assessment of supportive care needs of patients and families is imperative. A growing number of studies support the beneficial role of Lung Cancer Nurse Specialists (LCNs) in assessing and meeting the health needs of patients. A number of LCNs innovative care programs have shown enhanced health-related outcomes. Targeted therapeutic education focusing on self-management of symptoms (i.e. shortness of breath) has demonstrated effectiveness. Nurse-led models for follow-up care are associated with improved physical and psychosocial patient outcomes, contribute to continuity of care and are viewed positively by both patients and providers. These growing bodies of evidence indicate that novel models of care delivery should integrate early assessment and therapeutic education programs for patients and families. Developing patient knowledge and expertise on their illness, treatment, symptom management and available support can help promote self-management. Such interventions are critical for empowering patients as there is significant stigmatisation related to lung cancer and often self-blame linked to tobacco use.
Conclusion: Available literature supports the importance and promise of several approaches for patients with lung cancer: 1) a key role for early needs assessment; 2) a role for LCNs consultation at diagnosis, through treatment and continued through follow-up care; and 3) targeted therapeutic education to promote self-management. These emerging models of care have shown promising initial results and warrant further investigation as components of a multidisciplinary approach to patients with lung cancer.
No conflict of interest.

Scientific Symposium (Sat, 28 Sep, 11:15−13:15)
Induction Chemotherapy in the Treatment of Squamous Cell Head and Neck Cancer

9 INVITED

The current status of induction chemotherapy in head and neck squamous cell carcinoma

Abstract not received.

10 INVITED

Assessment of response after induction chemotherapy as the basis of subsequent local therapy

R. De Bree[1]. [1]*VUMC, Amsterdam, Netherlands*

The use of induction chemotherapy in the management of locally advanced head and neck squamous cell carcinoma (HNSCC) is growing. An understanding of the effects of induction chemotherapy on the biology of the tumour prior to delivery of chemoradiation is paramount to provide as much information as possible to tailor the treatment plan to the individual tumour: planning a radiation dose boost or reassessing the modality of treatment.
Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) provide the mainstay of imaging for treatment response assessment. Both rely on morphology to evaluate the disease whereas functional imaging such as positron emission tomography (PET) and diffusion weighted (DW) MRI provide complementary information on the underlying biology such as metabolic activity and cellularity.
Functional imaging potentially provides an earlier indication of the response to treatment than conventional imaging and allows for potential adaptation of treatment by changing the intervention at a time when this is still possible. Especially changes in 18-fuorodeoxyglucose (FDG) uptake (determined by standardized uptake values: SUV) and microscopic water motion (determined by apparent diffusion coefficient: ADC) are useful for assessment of treatment response. Other techniques include dynamic contrast-enhanced and perfusion CT and MRI. Optimal timing and interpretation criteria for use of functional imaging in daily practice have to be developed.
Several small studies showed that early therapeutic response on FDG-PET and DW-MRI after two cycles of induction chemotherapy in patients with advanced stage HNSCC seems to be a predictive factor for recurrent free survival after subsequent chemoradiation. Marked changes in functional imaging parameters following induction chemotherapy may guide adaptation of individualised treatment regimens.
The use of these imaging techniques and recent studies on assessment of response after induction chemotherapy in HNSCC patients will be discussed.
No conflict of interest.

11 INVITED

Role of induction chemotherapy in the treatment of nasopharyngeal carcinoma

A. Lee[1]. [1]*University of Hong Kong − Shenzhen Hospital, Center of Clinical Oncology, Shenzhen, China*

An overview of the therapeutic benefit of induction chemotherapy for nasopharyngeal carcinoma will be presented.
Nasopharyngeal cancer is a chemo-sensitive cancer; the effectiveness of induction chemotherapy followed by radiotherapy was first reported in the 1980s. The initial results showed conflicting conclusions. Despite the common experience of good initial response, only one of five randomized trials achieved significant improvement in event-free survival and none showed benefit in overall survival. Interests in induction chemotherapy waned in the late 1990s when the Intergroup-0099 Study made the first breakthrough by using concurrent-adjuvant chemoradiotherapy (CRT). A meta-analysis in 2006 confirmed that concurrent chemotherapy is the most potent sequence for combining with radiotherapy (RT) and the only sequence that showed significant survival benefit; induction chemotherapy per se could significantly reduce the risk of both locoregional failures and distant failures, but the impact did not translate into significant benefit in overall survival. Although subsequent trials did confirm the efficacy of regimens using cisplatin in concurrence with radiotherapy followed by combination of cisplatin and fluorouracil, controversy remains about the contribution of the adjuvant phase which is often poorly tolerated. Furthermore, there are concerns that improvement in distant failure remains unsatisfactory.
Hence, there are interesting interest to explore the benefit of induction-concurrent sequence, The induction phase is generally well-tolerated, full dose of potent chemotherapy combination could theoretically be more effective in eradicating micro-metastases. Furthermore, shrinkage of advanced locoregional disease, particularly those abutting neurological tissues, could enable wider margin for subsequent RT. Single-arm Phase II studies all reported encouraging early results, but two randomized Phase II trials showed conflicting results as to whether induction-concurrent CRT is superior to concurrent CRT. Five randomized Phase III trials are now on-going to confirm the therapeutic benefit, while four trials used concurrent CRT as the standard arm, the NPC-0501 Trial used the Intergroup concurrent-adjuvant CRT as the standard arm, 803 patients have been accrued and the preliminary results are being analyzed.
In conclusion, induction chemotherapy per se using cisplatin-based regimen with adequate dosage can achieve modest but significant improvement in tumor control. Adding induction chemotherapy to concurrent CRT is a promising strategy, confirmation by randomized trials is awaited.
No conflict of interest.

12 INVITED

Function-sparing radiation in curable head and neck cancer

H. Langendijk[1]. [1]*University Medical Center Groningen, Radiation Oncology, Groningen, Netherlands*

Introduction: The last decade, major progress has been made in the treatment of head and neck squamous cell carcinoma (HNSCC). There is growing evidence that more aggressive treatment regimens, either the delivery of radiotherapy with concomitant chemotherapy or altered fractionation schedules, improve tumour control and survival. However,

these new treatment regimens have come to the expense of increased morbidity, such as radiation-induced swallowing dysfunction, trismus and xerostomia. As health-related quality of life is particularly affected by these side effects, prevention may improve the therapeutic ratio of treatment for HNSCC.
NTCP-models: Several authors investigated the relationship between the dose distributions in potential organs at risk and side effects. These studies retrieved different results, which may be due to a number of methodological problems, including the relatively small number of patients in most of these studies, differences in eligibility criteria among the different studies, differences in study design and endpoints chosen and differences in the definition and delineation of the organs at risk.
To overcome these problems, we performed well-designed prospective cohort study are required in which all possible relevant pre-treatment, treatment and outcome determinants are prospectively collected according to well defined guidelines.
We developed a number of multivariable Normal Tissue Complication Probability (NTCP) models for different endpoints related to function. These multivariable NTCP-models can be used to:
1. Identify the most important anatomical structures that should be spared to obtain maximal sparing of function after curative radiation or chemoradiation;
2. Identify the dose-volume parameters that are most predictive for the development of functional problems;
3. Develop advanced and emerging radiation technology that enables sparing of the most important organs at risk, and
4. To identify patients who may benefit most from these new technologies.

Clinical validation: After completing the aforementioned steps, we performed a prospective study in which the efficacy of multiple function sparing IMRT was validated. In addition, we performed in silico planning comparison studies to investigate the potential benefit of protons to reduce functional problems.
The results of these studies will be presented.
No conflict of interest.

Society Session (Sat, 28 Sep, 11:15−13:15)
European Society of Surgical Oncology (ESSO)

13 INVITED

2013 a year of challenges in the technique of TME

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The concept of TME is important because it reflects the embryological determination of an envelope of tissue which represents a standard optimal oncological resection specimen. The basis of the detailed anatomy of the insertion of the lower part of this envelope into the pelvic floor, remains an area of challenge for surgeons and anatomists alike. Furthermore MRI radiology and 3-dimensional MRI based imaging have further contributions to make to all the disciplines involved.
Late in 2012, I was introduced by Antonio Lacy to the potential of dissection conducted transanally under positive gas pressure after circumferential incision around the rectum and purse string closure of the distal margin of the specimen. This has led to a number of established laparoscopic and open surgeons seeking to improve their dissection techniques in the low distal insertion of the mesorectal package into the pelvic floor. The essential claim from surgeons conducting the early series, which now encompass more than 200 patients in Europe alone, is that the dissection of this challenging part of a TME operation is actually EASIER. If this proves to be so then patients with middle third and lower third rectal cancer throughout the world may look forward to better outcomes with less nerve damage than in the past.
No conflict of interest.

14 INVITED

Training in cancer surgery across Europe: The trainees perspective

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Background: The European Parliament resolution on combating cancer in the European Union (2008) calls on the Member States to make nationwide provision for multidisciplinary oncology teams to give optimal individual treatment to all patients. Surgical oncologists lead the multi-disciplinary management of most forms of cancer and the increasing complexity of cancer management means that trainees in surgical oncology require a high level of specialist training. This training needs to encompass both generic oncology knowledge about the role of genetics, radiation and medical oncology but also they must achieve a high level of technical expertise in surgery relevant to their field of practice. Standards of training across Europe must be harmonized at the highest level to ensure patients across the Union have equal access to best practice and outcomes converge across Europe. The ESSO Young Surgeons and Alumni Club (EYSAC) was founded in 2010 to facilitate surgical oncology training across Europe. A survey of the members of this association has recently been undertaken to gain better understanding of their training needs and the challenges they face.
Material and Methods: A bespoke online questionnaire was sent out to all EYSAC members in early 2013; questions were related to training needs, perceived problems with training, careers and expectations.
Results: The main finding of the survey provisional results is that trainees perceive that surgical oncology training is still fragmented and poorly developed. The formal European Board of Surgical Qualification (EBSQ) examination in surgical oncology remains the only specific qualification but lacks National or European recognition as a formal certification. There is no single recognized training accreditation across Europe which hinders internal mobility across Europe. Many European countries still don't recognize surgical oncology as an independent discipline.
Conclusions: Since 1996 the EU law guarantees the right to practice of EU trained doctors and specialists in all EU member states, EYSAC will continue to make efforts to promote the harmonization and the quality of training in surgical oncology across Europe in order to optimize and standardize cancer patients' care and to open new avenues for surgical oncology.
No conflict of interest.

15 INVITED

Methods in training

Abstract not received.

16 INVITED

Quality control projects of the section of surgery of the European Union of Medical Specialists

Abstract not received.

Scientific Symposium (Sat, 28 Sep, 11:15−13:15)
Targeting the Microenvironment

17 INVITED

Lysyl oxidases in cancer progression

J.T. Erler[1]. [1]*University of Copenhagen, Biotech Research and Innovation Centre (BRIC), Copenhagen, Denmark*

Background: Metastasis is strongly influenced by the tumour microenvironment, in particular by hypoxia (low oxygen) and increased matrix stiffness.

Materials and Methods: We have identified two key mediator molecules, lysyl oxidase (LOX) and lysyl oxidase-like2 (LOXL2). These are hypoxia-induced secreted enzymes that increase matrix stiffness through mediating the crosslinking of collagens and elastin in the extracellular matrix. We have investigated their role in metastasis using a variety of *in vitro* and *in vivo* models.
Results: We showed that LOX expression is clinically correlated with hypoxia, metastasis and poor patient survival. Furthermore, inhibition of LOX through genetic, chemical or antibody means significantly reduces invasion and metastasis in several *in vivo* models of solid tumour metastasis. LOX enhances invasion through increasing matrix stiffness, thereby activating integrins, Src and FAK. LOX additionally enhances formation of distant metastases by playing a role in formation of pre-metastatic niches through recruitment of CD11b+ cells, which greatly enable metastatic colonisation. More recently, we have found LOX to mediate fibrosis-enhanced metastasis through matrix remodelling in response to chemical- or irradiation-induced fibrosis.
We have also investigated the role of LOXL2 in breast cancer metastasis and normal mammary tissue function. Like LOX, LOXL2 is clinically correlated with metastasis and poor patient survival. LOXL2 enhances invasion through regulation of matrix remodeling. Inhibition of LOXL2 through genetic, chemical or antibody means prevents invasion and metastatic dissemination *in vivo*. We further show that LOXL2 activity is highest during mammary gland involution, consistent with its role in matrix remodelling. More recently, we have found LOXL2 to regulate tumour–stromal interactions that drive cancer progression, and to drive abnormal mammary epithelial cell acinar formation.
Conclusions: These findings demonstrate pre-clinical effectiveness of anti-LOX/LOXL2 therapy, which may have important clinical implications.
No conflict of interest.

18 INVITED

Putting cancer stem cells in context

I. Malanchi[1], A. Santamaria-Martinez[2], J. Huelsken[2]. [1]*London Research Institute, London, United Kingdom;* [2]*EPFL, ISREC, Lausanne, Switzerland*

Metastatic growth in distant organs is the major cause of cancer mortality. Formation of metastasis is a multi-step process with several rate-limiting steps. While dissemination of tumour cells appears to be an early and frequent event, successful initiation of metastatic growth, a process termed “metastatic colonization”, is rather inefficient for many cancer types and accomplished only by a minority of cancer cells that reach distant sites. Prevalent target sites are characteristic for many tumour entities.
We found that a small population of cancer stem cells (CSCs) in a model of mammary gland tumour is critical for metastatic colonization. These CSCs represent a stable population of tumour cells which selectively survive and proliferate upon metastatic seeding and thereby drive the initial expansion of cancer cells at the secondary site. In contrast, non-CSCs fail to grow, are rapidly lost and do not de-differentiate into CSCs.
Furthermore, we find stromal niche signals to be crucial for this process. We identify the extracellular matrix (ECM) component POSTN to be expressed by fibroblasts in the normal tissue exclusively in response to tumour cell infiltration. Infiltrating tumour cells induce stromal POSTN expression in the secondary target organ via TGFb3 secretion. Importantly the induction of POSTN at the target site is essential for the metastatic process. Indeed, generation of a POSTN null mouse revealed that the metastatic process is heavily compromised in the absence of POSTN.
We show that this ECM protein is required to allow maintenance of cancer stem cells: the cells driving the metastatic process. We found that POSTN is able to bind Wnt ligands and therefore increase Wnt signaling. *In vivo* we observed Wnt signaling activity selectively in the CSCs population and this activity is abrogated in absence of POSTN. Thus, POSTN acts as a niche component that can promote stem cell maintenance and metastatic colonization by augmenting Wnt signaling.
In conclusion, this study suggests that the inefficiency of the metastatic process might be due to both: an intrinsic differential potential of the disseminated cancer cells to grow at the secondary sites and inadequate extrinsic signals to support metastasis establishment from distant tissues. We suggest that the education of stromal cells by infiltrating tumour cells is an important step in metastatic colonization and that preventing de-novo niche formation may represent a novel treatment strategy against metastatic disease.
No conflict of interest.

19 INVITED

Tumor elicited inflammation and malignant progression in colorectal cancer

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Colorectal cancer (CRC) is the third leading cause of cancer related deaths in the US and other Western countries. Whereas 2% of CRC arises in the context of pre-existing inflammatory bowel disease (IBD), especially ulcerative colitis (UC), and is known as colitis associated cancer (CAC), most CRC, including familial and sporadic cases, is found in individuals that do not show any signs of IBD. Yet, expression profiling has revealed the same inflammatory gene signature, which depends on activation of NF-κB and STAT3, in both CAC and CRC, findings that generate a question regarding the origin of the CRC-elicited inflammatory response. In early experiments we have shown that activation of NF-κB, which leads to production of the pro-inflammatory cytokine IL-6, a potent activator of STAT3, plays a critical role in the development of CAC. More recently we investigated the origin and role of inflammation in the development and progression of sporadic CRC, most of which is driven by loss of the tumor suppressor APC and activation of the β catenin signaling pathway. We focused our studies on IL-23, a heterodimeric cytokine, composed of a unique p19 subunit and a p40 subunit which it shares with IL-12. As observed by others, we also found that IL-23 expression is strongly elevated in CRC relative to adjacent non-tumor tissue and have extended these findings to the CPC-APC mouse model of colorectal tumorigenesis. In CPC-APC mice, the major source of IL-23 expression in colorectal adenomas are tumor associated macrophages (TAM). Importantly, ablation of IL-23 p19 either in all cells or only in bone marrow (BM)-derived cells attenuates the development and slows down the progression of CRC in CPC-APC mice and similar results were observed upon ablation of IL-23 receptor (IL-23R). As IL-23R is not expressed on adenoma epithelial cells, IL-23 must exert its pro-tumorigenic effect via an indirect mechanism. Indeed, IL-23 signaling promotes the polarization of IL-17 producing T cells (Th17) and the production of IL-6, both of which contribute to the development and progression of sporadic colorectal tumors in mice. Importantly, molecular epidemiological studies carried out by Galon, Fridman and their co-workers have revealed that an ‘IL-23-Th17’ signature that is upregulated in about 10% of human CRC patients, and that the presence of this signature in stage I/II CRC is associated with very poor prognosis and a marked decrease in disease free survival. We investigated the mechanism responsible for the specific induction of IL-23 in TAM and found it to depend on Toll like receptor (TLR) − MyD88 signaling, which appears to be activated in response to components of the colonic microflora that permeate the adenomas. We also detected eubacterial 16S RNA in both mouse and human colonic adenomas, as well as increased penetrance of bacterial endotoxin (LPS) into adenomas relative to surrounding non-cancerous tissue. The development of colorectal adenomas in both mice and men is associated with loss of protective mucins and junctional adhesion proteins and this is likely to be the primary mechanism that accounts for the selective entry of microbial products into the tumor and induction of the tumor promoting “IL-23−Th17” signature. Future studies should focus on the therapeutic value of anti-IL-23 or anti-IL-17 interventions and the genetic or environmental causes of the large variation in the magnitude of IL-17 production amongst human CRC patients.
No conflict of interest.

20 INVITED

Stromal factors and metastasis

Abstract not received.

Scientific Symposium (Sat, 28 Sep, 11:15−13:15)
Advances in Preclinical Research

21 INVITED

Frontiers of phase-contrast imaging

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Background: X-ray imaging has been the most important and widespread diagnostic tool in Medicine over the last century. Despite its huge success, for example in imaging bone structure, X-ray diagnostics ultimately reaches its limits in the examination of soft tissues, such as small tumours in healthy tissues, lungs or articular cartilage. Moreover, medical diagnostic imaging requires high contrast at low radiation dose: a condition that often limits

the sensitivity of the method. In this scenario, the application to biomedical imaging of coherent X-ray phase-contrast imaging (PCI) methods, which explicitly utilize the wave character of X-ray light, has attracted a vivid interest in medical imaging.
Material and Methods: PCI employs the dual property of X-rays of being simultaneously absorbed and refracted while passing through a tissue. Different PCI modalities have been developed (based on X-ray interference or diffraction mechanisms). The produced image contrast is a combination of X-ray absorption, refraction and ultra-small angle scattering. Whole or portions of human tissues such tumour-bearing breasts, pathological livers and osteoarthritic joints provided by the Ludwig Maximilians University (LMU, Phatology and Forensic medicine departments) were imaged in computed tomography (CT) mode. Blinded radiologists quantitatively evaluated the visual aspects of the PCI-CT images with respect to sharpness, contrast and the discrimination of different structures/tissues. IRB-approval for this study was granted by the ethics committee of the LMU.
Results: Low dose, high resolution PCI-CT images of clinically interesting specimens were obtained. Comparative studies in which PCI images were correlated to results produced with clinical diagnostic imaging tools (i.e. CT scans, magnetic resonance imaging, histology). The radiological blinded evaluation showed a statistically relevant difference in image quality in PCI-CT against conventional diagnostic images.
Conclusions: PCI-CT enables depiction of fine tissue changes previously not detectable by conventional diagnostics techniques. Results suggest that PCI-CT has the potential of becoming a valuable method in clinical imaging providing a 3D investigation of whole specimens and quasi-histological information of tissues at clinically compatible doses. In addition, PCI may represent a powerful tool in animal models investigations allowing for the longitudinal follow up of cancer evolution or therapeutical effects.
No conflict of interest.

22 INVITED

Intravital microscopy of tumor invasion and CTL effector function: Mapping and targeting niches of the tumor microenvironment

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Cancer progression, including growth, invasion and immunological control of the tumor are complex processes which depend upon both, cell intrinsic mechanisms and the tumor microenvironment. Using multiphoton excited three-fluorescence and higher harmonic generation microscopy (second and third harmonic) of B16F10 melanoma and HT1080 fibrosarcoma grafts, the niches responsible for tumor invasion, interaction with cytolytic T cells, and tumor therapy response were monitored over time. Invading tumor cells preferentially exploited preformed least-resistance tracks of complex, multi-interface topography, which determined single-cell or collective migration modes, without immediate anatomic tissue remodeling or destruction. The geometric tissue organization included 1D, 2D and 3D topology, which each resulted in unique invasion routes, patterns and efficacy. These invasion zones showed strongly enhanced resistance to radiation therapy, but were particularly sensitive to immunotherapy with adoptively transferred antigen-specific cytolytic T cells (CTL), suggesting that regimen-specific resistance is microenvironmentally controlled. Targeting beta1/beta3 integrins prompted enhanced radiosensitization of invasion strands, implicating integrin-mediated adhesion and/or anti-apoptotic signaling (anoikis) as key mediators of the radioresistance niche. In a different mechanism, improved elimination of invading tumor cells by cytotoxic T lymphocytes was mediated by enhanced migration and accumulation of CTL within the tissue guidance tracks, which locally enhanced serial CTL conjugations and consequently lead to increased tumor cell killing rates.
Thus, intravital microscopy represents a powerful approach to identify and mechanistically address niches of invasion, metastasis and therapy resistance, delivering innovation and new therapy concepts to preclinincal cancer research.
No conflict of interest.

23 INVITED

A dedicated small animal radiotherapy research platform

F. Verhaegen[1], P.V. Granton[1], S. Van Hoof[1], D. Trani[1], L. Dubois[1]. [1]*Maastricht University Medical Centre, Maastricht, Netherlands*

Background: New technology and treatment strategies have often been implemented in the past without thorough preclinical verification. Examples are intensity modulated radiotherapy, stereotactic body radiotherapy, proton radiotherapy etc. Recently it has been realized that useful knowledge may be gained from conducting preclinical radiotherapy studies in e.g. mice, to fully explore new forms of therapy. Examples are synergistic studies between radiotherapy and drugs (to enhance tumor damaging efficacy or normal tissue protection), or other forms of cancer therapy. In the past radiobiology studies were often performed with non-precise radiation beams, bearing little resemblance to modern highly precise targeted irradiation in clinical practice. To enable more precise preclinical irradiation studies, novel technology has been developed recently.
Materials and Methods: Several groups have made efforts towards developing precision irradiators for small animals, combined with x-ray imaging equipment to provide image-guidance, in analogy with what is available for human radiotherapy. The irradiation and imaging technology was downscaled to the spatial resolution of small animals. Also the energy of the photon beams was downscaled. To enable irradiation of small structures with complex spatio-temporal radiation patterns, the development of a dedicated treatment planning system for small animals was necessary.
Results: In our department a small animal irradiation system equipped with a high-resolution cone beam CT imaging system was fully commissioned and optimized. A treatment planning system, SmART-Plan was developed, based on Monte Carlo dose calculations. It was verified that planned doses agreed with delivered doses. A dose verification system, based on the onboard imager, was developed. First preclinical studies are now being performed on this system.
Conclusions: New technology is becoming available for preclinical research with an unprecedented accuracy and precision. It is expected that studies on this type of equipment may help to elucidate radiation interaction mechanisms in normal and cancerous tissues. New knowledge may be gained on the efficacy of complex spatio- temporal radiation patterns, the synergy of radiation with drugs (not restricted to chemotherapy), the influence of organ motion, and much more. It is hoped that this knowledge could then be translated to cancer patients; it is herein that the greatest challenge lies.
No conflict of interest.

24 INVITED

Monochromatic radiotherapy: From first experimental glioma bearing rat therapy up to the first clinical trial

F. Estève[1], J.F. Adam[1], J. Balosso[1], P. Berkvens[2], A. Bravin[2], H. Elleaume[2], J.F. Le Bas[1], C. Nemoz[2], A. Tessier[2], M. Renier[2]. [1]*Grenoble Institute of Neurosciences, CR U836, Grenoble, France;* [2]*ESRF, Grenoble, France*

In the early 80's, Norman's group proposed to treat brain tumors, after loading them with iodinated contrast agents, by using scanners as therapy machines to enhance the local dose deposition determined by the higher X-rays absorption of the iodine atoms. Theoretically, such physical conditions are optimal in the energy range 50 to 80 keV produced with synchrotron sources.
After several years of preclinical radiotherapy research mainly developed at the European Synchrotron Radiation Facility (ESRF), we have built a radiation therapy clinical trial. The clinical protocol has been submitted and approved by the DRRC (Direction de la Recherche Clinique) of the Grenoble CHU. We then obtained the agreement from the AFSSAPS* for medical purposes and from the ASN for the radiation safety aspects. In these clinical trials we wish to translate up to human patients what has been studied at the ID17 beamline on preclinical studies including dose computation on realistic human phantoms.
The first radiotherapy clinical trial currently being performed, is based on the dose enhancement that occurs when a tumor is loaded with heavy iodinated contrast agent. This technique has been studied for years in different places on patients and on animal models using conventional X-ray sources. The medical goal is to perform a phase I and phase II clinical trials to demonstrate the feasibility and acceptance of radiation treatment using a synchrotron X-ray source on patients. Furthermore, the secondary medical objectives are (in relation to phases I and II)
– To assess the onset of adverse effects, early and late effects related to the treatment.
– To assess the survival time without on site relapse, (survival criteria).
– To assess the survival time without cranial tumor relapse (no new metastasis).
– To assess the treatment efficiency using the RECIST criteria: evaluation of treated target lesions response is done with the measurement of the biggest diameter or sum of the diameters of the different metastasis.

To now, we have evaluated the accuracy of the ESRF CT technique on four patients by measuring the iodine distribution in brain metastasis, in comparison with conventional CT scanners. This imaging procedure has been followed by a 5 Gy single synchrotron fraction dose delivery, considering the iodine dose enhancement.
No conflict of interest.

Scientific Symposium (Sat, 28 Sep, 11:15−13:15)
Cancer in Teenagers and Young Adults

25 INVITED

Specialist care for teenager and young adults with cancer

Abstract not received.

26 INVITED

Specialist care for teenager and young adults with cancer

A. Ferrari[1]. [1]*Istituto Tumori Milano, Medical Pediatric Oncology, Milano, Italy*

Background: The last 5 years have been a key time in Italy for the development of projects dedicated to adolescents and young adults with cancer.
Material and Methods: National actions, taken in an effort to implement specific programs tailored to these patients arose from the pediatric oncology community, including the creation of the national Committee on Adolescents of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP), founded with the mission of ensuring that Italian adolescents with cancer have prompt, adequate and equitable access to the best care, in order to optimize their treatment outcome and quality of life.
Results: A first study of the Committee compared the number of patients treated at AIEOP-affiliated pediatric oncology centers to the number of cases expected to occur in Italy based on incidence rates obtained from population-based cancer registries. The ratio of observed to expected (O/E) was 0.10 for 15−19 year-old patients, as opposed to 0.77 for 0−14, emphasizing that the AIEOP network was far less effective in serving adolescents than children. A second study showed the existence of rigid upper age limits (as low as 16, 15, or even 14 years) for admission to pediatric cancer units. Further studies confirmed the problem of referral to specialized centers for adolescents, showing that they often arrived at the diagnosis after a considerable delay (as compared to children). The AIEOP Committee defined as priorities: increasing the number of adolescents referred to pediatric oncology units, improving awareness, improving cooperation with adult medical oncologists.
Conclusions: A more ambitious and forward-thinking national program is now necessary, requiring the following actions: a) fully involve adult medical oncology groups in the project, evolving from a pediatric oncology Adolescents Committee to a national broad-based Task Force which forms the official structure which may be accessed by the public authorities; b) achieve the formal support of the Ministry of Health and include in the next National Oncologic Plan the the required facilites to allow centers (no matter if they are pediatric or adult units) to treat adolescents with cancer: e.g. no restricted age cut-offs, multidisciplinary team, clinical trials availability, adequate setting and staff, fertility preservation program, transition program; c) establish cooperation with other international groups involved in the field.
No conflict of interest.

27 INVITED

Developing multi-professional education for TYA with cancer

D. Stark[1], S. Smith[2], S. Morgan[3]. [1]*St James's University Hospital, Medical Oncology Department, Leeds, United Kingdom;* [2]*Teenage Cancer Trust, London, United Kingdom;* [3]*St James's University Hospital, Leeds, United Kingdom*

Background: TYA with cancer have specific requirements, which place specific skills upon professionals working with them. Professionals need to understand the diseases they develop, the physiology at that age, the primacy of clinical trials for many young people, and the wider context of the young person including commmunication to support care and their role alongside their peer group and family.
Methods: We will present the TYA multiprofessional education opportunites and plans within the European Network for Cancer in Children and Adolescents (ENCCA) and their collaboration with ECCO, ESMO, the European Cancer Patients Coalition (ECPC) and others, as well as national-level TYA cancer care specialist groups.
Results: There are a growing number of professional education opportunities for learning these skills, for medics, nurses, and other professionals, and several further are developing within ENCCA and its wider collaborations. These will be described and discussed, and the audience challenged to contribute to overcoming barriers to develop this skill set.
Conclusion: There is much progress in this field, but much remains to do.
No conflict of interest.

28 INVITED

Improving access to clinical trials for teenagers and young adults

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The significant advances in survival for patients with cancer over the last 20 years can be attributed to the improvement of treatment through clinical trials. Survival of children as well as adults with cancer has increased dramatically in the last decades. At the same time, progress in treating adolescents and young adults (AYAs) has stagnated. All the studies focusing on the rate of accrual of AYA in clinical trials show a lack of enrollment as compared to patients under 15 years.
Several reasons can explain this gap, mainly:
1. low number of clinical trials available for AYA even at major cancer comprehensive centres,
2. lack of a coordinated AYA program with patients treated anywhere (most patients not treated at academic centers offering the few clinical trials for AYAs)
3. lack of cooperation among paediatric and medical oncologists developing programs for malignancies involving both adults and children

The consequences of the low inclusion of AYA into clinical trials are a great heterogeneity in the care delivered to these patients; little progress on the biology specificities due to obstacles to tumor samples access.
Several strategies have to be developed in order to overcome these barriers:
- to develop a network involving the disease-, and age-based expertise achieved by the cooperative groups involved in each tumour on a national/international basis. This network relying on pediatric and adult communities should allow to design clinical trials accessible for patients in this age group independently of the site of care
- to set biologically appropriate age eligibility criteria for clinical trials reflecting the disease. These eligibility criteria should allow the inclusion on young adults with paediatric tumours in protocols designed for children as well as paediatric patients in trials designed for adults.
- to improve accessibility of AYA to clinical trials through international policy with a key recommendation from the community of AYA oncologist allowing each AYA with cancer to be offered entry to any clinical trial for which they are eligible
- to create specific care structures for AYA able to offer enrolment of patients on clinical trials as well as offering an environment that is supportive to that group of patients.

The diverse needs of these patients may be addressed only by people dedicated to a new discipline; AYA oncology with dedicated research strategies that are not available through either pediatric or adult programs.
No conflict of interest.

29 INVITED

Role of patients and advocacy groups

Abstract not received.

Special Session (Sat, 28 Sep, 14:15−15:15)
Multidisciplinary Approach to Castration-Resistant Prostate Cancer

30 INVITED

Sequencing post-docetaxel therapy in CRPC − Identifying which agent for which patient

Abstract not received.

31 INVITED

Hormonal therapy and cytotoxic treatment in elderly men with CRPC: Factors to be considered

B. Tombal[1]. [1]*Cliniques Universitaires Saint Luc, Department of Urology, Brussels, Belgium*

The incidence of prostate cancer (PCa) increases with age, with a median age at diagnosis in the late sixties. Due to the increased life expectancy in developed countries, PCa represents a major public health problem. As a consequence of the "global aging" of the population, treatment of PCa in elderly adults (>75 years old) has become a critical issue.
In addition, the landscape of treatment for advanced PCa has been dramatically evolving, bringing the possibility of increasing overall survival and improving quality of life significantly beyond castration. The question of the risk/benefit profile of these drugs in elderly patients is a matter of controversy. It appears indeed that many older men are denied

chemotherapy based on their chronological age, not their health status. Each of the registration trials have included sub-analysis on age but have not generally included specific recommendations for use in the elderly. The SIOG (International Society of Geriatric Oncology) has developed general guidelines for these men. Overall, they conclude that treatment decisions for advanced prostate cancer in senior adult men should be adapted to health status and that specific prospective studies in senior adults men with metastatic prostate cancer are warranted.
Conflict of interest: *Ownership: None. Advisory board: Amgen, Astellas, Dendreon, Sanofi-Aventis, Ferring, Bayer. Board of directors: None. Corporate-sponsored research: None. Other substantive relationships: None*

32 INVITED

Role of palliative surgery and radiation therapy in locally advanced, non-metastatic CRPC

A. Heidenreich[1]. [1]*RWTH Aachen University Hospital, Universitätsklinikum der RWTH Aachen, Aachen, Germany*

Medical treatment with abiraterone acetate plus prednisone, docetaxel plus prednisone ± bone targeting agents while maintaining androgen deprivation represent the therapeutic approach in patients with even non-metastatic castration resistant prostate cancer (CRPC). A significant proportion of patients, however, suffer from locally progressive CRPC with consecutive subvesical obstruction, recurrent gross hematuria and bladder clotting, supravesical obstruction with hydronephrosis and the potential need for endoluminal or percutaneous stenting. In the majority of cases, medical treatment does not result in clinically meaningful remissions as it is observed in metastatic deposits. Therefore, various palliative surgical and radiooncological measures need to be discussed individually in order to improve quality of life. The presentation will discuss the various surgical options in detail.
In case of locally advanced CRPC infiltrating the bladder neck associated with or without gross hematuria, palliative transurethral resection of the prostate (TUR-P) followed by local radiation therapy represents the treatment of choice. Palliative TUR-P is associated with low morbidity, low frequency of complications and immediate relief of micturition symptoms. However, about one third to half of the patients will experience a local relapse so that surgery should be combined with radiation therapy. In case of significant local progression with infiltration of the bladder, the rectum and the pelvic floor, palliative radical surgery including anterior and posterior exenteration with an urinary diversion and/or a permanent colostomy might be indicated resulting in a symptom-free survival time which covers about 80% of the remaining lifetime. Patients have to be selected very carefully and surgery should be performed in experienced centres only. With regard to supravesical obstruction, diversion of the kidney becomes necessary in cases of symptomatic hydronephrosis or in uremia. Diversion can be performed ureteral reimplantation or a subcutaneous pyelovesical bypass in patients with a life expectancy >2 years. For palliative indications insertion of endoluminal stent or a percutaneous nephrostomy is more appropriate.
No conflict of interest.

Special Session (Sat, 28 Sep, 14:15−15:15)
Dilemma of Crossover in Clinical Trial Design of Agents With 'Obvious Activity'

33 INVITED

Crossover in clinical trials is not required

D. Cameron[1]. [1]*Edinburgh Cancer Research Centre, Edinburgh, United Kingdom*

This talk will introduce the subject from a clinician's perspective. Clinical trials are designed to answer specific questions, and when the results of a clinical trial could lead to changes in clinical practice, the trial design has to be mindful of this. In particular, in an age where new drugs may be required to pass both regulatory and health technology hurdles, the implications of cross-over may not always be what is intended and so may not be appropriate. Examples of clinical trials which have and have not allowed cross-over will be used to illustrate the possible consequences.
Patients enrolling in a randomised clinical trial know that there is no guarantee that they will get a more active therapy: even if the new therapy has "obvious activity". In randomised trials there has to be sufficient equipoise between arms to justify the study, so that if it is felt that it would be unethical to deny the patient the new treatment at cross-over then the primary question will be about sequence, not about added efficacy.
Options for how to deal with cross-over when it is felt essential will also be discussed, and the question of trials designed for primary health economic, rather than clinical efficacy, endpoints will also be considered.
No conflict of interest.

34 INVITED

Correcting for partial crossover to the experimental drug in a clinical trial

D.M. Finkelstein[1]. [1]*Massachusetts General Hospital/Harvard University, Biostatistics Department, Boston, USA*

Background: When patients on a clinical trial are selectively crossed over to the experimental arm, it becomes challenging to assess the impact of the experimental therapy on overall survival. In fact, if the therapy is effective, then those who cross over may receive survival benefit, thus diluting the test for comparison of the arms on this important outcome.
Material and Methods: Since a crossover can be necessary on ethical grounds, statistical methods must be applied that allow an assessment of what would have occurred had patients remained on their assigned treatment until death. We will discuss examples of trials that faced this challenge and explain the statistical approach using the inverse probability of censoring weighted (IPCW) method which attempts to remove the bias caused by treatment crossover.
Results: The IPCW method has been applied to assess the effects of treatment on survival in the context of clinical trials that allowed discretionary cross-over. We will describe the IPCW method and discuss the assumptions required for its use, as well as the interpretation of the results.
Conclusions: In the context of trials where patients selectively cross over to the experimental arm, statistical methods such as IPCW can provide insights to the interpretation of the results particularly on overall survival.
No conflict of interest.

35 INVITED

Cross over in oncology trials: Considerations for endpoints and trial design − arguments pro and contra

J. Bogaerts[1]. [1]*European Organisation for Research and Treatment of Cancer, Statistics Department, Brussels, Belgium*

In many cancer settings, the activity of later treatment lines has improved over time.
As a result, obtaining differences in overall survival in comparative phase III trials becomes a challenge.
In the future, more and more effort will need to be devoted to collecting more detailed information on later treatment lines. Regulators (e.g. EMA) have already opened this discussion, asking for Progression Free Survival 2 (PFS 2) data under certain circumstances. PFS 2 can be freely defined as the time from progression on the study drug until progression on the next (off-protocol) treatment line.
Interpretation of the impact of such further heterogeneous treatment lines, and their effect on the OS comparison for the original comparison, will be a daunting task.
A currently significant example of such undertaking is the class of trials where trialists allow patients progressing on the control treatment arm to 'cross over' to the experimental drug. The decision to allow this cross-over, and the difficulty of interpreting the resulting OS data, has far-reaching consequences for such varying interest groups as: trialists (accrual impact), clinical research, patients on the trial, future patients not on the trial, and HTA assessment.
In absence of a significant OS treatment effect, the question then becomes "what would the treatment effect have been in absence of cross-over?"
Attempts to answer this question have ranged from dismissive (there is no effect seen because the crossover to the experimental works so well), over statistically defective (exclude patients who cross over), to methods that are open to severe criticism.
These methods include censoring at time of cross-over, and inverse weighting methods.
The extent of the problem, and the possible misinterpretation by using some of these methods, will be further illustrated by some simulations.
No conflict of interest.

Special Session (Sat, 28 Sep, 14:15−15:15)
Young People Facing Cancer

36 INVITED

Evidence of a prolonged diagnostic journey for young people with cancer: What do we know now?

L. Fern[1]. [1]*Cancer Research UK, London, United Kingdom*

Cancer in teenagers and young adults is uncommon and overall five year survival rates are an impressive 80%. Despite this, cancer is the leading cause of disease death in developed countries. Whilst overall survival rates are high, this figure varies considerably by cancer type, around 99% for thyroid cancers but diseases such as soft tissue sarcoma conferring five year survival rates of 55% for males, and 58% in females.
Survival for some cancers in young people is less than in children and older adults, notably bone sarcomas. This may be related to a prolonged period to diagnosis, differences in cancer biology, lesser involvement in clinical trials and place of care. Young people frequently report a prolonged period to diagnosis and have strong perceptions of a perceived 'delay' in their diagnosis. Evidence from the UK is now supporting this with young people having more general practitioner consultations prior to referral to secondary care compared to adults and a higher frequency of accident and emergency admissions compared to adults.
Young people and often secondary healthcare professionals frequently point to primary care as a simplistic solution to improving the diagnostic journey for young people. However there are multiple components of the diagnostic pathway where actual or perceived 'delays' can occur. These range from appraisal and recognition of potential symptoms by young people, accessing appropriate healthcare services, referral from primary care and also system processes within secondary care.
This presentation will discuss current evidence suggesting a prolonged period to diagnosis for young people with cancer and importantly the need to determine whether it is related to poorer outcomes.
No conflict of interest.

37 INVITED

Quality of life in children and adolescents surviving cancer

M. Eilertsen[1], T. Jozefiak[2], T. Rannestad[1], M.S. Indredavik[2], T. Vik[3]. [1]*University College of Sør-Trøndelag, Faculty of Nursing, Trondheim, Norway;* [2]*NTNU and St. Olav's University Hospital, Department of neuroscience Regional Center of Child and Adolescent Mental Health and Department of Child and Adolescent Psychiatry, Trondheim, Norway;* [3]*NTNU, Department of Laboratory Medicine Children and Women's Health, Trondheim, Norway*

Background: Childhood cancer involves a crisis for the child and their family. The aim of this study was to explore subjective and proxy reported QoL (Quality of Life) in children and adolescents surviving cancer at least three years after their cancer diagnosis compared with healthy controls.
Material and Methods: Case-control study included 50 children and adolescents diagnosed with cancer between January 1, 1993 − January 1, 2003 and treated at the Paediatric Department of St. Olav's University Hospital in Trondheim, Norway. Data was collected by using The Inventory of Life Quality in Children and Adolescents Questionnaire (ILC) and the KINDL QoL questionnaire (parent and self reports), as well as by collecting data for any somatic late effects and psychological symptoms from the medical records of children surviving cancer.
Results: Adolescents surviving cancer as a group assessed their QoL as similar to that of their peers. However, adolescents surviving brain tumours or those with late effects reported lower QoL and an increased number of QoL domains perceived as problematic, even many years after diagnosis and treatment. Parents generally reported a poorer QoL for their children surviving cancer and a greater number of QoL domains experienced as problematic compared with parent controls.
Conclusion: To improve the child's total functioning and well-being we conclude that when planning long-term follow-up care and rehabilitation of children and adolescents with cancer, especially for survivors with brain tumours and with late effects, it is important to particularly take into account their subjectively perceived and proxy reported QoL, in addition to their psychological problems and psychosocial functioning.
No conflict of interest.

38 INVITED

Delivering age appropriate care for teenagers and young adults with cancer

S. Smith[1]. [1]*Teenage Cancer Trust, London, United Kingdom*

Background: Historically teenagers and young adults (TYA) within healthcare have been treated with younger children or much older adults. In contrast, TYA age- specific units in cancer care have developed over the past twenty years with TYA cancer care now recognized as a distinct speciality within its own right the UK. TYA's are now cared for within purpose built environments and by teams who are experts in the delivery of TYA care.
Material: Teenage Cancer Trust is a UK Charity recognized for being the catalyst in the development of age appropriate cancer services. The charity opened its first specialist Unit in 1990 and over the past twenty years has opened 27 further units across the UK. Centralization of care within Units has enabled a growing body of clinical expertise to develop through years of experience and a multidisciplinary approach. Particularly within nursing, the UK is now seen as a worldwide leader in TYA cancer care.
Results: The best standard of care for TYA patients is undoubtedly provided by those who have been specifically trained or have significant experience in managing this particular client group. The UK's experience in delivering age-appropriate, multidisciplinary and nursing care for the past twenty years has recently been captured within A Blueprint of Care (2012). This Blueprint provides guidance to professionals planning and providing services for young people with cancer and will assist those who are in the early stages of developing care for this age group.
Conclusion: Providing tailor made holistic care for TYA cancer patients requires a multidisciplinary approach and nurses who are highly trained, experienced and knowledgeable. Teenage Cancer Trust believes that investment into nursing is essential to ensure patients have access to the best quality of care, environment and support possible. The charity funds a growing number of specialist nurses and provides funding to support national educational and training programs for professionals. The UK is seen as leading TYA cancer care development and TYA specialist cancer nursing. International colleagues are now starting to develop TYA cancer care within their own countries. This is an exciting time, with TYA cancer care as a distinct specialty now developing beyond the UK and this provides an ideal opportunity for sharing best practice and international collaboration, to ensure the unique needs of this vulnerable patient group are met.
No conflict of interest.

39 INVITED

Developing a model of care for young cancer survivors: An Australian perspective

K. Thompson[1], L. Holland[1], S. Van Staalduinen[1], J. Zalcberg[2], L. Orme[1]. [1]*Peter MacCallum Cancer Centre, ONTrac at Peter Mac, Melbourne Victoria, Australia;* [2]*Peter MacCallum Cancer Centre, Cancer Medicine, Melbourne Victoria, Australia*

Background: Each year in Australia approximately 1000 new adolescent and young adult (AYA) patients, aged 15−25 years, are diagnosed with cancer. While much of the attention to date has focused on the diagnosis and disease management of this population group, the focus is now turning to developing models of care which prioritise young peoples' ongoing development, health, well-being and quality of life beyond the period of treatment completion.
In 2011 the ONTrac at Peter Mac Victorian Adolescent & Young Adult Cancer Service received funding to pilot a model of AYA Survivorship care. This model was informed by international research and clinical advances in the field of survivorship; Victorian government cancer care policy and an emerging understanding of patient experience and need during the post treatment period.
Aim: The aim of this project was to develop, implement and evaluate the efficacy and sustainability of a phase 1 model of survivorship care for young people with cancer in Victoria, treated in both metropolitan and rural centres.
Method: The project involves: a nurse/allied health-led intervention; care-coordination; the development of acute/primary partnerships; developmentally appropriate screening; care-planning and patient review. A total of 100 patients will be recruited over 12 month period from three sites across the Australian state of Victoria. Evaluation comprises the analysis of: patient reported outcome measures, including quality of life, distress and need; qualitative interviews with patients, carers and healthcare professionals in both acute and primary sectors who are involved in the project and; assessment of health economic sustainability.
Discussion: This presentation will describe the experience of the ONTrac at Peter Mac Victorian Adolescent & Young Adult Cancer Service in the delivery of AYA specific cancer care. It will discuss the current model of Survivorship Care being piloted and some preliminary learning to date; specifically in relation to transferability, sustainability and the unique, emerging post treatment survivorship issues for young people within the Australian context.
No conflict of interest.

Special Session (Sat, 28 Sep, 14:15−15:15)
The Role of Biological Imaging in the Assessment in Head and Neck Cancer

40 INVITED

BiGART: Integration of biological imaging in treatment planning, adaptation and treatment strategies for radiotherapy of head and neck cancer

C. Grau[1]. [1]*Aarhus University Hospital, Department of Oncology, Aarhus, Denmark*

Primary radiotherapy plays an important role in the management of squamous cell carcinoma of the head and neck. With novel technology (IMRT, IMPT) it is technically possible to increase the radiation dose, at least to smaller target volumes, without violating normal tissue constraints. Since head and neck tumors are known to be heterogeneous, a logical next step in IMRT is therefore to incorporate more biological features into the initial treatment planning (dose painting) and systematically adapt the treatment as the anatomical and biological features change during the course of treatment. This emerging concept is called Biology-Guided Adaptive RT (BiGART). Relevant biological features for BiGART include hypoxia, proliferation, cell density and intrinsic radioresistance. The principle in dose painting is redistribution and escalation of the radiation dose to these radioresistant parts of the tumour. Hereby, a biologically more effective dose distribution might be achieved while simultaneously sparing normal tissues. Functional imaging modalities for BiGART include dynamic CT with contrast, diffusion weighted MRI, dynamic contrast enhanced MRI, and PET/CT with various tracers. A number of studies have shown that functional imaging imaging information on e.g. hypoxia is prognostic for the outcome of radiotherapy.
The main challenges in BiGART are *resolution* and *dynamics:* The biological features are likely to be more heterogeneous on a microscopic level than what current imaging can pick up. If so, our current imaging and delivery techniques are probably too coarse to fully address the biological distribution. The dynamics of the biological features of interest determines how frequent the patient needs to be subjected to repetitive imaging during radiotherapy. A few early studies have shown that dose-painting and BiGART in principle is possible, although not yet practical nor cost-effective on a daily or even weekly basis.
No conflict of interest.

41 INVITED

Diagnostic biological imaging of early relapse

W.J.G. Oyen[1]. [1]*Radboud University Medical Centre, Department of Nuclear Medicine, Nijmegen, Netherlands*

Molecular imaging with positron emission tomography (PET) has become increasingly important for assessment of patients with head and neck cancer.Although a wide variety of radiopharmaceuticals depicting a variety of tumor characteristics has been studied, the vast majority of the clinical evidence has been established with PET using F-18-fluorodeoxyglucose (FDG). Nowadays, FDG-PET is almost exclusively performed on integrated PET/CT scanners. Integrated PET/CT was a major step forward for adequate evaluation of anatomically complex areas like the head and neck, especially in case of distorted anatomy or the presence of posttherapy changes. FDG-PET/CT is currently used e.g. for detection of unknown primaries, staging, radiation treatment planning, and response assessment and prediction.
Although there is little, if any, evidence to support routine PET/CT surveillance in low risk patients with complete clinical, radiological and PET/CT response after treatment, FDG-PET/CT may have an important role in the evaluation of patients suspected of disease recurrence. Due to its high negative predictive value, there is increasing evidence that FDG-PET/CT is very useful to stratify patients clinically suspected of local recurrence. A negative FDG-PET/CT may therefore prevent unnecessary invasive diagnostic procedures like panendoscopy. However, nonmalignant activity on FDG-PET due to previous treatment negatively affects its positive predictive value. Although timing of the procedure and careful assessment of the exact localization of the increased FDG-uptake may help to avoid treatment-related false-positive findings, histological conformation of PET-positive findings remains the gold standard for decision making on major therapeutic interventions or change of management. Additionally, whole body imaging allows simultaneous assessment of the presence of second primaries or distant metastases, both findings having a significant impact on patient management.
In conclusion, when used appropriately FDG-PET/CT has a significant impact on the management of head and neck cancer patients as it provides important information on disease activity when relapse is clinically suspected.
No conflict of interest.

Special Session (Sat, 28 Sep, 14:15−15:15)
Immune System Radiation Interactions

42 INVITED

Radiation-induced TGFβ suppresses immune cells in the tumor microenvironment

M.H. Barcellos-Hoff[1], I. Pelliccotta[1], S. Du[1], S.C. Formenti[1]. [1]*New York University School of Medecine, Dept Radiation Oncology, New York, USA*

Transforming growth factor-β (TGFβ) has a broad range of pro-tumorigenic and immunosuppressive effects that provide the rationale for strategies to block its activity in cancer. Our recent studies reveal that concurrent radiation is a novel means of unleashing the potential of TGFβ inhibitors in cancer therapy. We have shown that radiation induces TGFβ and that TGFβ is necessary for an effective DNA damage response. Pre-clinical experiments in syngeneic breast, brain and lung cancer models show that TGFβ inhibition compromises DNA damage repair, increases tumor cell kill and significantly improves tumor growth control. Here we show that TGFβ inhibition during fractionated radiotherapy concomitantly alleviates detrimental effects on antigen-presenting cells, reduces the abundance of host tumor associated macrophages (TAM) and suppresses systemic production of myeloid derived suppressor cells (MDSC). As TGFβ inhibition promotes radiation-induced tumor cell death, an immunogenic signal, and blocks radiation effects that suppress immune cells in the tumor microenvironment, we propose that concurrent TGFβ inhibition and radiotherapy provides an innovative therapeutic combination to improve tumor control and activate anti-tumor immune responses.
No conflict of interest.

43 INVITED

Immune modulation and radiotherapy: Ipilimumab and melanoma

M. Postow[1]. [1]*Memorial Sloan-Kettering Cancer Center, New York, USA*

Ipilimumab is a human antibody that blocks the normally negative T cell regulator, cytotoxic T lymphocyte antigen (CTLA-4) and has improved the overall survival of patients with advanced melanoma. Additional research is necessary to improve upon the number of patients who benefit from treatment. Investigations are ongoing to evaluate whether combining ipilimumab with other cancer treatments such as chemotherapy and targeted therapy can be effective in increasing the efficacy of ipilimumab. One equally promising, yet underexplored possibility, involves combining ipilimumab with radiotherapy. Preclinical investigations suggest that radiotherapy can result in immunologic effects that are important for tumor eradication. Murine models have also demonstrated synergy when CTLA-4 blocking antibodies were combined with radiotherapy. Anecdotal cases of synergy between ipilimumab and radiotherapy such as the abscopal effect have also been described in patients. This talk will introduce the preclinical rationale for combining radiotherapy with CTLA-4 blockade and share our experience performing a detailed immunologic assessment of one patient who experienced an abscopal effect. We will also discuss ongoing prospective trials evaluating various aspects of the combination of ipilimumab and radiotherapy.
Conflict of interest: *Advisory board: Participate as a non-paid advisor for Bristol-Myers Squibb. Corporate-sponsored research: Receive research funding from Bristol-Myers Squibb*

Special Session (Sat, 28 Sep, 14:15−15:15)
Minimally Invasive Cancer Surgery: What is the Benefit?

44 INVITED

Robotic surgery

D. Jayne[1]. [1]*St James's University Hospital, Professor of Surgery, Division of Clinical Sciences, Leeds, United Kingdom*

Robotic surgery was introduced into clinical practice in 1999. It quickly found a niche in radical prostatectomy and subsequently attracted attention in other pelvic procedures, including rectal cancer surgery and gynaecological malignancy. In this presentation the evolution of robotic colorectal surgery will be scrutinized with particular focus on rectal cancer.

The evidence base will be considered in addition to the knowledge gaps in an attempt to rationalise its implementation into routine clinical practice. The benefits of robotic assistance as put forward by protagonists will be presented alongside criticisms of wider adoption. An update on the MRC NIHR ROLARR trial (robotic versus laparoscopic surgery for rectal cancer) will be presented.
No conflict of interest.

45 INVITED

NOTES − Natural Orifice Transluminal Endoscopic Surgery

R. Cahill[1]. [1]*Beaumont Hospital, Department of Colorectal Surgery, Dublin, Ireland*

Since its advent in 2008, Natural Orifice Transluminal Endoscopic Surgery (N.O.T.E.S.) has proved a very provocative concept and has spawned very considerable technical and technological innovation. In basic principle, the ability to perform abdominal or thoracic intervention without parietal wall injury is intuitively appealing at least in terms of patient postoperative convalescence and cosmesis. However, its clear that simple replication of procedures already well performed by conventional laparoscopy may not provide large clinical benefit and perhaps may be associated with increased complication rates especially during the learning curve. To develop as a useful and important innovation and step-advance, N.O.T.E.S. needs its own niche application and should be best viewed as a compliment rather than as a competitor to more established operative approaches. Especially interesting in this regard is the recent advent into clinical practice of the PerOram Endoscopic Myotomy (POEM) technique for achalasia and Transanal Proctectomy for benign and malignant conditions of the rectum. In both these cases, N.O.T.E.S. concepts and practice prove additive value to the standard operative portfolio of practicing surgeons and represent prototypicaland template natural orifice procedures for the future.
No conflict of interest.

46 INVITED

Laparoscopic surgery

M. Cuesta[1]. [1]*VU University Medical Center, Department of Surgery, Amsterdam, Netherlands*

Since the systematic introduction of Minimally Invasive Surgery (MIS) beginning 1990, questions continue to arise whether MIS for digestive cancers compares to conventional surgery in terms of efficacy and safety. Minimally invasive techniques to resect the oesophagus in patients with cancer were confirmed to be safe and comparable to an open approach with respect to postoperative recovery and cancer survival.
The only randomized study on this subject, the TIME trial, compared the thoracoscopic in prone position (and laparoscopy) versus the conventional transthoracic (and laparotomy) with intrathoracic or cervical anastomosis. In conclusion, this randomized trial comparing open oesophagectomy for cancer with minimally invasive oesophagectomy shows that MIO results in a lower incidence of pulmonary infections, a shorter hospital stay, and a better short-term quality of life without compromise of the quality of the resected specimen.
Hulscher et al. published the randomized study titled: Laparoscopic versus open subtotal gastrectomy for distal gastric cancer: five-year results of a randomized prospective trial.
They concluded that Laparoscopic radical subtotal gastrectomy for distal gastric cancer is a feasible and safe oncologic procedure and that its short- and long-term results are similar to those obtained with an open approach. Additional benefits for the LG were reduced blood loss, shorter time to resumption of oral intake, and earlier discharge from hospital.
The first published randomized study comparing laparoscopic versus open approach for segmental colon cancer was the “Barcelona trial” by Lacy et al., published in the Lancet in 2002. The astonishing result was that a stage III colon cancer showed a better survival rate in the laparoscopic group than in the open group. This finding positively triggered an increasing use of laparoscopic colon approach to colon cancer in daily surgery all over the world.
Since then, additional multicentric trials have been published, such as the CLASSIC study, the COST study, the COLOR I study, and the Transatlantic study.
The COLOR II trial, has been designed for determining the safety of minimally invasive surgery for patients with rectal cancer. Primary goal of the study was to observe if there were differences in local recurrence between the laparoscopic and open group at three years postoperatively. The interpretation of the results has been that in selected patients with rectal cancer treated by skilled surgeons, laparoscopic surgery resulted in similar safety, resection margins, and completeness of resection to that of open surgery, and recovery was improved after laparoscopic surgery.
No conflict of interest.

Special Session (Sat, 28 Sep, 14:15−15:15)
Treatment of Chronic Lymphocytic Leukaemia

47 INVITED

Genetics of chronic lymphocytic leukemia

P. Ghia[1]. [1]*Vita-Salute San Raffaele University, Milan, Italy*

The heterogeneous biological and clinical profile of Chronic Lymphocytic Leukemia (CLL) has long been appreciated but only over the last decades the genetic complexity hidden by its homogenous phenotype started being unraveled.
First hints derived from immunogenetic and cytogenetic studies in the 1990s, demonstrating that immunoglobulin heavy variable (IGHV) gene mutational status identifies two main subsets, with a clear prognostic implication, as mutated cases usually follow a favourable clinical course while the unmutated ones show a dismal outcome.
Along the same line, studies on genomic aberrations by fluorescence-in situ hybridization (FISH) were able to identify four most frequent alterations and led to a hierarchical model where patients with 13q deletion>normal karyotype>trisomy 12>11q deletion>17p deletion show a progressively worsening disease course. In terms of molecular pathogenesis, the favourable prognosis of patients bearing del13q has been recently linked to specific microRNAs (miR15a/16−1) loss. These two non-coding RNA molecules act as epigenetic negative regulators of several genes, including the pro-apoptotic protein BCL2. Interestingly, the 13q deletion was found in CLL-like monoclonal B-cell expansions (so-called MBL) even in clones with <1 cell/μl, suggesting a potential association of this lesion with the acquisition of a CLL-phenotype rather than with a true leukemic condition. On the other side the unfavourable clinical outcome of patients with 17p deletion is explained by the loss of TP53, a well-known tumour-suppressor gene.
Interestingly, recent next generation sequencing studies gave additional insights into the genetic landscape of CLL. Beside the previously known alterations of the TP53 gene, novel mutations involving different pathways (NOTCH1 or non-canonical NFkB signalling, the spliceosome machinery) were reported and showed to play a relevant role in chemoresistance and disease transformation. None of these mutations seem to explain early events in disease pathogenesis, being mostly related to advanced phases of the disease.
Future research efforts will be focussed on dissecting the genetic complexity of CLL in relationship with the microenvironmental interactions occurring in the disease. This will help to reach a better understanding of CLL pathogenesis and to the identification of univocal molecular signatures able to define progression risk and likely to guide a tailored treatment approach.
No conflict of interest.

48 INVITED

First-line treatment of chronic lymphocytic leukaemia

Abstract not received.

49 INVITED

Treatment of relapsed chronic lymphocytic leukaemia

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Chronic lymphocytic leukemia (CLL) is characterized by a highly variable clinical course. Among the biological features underlying this heterogeneity, genetic lesions and the mutational status of the immunoglobulin heavy chain variable genes (*IGHV*) are of importance. Therapeutic options in CLL have been considerably expanded during recent years. The combination of fludarabine, cyclophosphamide and rituximab (FCR) has become gold standard in the first-line treatment of physically fit patients. Bendamustine plus Rituximab (BR) is currently evaluated in comparison to FCR and chlorambucil is still of relevance for elderly patients with comorbidities. Alemtuzumab is an alternative for high-risk patients (refractory CLL, 17p deletion, *TP53* mutation). Allogeneic stem cell transplantation (allo-SCT) offers the only chance of cure but not without substantial mortality. Innovative approaches focus on individualized, targeted therapies. A number of novel agents are in clinical trials and show marked efficacy combined with good tolerability. This review provides an overview of the current therapeutic options and of promising novel approaches.
No conflict of interest.

Special Session (Sat, 28 Sep, 14:15−15:15) **Genetics and Epigenetics for Biomarker Development for Treatment Response**

50 INVITED

DNA methylation alterations: Promising biomarkers for diagnosis and treatment response in cancer

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Cancer is probably the best-studied disease with a strong epigenetic component. The recent advances in microarray- and sequencing-based technologies for the analysis of high-resolution genome-wide DNA methylation patterns have led to an exponential growth in the number of genes and genomic regions reported as being differentially methylated in specific cancers and has demonstrated a crucial role for epigenetic changes in cancer initiation, progression and treatment.
As a stable nucleic acid based modification with limited dynamic range that is technically easy to handle, DNA methylation is a promising biomarker for many applications. DNA methylation can be detected and quantified by a number of technologies including genome-wide screening methods as well as locus- or gene-specific high resolution analysis in different types of samples such as frozen tissues and FFPE samples, but also in body fluids such as urine, plasma, and serum obtained through non-invasive procedures. The knowledge of epigenetics in drug response is still in its infancy. However, the analysis of DNA methylation patterns for treatment response, also termed pharmacoepigenomics, is expected to identify novel biomarkers that can be useful for understanding response to chemotherapy as well as resistance to drugs before the beginning of the treatment. DNA methylation might help to predict the clinical phenotypes in individual patients and may be a proper biomarker to optimize individualized cancer treatment. In some cases, DNA methylation-based biomarkers have already proven to be more specific and sensitive than commonly used protein biomarkers, which could clearly justify their use in clinics. However, very few of them are at the moment used in clinics and even less commercial tests are currently available.
The objective of this presentation is to discuss the advantages of DNA methylation as a biomarker, the practical considerations for their development, and their use in disease detection, prediction of outcome or treatment response, through selected examples.
No conflict of interest.

51 INVITED

Early response biomarkers in cell-free DNA

Abstract not received.

52 INVITED

Genomic instability − relevance for progression and outcome in breast cancer

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Patterns of genomic aberrations have been defined that underlie specific expression subgroups of breast cancer (BC) that may infer paths of tumor progression and shed light on mechanisms involved. Classifications built on levels of genomic distortion have been shown to have prognostic value. We have developed two platform-independent algorithms to explore genomic architectural distortion using aCGH data to measure whole-arm gains and losses [whole arm aberration index (WAAI)] and complex rearrangements [complex arm aberration index (CAAI)]. By applying CAAI and WAAI to data from 595 BC patients, we were able to separate the cases into eight subgroups with different distributions of genomic distortion. Within each subgroup data from expression analyses, sequencing and ploidy indicated that progression occurs along separate paths into more complex genotypes. Histological grade had prognostic impact only in the luminal-related groups, whereas the complexity identified by CAAI had an overall independent prognostic power. The results emphasized the relation among structural genomic alterations, molecular subtype, and clinical behavior and showed that objective score of genomic complexity (CAAI) is an independent prognostic marker. We have recently validated the prognostic power of the CAAI index in a large series of breast cancers from the METABRIC cohort.
To investigate the significance of altered gene dosage on expression, both in-cis and in-trans, a stepwise gene selection method was developed, aiming to identify gene dosage that are strongly associated to expression and associated in-trans to specific biological processes. Several potentially new cancer genes were identified and their biological relevance supported by enrichment analysis of their in-trans correlated genes. These include known breast cancer driver genes (e.g. ATAD2), known oncogenes not yet associated with breast cancer (e.g SETDB1) and novel candidates (e.g. MTL5).
No conflict of interest.

Scientific Symposium (Sat, 28 Sep, 16:00−18:00) **Therapeutic Implications for New Targets in Lung Cancer**

53 INVITED

Immune-checkpoints (PD1, PDL1)

Abstract not received.

54 INVITED

PI3K-AKT-mTOR

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Due to successful therapeutic development (and partly to biomarker discovery), recent clinical developments in non small cell lung cancer (NSCLC) have mainly focus on EGFR targeted drugs and anti-angiogenic agents. The mammalian target of rapamycin (mTOR) is a protein kinase of the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway with a central role in the control of cell proliferation, survival, mobility, and angiogenesis. In more than 50% of lung carcinomas, AKT and mTOR are activated. In response to growth factor stimulation, PI3K is activated, leading to the recruitment of AKT to the plasma membrane where it is activated by phosphorylation. AKT phosphorylates many effectors including TSC (tuberous sclerosis complex)-1/2, leading to its inactivation. The inactivation of TSC2 leads to the activation of mTOR. Mutations in these components or in PTEN, a negative regulator of PI3K, may result in the upregulation of this pathway.
mTOR inhibitors are a class of signal transduction inhibitors with anti-cancer activity that were initially developed as immunosuppressive agents. Temsirolimus and everolimus are both approved in metastatic kidney cancer. Everolimus has been actively developed in NSCLC. It has limited efficacy as a single agent (10 mg/d). In a phase I/II, daily or weekly everolimus has been combined to 150 mg/d erlotinib and dose limiting toxicities were stomatitis, diarrhoea and skin rash. There was no improvement of overall survival compared to erlotinib alone. No predictive factor of mTor inhibitor efficacy has been reported so far. In particular, the efficacy of the mTOR inhibitor ridafolimus in the subgroup of *KRAS* mutated tumors has not been confirmed. Pan-PI3K inhibitors target the catalytic domain of the class IA PI3K p110 subunits, the class most widely implicated in cancer. Combination with second line or first line chemotherapy implies various Pi3K inhibitors such as BKM120, SAR245408 (XL147), PX-866, GDC-0941, and BAY-80–6946. BKM120 is been evaluated as a single agent in the subgroup of *PI3KCA* mutated (2−5%) or PTEN loss (24−44%) NSCLC. The catalytic domains of the p110 subunits and mTOR1/2 share a structural homology. Dual inhibitors are under investigation as BEZ235, SAR245409, GDC-0980, and GSK2126458. Finally, AKT inhibitors are being developed in early trials. mTOR, PI3K and ALK inhibitors share the same pattern of toxicities, including hyperglycemia, hypertriglyceridemia, hepatotoxicity, mucositis, and fatigue.
No conflict of interest.

55 INVITED

Ras-Raf-MEK Pathway

J. Schellens[1]. [1]*The Netherlands Cancer Institute, Medical Oncology, Amsterdam, Netherlands*

The Ras-Raf-MEK, i.e. the MAPK pathway is “hot” in the treatment of non-small cell lung cancer (NSCLC) and other solid tumors. KRAS mutations (KRASm) have been associated with NSCLC since many years and recently also mutations downstream of KRAS especially BRAF, albeit at low frequency, have been detected in NSCLC. Besides, NRAS mutations have been identified as well in NSCLC. About a decade ago attempts to block KRAS signalling by farnesyltransferase inhibitors turned out to be ineffective, confirming the wrong concept behind this approach. Recently novel inhibitors of KRAS signalling have been presented acting through impairment of the interaction between the prenyl-binding protein PDEδ and KRAS. Clinical studies testing MAPK inhibition downstream of KRASm at the level of MEK have shown promise. Combinations of a MEK inhibitor (MEKi; for example selumetinib) and docetaxel have been selected for pivotal studies. Furthermore, in clinical proof of principle studies the concepts of dual intrapathway and interpathway inhibition in the case

of KRASm is tested. Dual intrapathway inhibition of tyrosine receptor kinase activity (TKI) downstream of KRASm by combining BRAFi and MEKi was found to be active in preclinical models. Clinical validation is warranted. In view of crosstalk with other pathways dual interpathway inhibition by MEKi plus IGF1Ri is of interest as well. Epigenetic therapy by combining azacitidine at relatively low dose and entinostat, inhibitors of DNA methylation and histone deacetylation, was found to be active in phase I/II studies, however activity in patients with mutations in the MAPK pathway needs to be established. These novel concepts hold promise for patients with NSCLC and well established biomarker profile of the tumor.
No conflict of interest.

56 INVITED

ALK and HSP90

Abstract not received.

Scientific Symposium (Sat, 28 Sep, 16:00−18:00) **Castration Resistant Prostate Cancer Targeting Cancer Cells, Microenvironment and Stem Cells**

57 INVITED

Targeting stem cells in castration-resistant prostate cancer

N. Maitland[1]. [1]*University of York, Department of BiologyYCR Cancer Research Unit, York, United Kingdom*

Fatal, therapy-resistant cancers like castration-resistant prostate cancer (CRPC) arise from an adaptive process, by which a cell develops the intracellular signalling mechanism(s) to resist or even thrive in the new environment induced by the therapeutic agent. Most cells, and stem cells in particular, are programmed with salvage pathways to preserve integrity in the face of mutagenic insults. The cancer stem cell (CSC) hypothesis states that the resistant tumours arise from a therapy resistant stem cell, rather than by adaptive mutation of a mature cancer cell. The CSCs are now proven to have a quiescent and undifferentiated phenotype, closely related to that of the normal stem cell. Stem cell quiescence is maintained until a tissue is damaged, when it participates in the repair process. In a cancer this corresponds to therapy-induced cytotoxicity. The success of therapy resistance is therefore measured by the restoration of tumour bulk, but the true 'founder changes' which permit the tumour to establish at metastatic sites and resist elimination of aberrantly proliferating cells, should also be present in the CSCs.
I will present evidence that the bulk of tumour cells in prostate cancers i.e. the tumour component against which current therapies are directed, have no or minimal tumour inducing properties, and that lower Gleason grades (<7) of prostate cancer are unable to initiate tumour growth in an improved xenograft model of invasive prostate cancer. Furthermore, the identification of changes in the expression of cancer-specific, cell surface genes in primary cell cultures enriched for CSCs, has provided new therapeutic targets. When expression of these genes is eliminated by SiRNA treatment, the greatest effect on colony formation is seen in the castration resistant cancer cell line PC3, compared to benign and non-malignant cell lines. The SiRNA knockdowns had fewer effects on cell growth: the usual paradigm for an anti-cancer agent. When used *in vivo*, prior inhibition of cancer-specific gene expression in the CSCs, from both cancer cell lines and near-patient human xenografts, eliminated cancer induction, even after inoculation of up to 10^6 viable cells. The *in vivo* model corresponds most closely to the initiation of metastasis, the fatal lesion in CRPC.
We also find that application of such agents has only minimal effects on established xenograft tumour growth in vivo, in agreement with the absence of the treatment targets in the bulk tumour cells, but preliminary data suggests that secondary tumour growth, upon re-transplantation, is severely impaired. The challenge in applying such therapies for clinical trials will be to achieve discrete endpoints. We propose that CSC cytotoxic treatments should be combined with traditional therapies to achieve the desired clinical efficacy. Alternatively, based on the outcome of experimental treatments which indicate that many agents achieve a loss of clonogenicity by differentiating the CSCs rather than killing them, that such agents (some of which have already been approved for clinical use) should be used to modify the fate of the SC into mature differentiated tumour cells. The general applicability of CSC therapies in CRPC could nevertheless be confounded by the presence of oligoclonal disease in which the resistant CSC has solved the problem of resistance by perturbation of multiple different signalling pathways. Furthermore, our strategy of identifying cancer-specific changes in CSCs, which are essential for CSC maintenance, has real advantages over inhibition of signalling associated with 'stemness' as a therapeutic strategy, which could have unwanted effects in other stem cell compartments.
No conflict of interest.

58 INVITED

Targeting immunosystem

W. Gerritsen[1]. [1]*Radboud University Nijmegen Medical Centre, Department of Medical Oncology, Nijmegen, Netherlands*

Sipuleucel-T (dendritic cells loaded with prostate acid phosphatase/GM-CSF) was the first immunotherapy product, which was registered for CRPC and even for all solid tumors. Sipuleucel-T guided us that progression free survival (PFS) and PSA responses were not reliable end points for immunotherapy trials. Overall survival is the only significant endpoint of clinical trials. Toxicity is very mild. Sub analyses have indicated that this product prolonged survival especially in elderly men. Functional T-cell studies have not yet revealed immunomarkers predictive for survival or prognosis.
Prostvac (vaccinia/fowl pox virus transduced with PSA gene) did not induce significant responses or PFS, but a remarkable survival advantage of 9 months over placebo in a phase II study. Toxicity is mild. In a small study patients with a T-cell response against PSA had a superior survival compared to those who did show any T-cell response. Encouraging phase II studies have indicated that Prostvac works well in combination with other agents, such as the radio-isotope samarium. A large phase III trial is accruing patients.
Ipilimumab (monoclonal antibody against the checkpoint CTLA-4) have shown anti-tumor activity in CRPC in several phase II studies with some long lasting survival. Toxicity is mild in most patients. Two phase III studies (one in chemo-naive patients and one in patients pretreated with docetaxel) have finished accrual. The results of the phase III study combining irradiation of metastases and Ipilimumab will be presented at this meeting.
Targeting the immune system, we should learn from all the immunotherapy trials; which patient to treat with immunotherapy (low versus high tumor burden, low versus high Gleason score), when can you expect a clinical response, and what is the influence of subsequent treatments on the outcome of an immunotherapy trial.
Inducing an immune response is a first step in immunotherapy. Both Sipuleucel-T and Prostvac are designed for this critical first step. However, the next step is more crucial; elimination of tumor cells within the microenvironment. At present, we learn more and more about immunosuppressive cells, like the myeloid derived suppressor cells and T-regs, and immunosuppressive cytokines which play an essential role at the effector phase of immunotherapy. Drugs, such as Ipilimumab, play an important role to change the microenvironment within a tumor, but also chemotherapy and other agents could be applied to boost the effector phase of immunotherapy.
Conflict of interest: *Advisory board: Amgen, BMS, Sanofi, Astellas, Johnson & Johnson, BNIT*

59 INVITED

Targeting bone microenvironment

F. Saad[1]. [1]*CHUM − Notre-Dame Hospital, Montreal Quebec, Canada*

Bone metastases will occur in over 90% of men with lethal castration-resistant prostate cancer (CRPC). Due to the combined effect of bone fragility due to ADT and the presence of bone metastases almost all patients will experience some form of morbidity related to bone metastases prior to succumbing from the disease. Complications include severe pain, pathologic fracture, the need for palliative radiation or surgery and spinal cord compression. These events impair quality of life and place a significant burden on health-care resources.
Zoledronic acid is the only bisphosphonate that has shown a protective effect against skeletal-related events (SRE) in patients with metastatic castration-resistant prostate cancer. The phase 3 study showed a 48% reduction in the mean annual incidence of SRE ($P = 0.005$), 5 months prolongation in the median time to first SRE ($P = 0.009$) and 36% reduction in the ongoing risk of SRE's at 24 months. **Denosumab** is a fully human monoclonal antibody that specifically targets RANKL thus effectively inhibiting osteoclastic function and bone resorption, In the setting of metastatic CRPC, denosumab (120 mg SC every 4 weeks) compared to zoledronic acid (4 mg IV every 4 weeks) significantly improved the time to first SRE (20.7 vs 17.1 months; $P<0.001$ for non-inferiority; $P = 0.008$ for superiority). Overall survival and progression free survival were similar for both drugs. Hypocalcemia was more common with denosumab (13%) than with zoledronic acid (6%) ($P<0.0001$) and a non-significant trend toward higher osteonecrosis of the jaw was seen with denosumab (2.3% vs 1.3%; $P = 0.09$) (12).
In a placebo controlled trial in non metastatic CRPC, denosumab significantly increased the bone-metastasis-free survival in patients with non-metastatic CRPC by a median of 4.2 months (29.5 vs 25.2 months; HR, 0.85; 95% CI, 0.73–0.98; $P = 0.028$) [18]. Although hypocalcemia was much lower in the setting of non-metastatic CRPC the risk of ONJ was higher given the longer exposure time to denosumab.

A recently completed phase III study of patients with metastatic CRPC were randomized on a 2:1 basis to either **radium-223** (an alpha emitting bone seeker) or placebo. To be eligible for the study patients had to have bone metastases and have progressed after chemotherapy or were not eligible to receive chemotherapy. Patients received 6 cycles of either radium 223 or placebo every 4 weeks. Median survival was 14 months for the treated patients as opposed to 11.2 months for those who received a placebo, conferring an approximate 30% improvement in OS (HR 0.699, p 0.0022). The study also showed a 5 month delay in time to skeletal related events. This agent has recently been approved by the FDA and is the first bone targeted agent to demonstrate a survival advantage.
Conflict of interest: *Advisory board: Novartis, Amgen, Bayer. Corporate-sponsored research: Amgen, Bayer*

60 INVITED
Cancer cells in general and specific pathways

J. De Bono[1]. [1]*The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Drug Development Unit & Institute of Cancer ResearchSection of Medicine Sycamore House, Sutton, United Kingdom*

Prostate cancer is the commonest cancer in men in the Western world and remains the second commonest killer from cancer. Increasing evidence is mounting that this disease is at least in part generated by double strand DNA breaks induced by androgen driven transcription involving topoisomerase 2 beta. This leads to the common occurrence of hormone driven rearrangements, involving androgen response elements driving potent oncogenes including ETS genes, RAS and RAF. The loss of key tumour suppressors activating the PI3K/AKT pathway is also implicated as being critical to prostate carcinogenesis. Whole genome sequencing efforts have identified multiple aberrations involving AR and its co-regulators, its pioneer factor FOXOA1 as well as other genes including SPOP and MED12, DNA repair genes and other genes. These studies are fuelling hope for an improved understanding of prostate cancer disease biology and castration resistance, with an increasing volume of functional data elucidating the mechanisms of castration resistance. This presentation will focus of the recent advances in therapeutics including abiraterone, cabazitaxel, enzalutamide, radium 223 and sipuleucel T as well as how our improved understanding of prostate cancer disease biology can impact therapeutic advances for this disease.
No conflict of interest.

Scientific Symposium (Sat, 28 Sep, 16:00−18:00)
New Classification of Melanoma and its Consequences for Treatment

61 INVITED
New developments in the inherited molecular epidemiologic field

J. Newton Bishop[1]. [1]*University of Leeds, Leeds, United Kingdom*

Cutaneous melanoma is strongly genetically determined as the majority of cases occur in pale skinned peoples. Within these pale skinned populations, furthermore, inherited phenotypes are strong predictors of risk (skin which tends to burn in the sun and large numbers of melanocytic nevi. Progress in the identification of common but relatively low risk susceptibility genes using genome wide association studies (GWAS) has been rapid in recent years: 16 single nucleotide polymorphisms (SNPs) associated with risk are described and some of these are (predictably) associated with skin type (*MC1R, Tyr, Agouti, SLC45A2 and IRF4*). Others are associated with nevus number (*PLA2G6*, a SNP on chromosome 9 and *TERT*). Some are in or near to genes which are as yet of unknown function with respect to melanoma evolution, such as in the *FTO* gene (normally associated with obesity) and efforts are currently being expended to understand their role because of what more this will tell is about melanomagenesis.
Intermediate to high penetrance susceptibility genes have also recently become better understood. Inherited mutations in the *CDKN2A* gene (which codes for two proteins p16 and p14ARF) were first identified many years ago and it has taken some time to identify additional genes. *CDK4* mutations (at the p16 binding site) have been identified in 17 families worldwide, and more recently an intermediate penetrance variant in *MITF* was described by two groups simultaneously. Most recently of all a rare familial promoter mutation in the *TERT* gene coding for telomerase reverse transcriptase was described in a large family with 14 melanoma cases.
A number of these gene associations support the model developed by Dot Bennett and others, in which the control of cell growth in cells of the melanocyte lineage was postulated to be dependent upon tumor suppressor proteins such as p16 (leading to senescence) and that growth inhibition could be overcome by telomerase: highlighting the particular role of p16 and the telomere in melanoma carcinogenesis.
Conflict of interest: *Advisory board: I have in the past served on advisory boards for ROCHE re skin toxicity of BRAF inhibitors*

62 INVITED
Clinical consequences of sequencing (TBC)

Abstract not received.

63 INVITED
Towards an integrated taxonomy of melanocytic neoplasia

B. Bastian[1]. [1]*UCSF Comprehensive Cancer Centre, San Francisco, USA*

Melanomas are comprised of multiple biologically distinct categories, which differ in cell of origin, age of onset, clinical and histologic presentation, pattern of metastasis, ethnic distribution, causative role of UV radiation, predisposing germ line alterations, mutational processes, and patterns of somatic mutations. Neoplasms are initiated by gain of function mutations in one of several primary oncogenes, typically leading to benign melanocytic nevi with characteristic histologic features. The progression of nevi is restrained by multiple tumor suppressive mechanisms. Secondary genetic alterations override these barriers and promote intermediate or overtly malignant tumors along distinct progression trajectories. Some types of melanomas arise without a recognizable benign stage. The current knowledge about pathogenesis, clinical, histological and genetic features of primary melanocytic neoplasms is reviewed and integrated into a taxonomic framework.
No conflict of interest.

64 INVITED
BRAF and RAS signalling in melanoma: From basic biology to clinical exploitation

R. Marais[1]. [1]*Paterson Institute for Cancer Research, Manchester, United Kingdom*

The BRAF protein controls cell growth, differentiation and survival. The *BRAF* gene is mutated in ~45% of melanomas, and its upstream activator, the small G-protein NRAS is mutated in a further ~20% of cases. Drugs that inhibit BRAF can achieve impressive clinical responses in BRAF mutant melanoma patients. However, general these responses are short lived and most patients develop resistance after a short period of disease control. Thus, improved knowledge of melanoma biology is essential to underpin the development of personalised/precision treatments for melanoma patients. We have found that in some patients resistance to BRAF drugs is mediated by increased EGF receptor (EGFR) signalling and that BRAF and EGFR drugs cooperate to suppress the growth of resistant tumours. Thus, a combination of BRAF and EGFR drugs may suppress the emergence of resistance in some patients.
We are also developing mouse models of melanoma to study the role of BRAF and NRAS in melanomagenesis. Oncogenic BRAF induces melanoma when expressed in adult mice, but not when expressed in embryonic mice. However, our data also shows that although BRAF can be an initiating event in melanomagenesis, it is not sufficient and other cooperating events are required. Notably, oncogenic NRAS does not induce melanoma when expressed adult mice, but does induce melanoma of the brain that resembles leptomeningeal melanocytosis in children. Thus, the different populations of melanocytes appear to display distinct susceptibility to transformation by the individual oncogenes from this pathway.
Conflict of interest: *Other substantive relationships: Unpaid consultant for GSK, Novartis and Servier. Participant in Roche sponsored speaker's bureau.*

Scientific Symposium (Sat, 28 Sep, 16:00−18:00)
Cancer Pain Management Barriers: Can We Overcome Them?

65 INVITED
Patient-related barriers

S. Gunnarsdottir[1]. [1]*Landspitali University Hospital, Research and Development, Reykjavik, Iceland*

Pain management remains a challenge in patients with cancer. The reasons are numerous, among them attitudinal barriers that have been found to negatively affect the quality of pain management and in turn quality of life. These attitudinal barriers include fatalistic beliefs about cancer pain,

fear of addiction, concerns about tolerance and side effects, concerns that strong pain medication mask changes in one's body, and harm the immune system, the belief that 'good patients' do not complain about pain, and that reports of pain may distract physicians from treating the underlying disease. Such barriers are prevalent among patients, family members, the general public and health care professionals including physicians and nurses. Prior research suggests that patients' who have attitudinal barriers to cancer pain management use less potent analgesics than those who do not have such barriers. In turn these patients have more pain, experience more pain related interference with life activities and more impairment in QOL. Numerous interventions have been tested to overcome patient related barriers, some of which have shown promising results. The focus of this presentation will be on interventions aimed at patients to overcome patient related barriers to cancer pain management.
No conflict of interest.

66 INVITED
Nurse-related barriers

Abstract not received.

67 INVITED
Nursing interventions

S. Piskorjanac[1]. [1]*University Hospital Osijek, Department of Radiotherapy and Oncology, Osijek, Croatia*

As a nursing diagnosis pain is defined as: "The state in which an individual experiences and reports the presence of severe discomfort or an uncomfortable sensation." The most frequently cited definition of pain is from pain management pioneer Margaret McCaffery, RN: "Whatever the experiencing person says it is, existing whenever he says it does."
Sadly, pain is all too often undertreated. The WHO describes cancer pain as "commonly undertreated and frequently neglected as health care problem". The reasons for this are multifactoral; poor identification of just how much pain the patient is experiencing, reluctance on the part of the sufferer to admit to pain and, most frequently, a poor understanding of analgesics.
The nurse is in a prime position to allay the patient's fears, to educate him and to ensure that effective pain control is integrated into the complete programme of healthcare provided for the patient. In particular, when nursing patients for whom the prospect of cure is remote or non-existent, putting pain control at the forefront of palliative care is crucial. Nurses have more constant contact with patients than other healthcare professionals and this places them in a unique position to assess patient's needs for pain control and to monitor the success of interventions in bringing pain relief. They need to understand the physiology of pain, the pharmacology of analgesic drugs, the nursing management of pain and complementary (or alternative) techniques which are available for pain control. Nurses need to be familiar with scales for measuring pain and be aware of other factors that are important in assessing patient distress. The nurse will need to explain treatment and strategies to patients and their families and be able to make informed contributions to discussions of patient care with other members of the healthcare team.
Despite these considerations, pain control is given low priority in nursing training.
No conflict of interest.

68 INVITED
Barriers in patients and their family caregivers

Abstract not received.

Scientific Symposium (Sat, 28 Sep, 16:00−18:00)
Novel Targets in Radiation Oncology

69 INVITED
In vitro and In vivo discovery of novel therapeutic targets using functional genomics

B. Wouters[1]. [1]*Ontario Cancer Institute, Toronto Ontario, Canada*

Radiotherapy is used as a curative treatment in many types of cancer with tumour control rates that vary significantly by disease type and tumour stage. Several known biological factors adversely influence treatment efficacy in a patient specific manner, including DNA repair mechanisms, tumour cell proliferation, and tumour hypoxia. These biological phenotypes have served as the basis for development of alternative therapeutic approaches incorporating alternative treatment schedules and/or addition of chemotherapy or molecularly targeted agents. However, it is clear that each of these biological mediators of tumour radioresistance is influenced by a large number of underlying genes and cell signaling pathways, many of which are altered during carcinogenesis. Thus, there is a need for development of investigational approaches that are able to interrogate the potential of targeting individual genes and pathways to improve radiation sensitivity in a high throughput manner. To do so, we have initiated a series of functional genomic screens to identify genes that play essential roles in promoting cellular resistance to hypoxia and cellular radiosensitivity. Our approach utilizes lentiviral delivered shRNA libraries ranging in size from 200–80,000 unique shRNAs. Highly complex shRNA pools targeting ~16,000 human genes have been used to discover a series of novel genes and pathways that confer sensitivity to hypoxia and to radiation treatment in vitro. In addition, smaller focused pools targeting receptor tyrosine kinases, or the entire human kinome have been interrogated both under in vitro conditions as well as in xenografts growing in vivo. Our results reveal a number of novel targets that function in a contextual synethetic lethal manner to increase tumour radiosensitivity and which are thus potential new targets for combination therapy.
No conflict of interest.

70 INVITED
Modifying checkpoint signaling for radiosensitization

Abstract not received.

71 INVITED
Reprogramming metabolism with metformin improves tumor oxygenation and radiation response

M. Koritzinsky[1]. [1]*University Health Network, Princess Margaret Cancer Center, Toronto, Canada*

Background: Tumor hypoxia contributes to poor outcome in patients treated with radiotherapy due in part to the high radiation resistance of hypoxic cells. Oxygen gradients form around perfused vessels due to oxygen consumption, and at distances of 100–150 μm reach levels low enough to cause profound resistance to radiation. Inhibition of oxygen consumption therefore represents a potential strategy to increase the diffusion distance of oxygen in tumor tissue, reduce tumor hypoxia and increase radiation response. Metformin is a commonly prescribed anti-diabetic drug that reduces cellular oxygen consumption by inhibiting complex I in the mitochondrial electron transport chain. We therefore hypothesized that metformin can reduce therapeutically relevant hypoxia in tumors.
Materials and Methods: Oxygen consumption rates were measured in a panel of cancer cell lines exposed to various concentrations of metformin. We investigated whether an acute dose of metformin could reduce levels of hypoxia in established colon cancer xenografts in vivo. To that end, we used a double labelling approach with the hypoxia markers pimonidazole and EF5 detected by immunohistochemistry (IHC) and flow cytometry. We also measured tumor hypoxia by non-invasive 18F-FAZA-PET imaging in the same tumor models. Finally, we administered metformin immediately prior to a subcurative irradiation dose of 15 Gy and measured tumor growth delay and ex vivo clonogenic survival.
Results: We observed a dose- and time-dependent reduction in oxygen consumption in response to metformin, with some sensitive cell lines responding acutely to concentrations that are similar to the steady-state plasma levels in diabetic patients. Metformin administration resulted in rapid tumor reoxygenation in two colon cancer xenograft models as measured by IHC, flow cytometry or 18F-FAZA-PET. Furthermore, metformin substantially potentiated radiation-induced tumor growth delay, consistent with less hypoxic, more radiosensitive tumors. Data from in vitro and ex vivo clonogenic assays confirmed that metformin increases radiation response of tumors by decreasing the fraction of radiation resistant hypoxic cells.
Conclusion: Metformin inhibits oxygen consumption, reduces tumor hypoxia and consequently increases tumor radiation response. These data suggest that a commonly prescribed, affordable and safe drug, metformin, can be repurposed as a cancer therapeutic in order to improve outcomes after radiotherapy.
No conflict of interest.

72 INVITED
Focal adhesion as important determinant of radiation survival

N. Cordes[1]. [1]*Oncoray, Medical Faculty Carl Gustav Carus, Dresden, Germany*

Background: A plethora of intra- and extracellular factors coact for therapy resistance of malignant tumors. Major points of intersection of prosurvival signaling are focal adhesions. Located at the cell membrane and composed

of cell adhesion molecules, growth factor receptors, protein kinases and adapter proteins, these structures act as most upstream and powerful sources of promitogenic biochemical cues, on the one hand, and, on the other hand, serve as easily druggable and frequently overexpressed cancer targets. In this overview, the latest findings about focal adhesion function in cancer, how potent preclinical approaches are and what we have learnt about recent clinical failure of inhibition of integrin cell adhesion receptors (e.g. Cilengitide) will be discussed.
Conclusions: Focal adhesion proteins, especially integrins and growth factor receptors, co-regulate cancer progression and therapy resistance. Combined therapeutic targeting of these cell surface receptors simultaneously with conventional radio- and chemotherapy might substantially improve cancer cure rates.
No conflict of interest.

Society Session (Sat, 28 Sep, 16:00−18:00)
European Organisation for Research and Treatment of Cancer (EORTC) − Multidisciplinary Cancer Clinical Research: What are we up to in 2013?

73 INVITED
An analysis of the clinical cancer research landscape in 2013

Abstract not received.

74 INVITED
Challenges and opportunities to develop novel drugs on the backbone of radiotherapy

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Radiotherapy is one of the most effective modality to cure cancer at a loco-regional stage, and its use as a primary modality or in the post-operative setting has been recognized in a variety of tumor types. Furthermore, with the introduction of modern way of delivering dose such as Intensity Modulated Radiation Therapy (IMRT), radiotherapy has proven to be not only effective, but also much less toxic than in the past. However, despite these improvements it is estimated that on average around 20% of patients may ultimately die of a lack of loco-regional tumor control, and in this setting, there is a growing appreciation of the potential value of combining novel targeted drugs with radiotherapy. Such approaches have the potential to further improve loco-regional disease control and cure rates across a diverse range of tumor types.
Combining radiation with novel drugs requires the appreciation of how these agents could potentially affect key cellular pathways involved in response to ionizing radiation, and then, how they should be properly combined with radiotherapy to maximize tumor interaction and minimize normal tissue toxicity. Such objective requires the development of research programs starting from pre-clinical proof of concept studies, moving quickly to clinical phase I−II trials, and ending with validation phases-III studies. However, such studies will have to be launched early on in the development phase of a new agent, and embark comprehensive translational biological and imaging surrogates of efficacy and/or toxicity aiming at individualizing those patients that are the most likely to benefit from the new concept, and thus on whom dedicated validation studies will have to be conducted.
In conclusion, despite the challenges, radiation therapy combinations with novel drugs present a significant opportunity to further improve cancer cure. In this framework, as an international infrastructure combining high methodological and quality assurance standards, together with a network of dedicated investigators, EORTC is an ideal platform to conduct such research programs in a new collaborative model with the pharma sector.
No conflict of interest.

75 INVITED
Challenges and opportunities for surgical trials, the role of quality assurance

M. Den Dulk[1], G.J. Poston[1], C.J.H. Van de Velde[2]. [1]*Aintree University Hospital, Surgery, Liverpool, United Kingdom;* [2]*Leiden University Medical Center, Surgery, Leiden, Netherlands*

For almost all solid organ cancers, randomised trials have been performed to study different treatment strategies. For these tumours, surgery is the most important variable for recurrence and survival. For example in rectal cancer 5 year overall survival was 48% without preoperative radiotherapy before the introduction of TME surgery, but increased to 64% with TME surgery if no preoperative treatment was given. This large improvement of survival was mainly attributed to a change in surgical technique.
The effect of surgery on recurrence and survival for solid organ tumours has been neglected in many earlier trials aiming to evaluate the efficacy of systemic treatment and radiotherapy. In a trial for e.g. breast cancer preoperative radiotherapy has been shown to decrease locoregional recurrence from 32 to 9% for high risk women treated with mastectomy and adjuvant chemotherapy. However, the high local recurrence rates question surgical quality. Besides, a treatment effect of a (neo)adjuvant treatment found in patients with inadequate surgical treatment should be doubted. In rectal cancer e.g. the effect of preoperative radiotherapy became stronger as the distance from the anal verge increased. However, when patients with a positive circumferential resection margin were excluded, the relation between distance from the anal verge and the effect of radiotherapy disappeared. Quality assurance is therefore both a challenge and a necessity to account for the surgical variance and should be a condition for all future surgical trials.
Trials have an educational effect. Some of the effects of trials are seen on a national level. However, only the minority of our patients are treated within a trial. To structurally gain insight in (inter)national cancer care an audit is necessary. An audit should be seen as a quality instrument and feedback should be given to individual hospitals and surgeons (or oncologists). Currently European audits are initiated by the ESSO for colorectal cancer, breast cancer, upper GI cancer, and HPB cancer with information related to treatment and including radiology and histopathology results aiming for transparency throughout Europe for both surgical and multidisciplinary outcomes. Quality assurance remains a challenge, but generates even more opportunities to optimise the care for all our future patients.
No conflict of interest.

76 INVITED
Clinically meaningful end-points: Long term survival end-points versus early time to event based end-points

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The European Medicines Agency (EMA) has recently revised its Guideline on the evaluation of anticancer medicinal products in man (Revision 4, 2012), including guidance on choice of endpoints for confirmatory studies and methodological considerations on progression-free survival (PFS).
Generally, confirmatory (phase III) clinical efficacy trials should demonstrate that the experimental agent provides clinical benefit. In oncology, from a clinical and methodological perspective, the most persuasive outcome of a trial is the demonstration of a favourable effect on overall survival (OS), supported by secondary efficacy endpoints. Prolonged PFS or disease-free survival (DFS) is also considered to be of clinical benefit, particularly if the effect is large. The choice of primary endpoint between OS and PFS should include considerations about the relative toxicity of the experimental therapy, expected survival after progression, and availability of next-line therapies.
When comparing treatments in terms of PFS it is important to consider that treatment with an experimental agent, even if advantageous in terms of PFS, may however be associated with poorer OS (for instance, due to long term-toxicity or increased drug resistance). Thus, whenever possible, when PFS is the primary endpoint, adequate follow-up should be available for OS to provide sufficient reassurance that there is no detrimental effect. One-way cross-over to the experimental arm after progression is likely to hamper any subsequent comparisons in terms of OS and other long-term secondary endpoints. If this type of cross-over is considered unavoidable, the timing should be carefully chosen to ensure that sufficient data are available for OS and any other important secondary endpoints to meet the objectives of the trial. Similar considerations apply to timing of interim PFS analyses designed to stop the trial early for efficacy.
Where mature OS data cannot reasonably be available at the time of the primary PFS analysis, it is important to at least exclude a detrimental effect on next-line therapy (PFS2, time from randomisation to second objective disease progression, or death from any cause) or, if PFS2 is not available, end-of-next-line-treatment (time from randomisation to end or discontinuation of next-line treatment, second objective disease progression, or death from any cause). However, there is limited regulatory experience with these approaches and EMA scientific advice is recommended.
No conflict of interest.

Scientific Symposium (Sat, 28 Sep, 16:00–18:00)
Dissecting Total Therapy for Multiple Myeloma

77 INVITED

First-line treatment in elderly patients

V. Montefusco[1]. [1]*Istituto Nazionale Tumori, Department of Medical Oncology, Milan, Italy*

Currently, elderly multiple myeloma (MM) patients have several treatment options, that derive from the historical regimen of oral melphalan and prednisone (MP) in combination with a new drug, namely: thalidomide (MPT), bortezomib (MPV), and lenalidomide (MPR). In all cases the new regimens have shown a statistically significant superiority respect to MP in phase III trials. The first combination to be described was MPT (Palumbo et al. Lancet 2006). Since then, several versions of this regimen have been reported. The most effective MPT was described in the IFM 99–06 trial. In this study patients received 12 courses of therapy without maintenance. MP median time of progression-free survival (PFS) was 18 months, compared to 27 months for MPT. Similarly, MP median time of overall survival (OS) was 33 months, compared to 52 months for MPT. Outcome after retreatment was not different in either groups, suggesting a low risk of induction of chemoresistance. The second combination to be tested was MPV in the VISTA trial. Patients were randomized to receive 9 courses of either MP or MPV. The first 4 MPV cycles were delivered with an intensified dose of bortezomib. Median time to progression was 17 months in the MP, and 24 months in the MPV group. Three-year OS was 54% in the MP, and 68% in the MPV group. The rate of serious adverse events was higher in the MPV group (46% vs. 36%), in particular 14% of bortezomib-treated patients developed grade 3–4 peripheral neuropathy. Interestingly, MPV was superior also in patients older than 75 years, in ISS III patients, and in case of renal failure. MPV did not increase the risk of second malignancies. The most recent combination is MPR. In the MM-015 trial MP was compared to MPR, and to MPR with lenalidomide maintenance (MPR-R). After 9 cycles the outcome was quite similar, however, with a median follow-up of 30 months, patients who received lenalidomide maintenance had a significant advantage. PFS was 13 months for MP, 14 months for MPR, and 31 months for MPR-R. However, to now, this PFS differences did not translate into an OS advantage. Clinical benefits of MPR-R were limited to patients 65 to 75 years of age. On the other side, toxicity was more pronounced for MPR and MPR-R, and 3-year rate of second primary malignancies was 3% with MP, 7% with MPR, and 7% with MPR-R. In conclusion, elderly patients have now several treatment options, with the real chance of transforming MM into a chronic disease.
No conflict of interest.

78 INVITED

First-line treatment in young patients

J. San Miguel[1]. [1]*Hospital Universitario de Salamanca. IBSAL IBMCC (USAL-CSIC), Servicio de Hematologia, Salamanca, Spain*

Current treatment of newly diagnosed transplant candidate patients usually includes 3–6 cycles of induction therapy, consolidation with ASCT and the possibility of maintenance therapy.
1. Induction: Triple drug combinations based on Thalidomide (T) (TAD or TCD) induces 80% responses although the CR usually is <15%; by contrast the TD combination is suboptimal. Regarding Lenalidomide (Len), in combination with dex the majority of patients (>85%) respond, but probably a minimum of 4–6 cycles would be required to achieve >10% CRs. With Bortezomib (Bz) based regimens, particularly triplets such as BzAD, BzCD or even better BzTD or BzLenD the RR is around 90% with up to 30%CR. Moreover, several randomized trials have shown that triplets based on bortezomib (BzAD, BzTD) are not only superior to VAD in terms of response rate but does also induce longer progression free survival (PFS). Thalidomide or bortezomib combinations did not affect stem cell collection, while for lenalidomide it is recommended to harvest stem cells after no more than 3–4 cycles.
2. Autologous Stem Cell Transplant: Several randomized trials have shown that high dose therapy after induction with novel agents results in an upgrade of the CR rate and prolonged PFS suggesting that induction with novel agents and ASCT are complementary rather than alternative treatment approaches. Nevertheless randomized trials comparing early versus late transplant are underway. Regarding tandem ASCT, its use has significantly decreased in favour of consolidation or maintenance therapies, however in two large trials based either on BzTD or BzAD induction, the use of tandem transplant appears to be of benefit for patients with high-risk cytogenetics.
3. Consolidation and Maintenance: The use of 2–3 cycles of consolidation therapy (BzTD or BzLenD) after ASCT is associated with further improvement in depth of responses, including molecular responses. As far as maintenance is concerned, interferon +/− corticosteroids have shown a prolongation in PFS and OS of approximately 6 months, but due to the poor tolerability have been abandoned in most centers. Six randomized trials based on T or TD have shown a significant prolongation in PFS, but in only 3 of them this translated into an OS prolongation. Moreover the benefit was modest (approximately 6 months) and this together with the toxicity and possibility of inducing more resistant relapses is an important concern. Two randomized trials have reported a highly significant benefit for lenalidomide maintenance in terms of PFS (42 vs 24 months in the placebo arm) but only in one there is so far benefit in OS. The initial concern about a higher incidence of second primary malignancies has decreased with longer follow-up, but close follow-up is still needed, and although maintenance therapy cannot be recommended yet as an standard of care, it is becoming an attractive possibility.
4. Allogeneic Transplant: Six randomized trials have compared the use upfront of double ASCT versus single ASCT followed by allo-RIC; only in two of them the allo approach was superior in terms of PFS and OS. Moreover, unfortunately, a high proportion of patients develop extramedullary relapses without bone marrow involvement indicating that, although the disease may be under control in the bone marrow milieu, extramedullary spread may occur. These transplants should be performed by experienced groups and within clinical trials.
Conflict of interest: *Advisory board: Millennium, Celgene, Novartis, Onyx, Janssen*

79 INVITED

Defining and maintaining response

Abstract not received.

80 INVITED

New drugs

M. Dimopoulos[1]. [1]*Medical School Athens University, Department of Clinical Therpeutics, Athens, Greece*

Patients with multiple myeloma (MM) who have received “novel” agents (thalidomide-, lenalidomide- and/or bortezomib-based regimens) and their disease has relapsed or has become refractory to these treatments present a particular challenge. These patients can be treated with the novel proteasome inhibitor, carfilzomib or with the novel immunomodulatory drug (IMiD), pomalidomide or they can be encouraged to participate in clinical trials of novel experimental agents.
Carfilzomib has been approved by FDA in July 2012 based on the results of a phase IIb trial. This study included 266 MM patients who had been exposed to both bortezomib and an IMiD and who were relapsed and refractory to their most recent line of therapy. Carfilzomib was administered on days 1, 2, 8, 9, 15, and 16 of 28-day cycles (20 mg/m^2 in cycle 1; 27 mg/m^2 in cycles 2–12). The response rate was 23.7%. The median time-to-response was <2 months and the response duration was 7.8 months. The median TTP was 3.9 months, and the OS was 15.6 months. Carfilzomib showed very low rates of peripheral neuropathy.
Pomalidomide was approved by FDA In February 2013 for the same MM population based on the results of a phase III study in relapsed or relapsed and refractory MM patients who had failed to both bortezomib- and lenalidomide-based regimens and were refractory to last tretment: 302 received pomalidomide at a dose of 4 mg/day for 21 days in a 28-day cycle with low dose dexamethasone and 153 patients received high dose dexamethasone. The objective response rate was 21% in Pom/Dex arm vs. 3% in high-dose Dex. Median PFS and OS were 4.0 and 12.7 months, respectively for Pom+Dex vs. 1.9 ($p < 0.001$) and 8.1 months ($p = 0.028$), respectively for high-dose Dex arm.
The most promising novel agent that is under investigation is daratumumab. Daratumumab is an anti-CD38 monoclonal antibody and has been given as monotherapy in relapsed or refractory patients to at least two different prior lines of therapy who were ineligible for ASCT. To-date there is limited reported data: 4/9 patients who received $\geqslant$4 mg/kg achieved a PR. No DLTs were reported in the 2, 4, 8 and 16 mg/kg cohorts, while the most common adverse events reported were infusion related events.
Elotuzumab is a monoclonal antibody against CS1 and is combined with lenalidomide and low dose Dex in phase III studies. This combination has produced very encouraging results in phase II study in relapse/refractory MM: ORR 92% and median PFS of 27 months.
Conflict of interest: *Advisory board: ONYX, CELGENE. Other substantive relationships: JANSSEN-CILAG: honoraria*

Scientific Symposium (Sat, 28 Sep, 16:00−18:00) **Cancer Screening – Redefining the Modality of Screening**

81 INVITED

Cervical cancer screening in light of HPV testing and immunisations

E. Franco[1]. [1]*McGill University, Montreal, Canada*

Since 2006, when the first human papillomavirus (HPV) vaccine was approved, there has been much progress on the prevention of diseases associated with HPV infection, particularly cervical cancer. A decade earlier, the first clinically validated HPV assay was approved as an adjunct test in cervical cancer screening. As the two cervical cancer prevention fronts, i.e., primary via vaccination and secondary via screening, progressed more or less in parallel they have begun to intersect in recent years, as it has become clear that effective deployment of these strategies requires integration of resources and planning. However, acceptance of these technologies has not been without obstacles. Although the evidence for the superior value of HPV testing in cervical cancer screening had become unequivocal, up until recently consensus guidelines tended to indicate uncertainty as to the degree and strength of evidence for this test's efficacy. This state of affairs changed in March 2012 with the simultaneous publication of the guidelines from the US Preventive Services Task Force and from the joint society consortium that involved the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society of Clinical Pathology. These guidelines placed greater emphasis on HPV testing in primary screening and discouraged unnecessary screening at younger ages and overly frequent screening. While co-testing is still favored by the new guidelines, other high-resource countries began to pilot or even to implement programmatically the strategy of HPV testing as the sole primary screening test, reserving Pap cytology for the triage of women who are HPV positive. The author will review the historical milestones of how HPV-based strategies have moved to center stage in cervical cancer prevention and discuss the research directions in the area, particularly with respect to how screening is to be performed in vaccinated women.

Conflict of interest: *Other substantive relationships: Occasional consultant to companies involved with HPV vaccines (GSK and Merck), cervical cancer screening (Cytyc, Ikonisys), and HPV diagnostics (Roche, Qiagen, BD, Gen-Probe)*

82 INVITED

New opportunities and challenges in colorectal cancer screening − FIT vs FOBT vs sigmoidoscopy

N. Segnan[1]. [1]*CPO − Piemonte, Department of Cancer Screening and Unit of Cancer Epidemiology, Turin, Italy*

There is a general consensus that screening for colorectal cancer reduces mortality from and incidence of the disease. However, the debate about which routine screening strategy should be adopted is everlasting. Sundry technologies for colorectal cancer screening (CRC) are currently available: Faecal Occult Blood Test (FOBT), Faecal Immunochemical Test (FIT), Flexible Sigmoidoscopy (FS), Total Colonoscopy (TC), CT Colonagraphy (CTC), Capsule Endoscopy, DNA Test and other biomarkers.

Different colorectal cancer screening strategies can be compared through several non mutually exclusive criteria: cancer prevention and mortality reduction, stage distribution of screening detected cancer, distal vs proximal incidence and mortality rates of colon cancer, screening interval, cost, side effects, preparation, participation, Number Needed to Screen, Number Needed to Invite.

The focus of this intervention is on FIT, FOBT, and FS.

Guaiac test to detect faecal occult blood showed to be less accurate than immunochemical tests. According to a trial performed by the Erasmus University in Rotterdam, FIT slightly outperforms gFOBT with a lower level of reported discomfort and overall burden. The ultimate of a screening programme with a given method is strongly determined by participation rates and detection rates. An RCT performed in Italy found similar participation rates for sigmoidoscopy and FOBT, whereas the detection rate for advanced neoplasia was three times higher following screening by sigmoidoscopy than by FOBT. The Erasmus University study found that adherence to sigmoidoscopy (32%) was lower than for FOBT (50%) and FIT (62%).

However European FS trials (SCORE, UK Flexible Sigmoidoscopy Trial) showed that, after 10−11 years of follow up, the reduction of incidence of colon cancer in not yet declining. Ten years cumulative detection rates and ten years cumulative participation rates should be estimated for comparing the impact of FS and FIT in cancer screening.

All these technologies show advantages and disadvantages when used in colorectal cancer screening. Choice depends on the concrete possibility, in a given context, to set an organized screening programme, that must be sustainable (in economic and human resources) and cost-effective. Anyhow an expectation to prevent 100% of cases, whatever the chosen strategy is, cannot be realistic.

Conflict of interest: *Advisory board: Roche Diagnostics LTD*

83 INVITED

Should all men receive PSA screening?

J. Cuzick[1]. [1]*Cancer Research UK, Centre for Epidemiology Mathematics and Statistics Queen Mary University of London Wolfson Institute of Preventive Medicine, London, United Kingdom*

Two major trials have addressed the issue of PSA screening for prostate cancer. The European ERSPC trial found a highly significant 21% reduction in prostate cancer in men invited for screening and at 29% reduction in those who actually were screened, while the US based PLCO trial found no effect. The difference can largely be explained by the trial design − in that screening in the European trial was very uncommon in controls, but almost routine in the US study, so that it was in reality a trial of organised vs opportunistic screening. However over-diagnosis is a major issue and in the European trial 37 cancers would need to be diagnosed and treated to prevent one death after 11 years of follow up, and the morbidity associated with these diagnoses has been clearly documented. A major research priority remains to clearly separate low risk cancers with minimal risk of mortality, which can be safely watched, from more aggressive ones in need of immediate radical treatment. A range of options for achieving this goal will be examined. Until this need is met, population based screening should not be recommended and the decision for PSA based screening should remain an individual choice based on risk factors, symptoms and other personal factors.

Conflict of interest: *Advisory board: Myriad. Corporate-sponsored research: Myriad Genetics provided research funding to my institution.*

84 INVITED

UK Breast cancer screening

D. Cameron[1]. [1]*Edinburgh Cancer Research Centre, Edinburgh, United Kingdom*

This talk will outline the basis of the UK breast cancer screening programmes, and the approach of the 2012 Marmot review to establish the benefits and harms of breast cancer screening.

The Marmot review concluded that randomised trials still gave the best estimates of mortality benefits and overdiagnosis, even though much has changed since then in terms of screening techniques, diagnostic pathways, and treatments. In the context of the UK screening programme that review concluded that around 1300 premature deaths from breast cancer were prevented, but this came at the "cost" of overdiagnosis, with some 4000 breast cancers each year being overdiagnosed, and therefore "overtreated".

The discussion will touch on how this could be addressed in terms of future research.

No conflict of interest.

85 INVITED

The cost-effectiveness of cancer screening

H. De Koning[1]. [1]*Erasmus MC, Dept. of Public Health, Rotterdam, Netherlands*

Population-based cancer screening is a major effort to try and reduce morbidity and mortality from the disease. The European code against cancer presently stipulates screening for 3 types of cancer sites: cervical cancer screening by a Pap smear for women aged 30 and over, breast cancer by mammography screening for women aged 50 and over, and colorectal cancer screening for persons 50 and over by FOBT. Many countries' public health policies endorse these guidelines, but differences may exist in screening interval, ages invited and tests applied.

Randomised controlled trials or clear-cut geographical differences in the past have formed the evidence-base on benefits, but these basically apply to one specific design. Modelling is often needed to estimate long-term benefits, harms, cost and savings, and to guide policies. Mostly, cancer screening programmes require additional funds, but this may lead to substantial benefits and even some savings.

At present debate exists whether new more effective treatments may be so effective, that benefits seen in the population as a whole may be contributed to treatment rather than screening (and early treatment). Sometimes screening is considered to be expensive given the annual number of screens needed.

However, new screening techniques may lead to alterations and more effective screening programs. It may also lead to new screening programs, e.g., for prostate cancer screening and lung cancer screening, or screening in high risk groups.
In this presentation, effects and cost of cancer screening are presented, including the debate on breast cancer screening versus treatment, and prospects for new screening programs are being addressed.
Conflict of interest: *Advisory board: Roche Diagnostics. Corporate-sponsored research: Beckmann, to estimate cost-effectiveness phi-testing for prostate cancer (2 years ago) (independent for department). Other substantive relationships: NELSON lung cancer screening trial (PI) received workstations from Siemens and money from Roche to do proteomics-research*

Scientific Symposium (Sat, 28 Sep, 16:00−18:00)
Imaging to Support Drug Development

86 INVITED

Use of advanced imaging in drug development: An industry perspective

B. Fine[1]. [1]*Genentech, Research & Early Development, South San Francisco CA, USA*

In clinical drug development, particularly in oncology, long timelines and high failure rates remain critical challenges. These challenges may be addressed, at least in part, by the information provided by advanced imaging approaches that reflect biological processes relevant to cancer and its treatment. While using these approaches to improve endpoints in registrational clinical trials is a longer-term possibility, in the shorter term, advanced imaging approaches are already providing information that could improve the accuracy and efficiency of decision-making early in clinical development. A number of novel imaging techniques are now well positioned to inform these decisions. Examples include positron emission tomography (PET) using ^{18}F-deoxyglucose (FDG-PET), ^{18}F-fluorothymidine (FLT-PET) or radiolabeled antibodies (immunoPET) and magnetic resonance imaging techniques using dynamic contrast enhancement (DCE-MRI) or for vessel size imaging (VSI). A review of these examples highlights the importance of clearly defining expectations at the outset for how the imaging data will be used in development decision-making. With this clear definition of expectations other key consideration then follow that facilitate well designed and executed clinical imaging studies, including: (1) appropriate use and interpretation of preclinical models, (2) appropriately matching the imaging technique to the mechanism of action of an investigational treatment and (3) appropriately rigorous standardization of clinical image acquisition and analysis to ensure consistent and reliable information from imaging, particularly in multicenter trials. As the number of well designed and executed studies using advanced imaging increases over the coming years, the impact of advanced imaging on improving decision-making in clinical drug development will likely become increasingly apparent.
Conflict of interest: *Ownership: Roche. Other substantive relationships: Employee, Genentech*

87 INVITED

Minimising lymphoma treatment using PET

M. Hutchings[1]. [1]*Finsen Centre, Copenhagen, Denmark*

Most malignant lymphomas can be cured with available treatment regimens. However, the high cure rates are accompanied by a serious risk of long-term treatment-related complications, including second malignancies, infertility, and cardiopulmonary disease. It is widely acknowledged that even within the refined existing histological entities and risk groups, some patients need more intensive therapy to achieve cure, while many patients are prone to some degree of overtreatment even with existing regimens. In order to balance efficacy of treatment with the risk of late effects, a patient-tailored approach requires that treatment be adapted to the individual patient's risk profile and treatment response.
Selection of treatment for lymphoma is based on clinical staging, on well-established clinical prognostic factors, and on the age and general state of the patient. A number of biologic markers and cytokines have prognostic abilities, but they have yet no proven therapeutic value for the patients.
PET/CT has emerged as the most accurate tool for staging, treatment monitoring and response evaluation in Hodgkin lymphoma and aggressive non-Hodgkin lymphoma. While accurate staging and restaging are very important for the choice of therapy in lymphoma, we are only beginning to understand how to use PET/CT to improve our patients' outcomes. More precise determination of disease extent may result in more precise pre-treatment risk stratification, and is also essential to the minimal and highly individualised radiotherapy volumes of the present era.
A number of trials currently investigate the use of PET/CT for early response-adapted therapy, with therapeutic stratification based on interim PET/CT results. Some trials use early PET/CT to select patients for less intensive or abbreviated chemotherapy in patients with a favourable prognosis based on a negative scan, or to select early-stage patients where radiotherapy can be omitted without a loss of efficacy. Other trials use a positive early PET/CT to select less optimally responding patients who might benefit from a change to a more intensive strategy. Post-treatment PET/CT is a cornerstone of the most recent revisions of the international response criteria for malignant lymphoma, and enables selection of advanced stage Hodgkin lymphoma patients without need for consolidation radiotherapy. PET/CT also looks promising for selection of individualised, response-adapted therapy in relapsed and refractory disease.
No conflict of interest.

88 INVITED

Optimising treatment schemes using PET

Abstract not received.

89 INVITED

Molecular imaging using radiolabeled drugs

E. Smit[1], A. Van der Veldt[2], A. Lammertsma[3]. [1]*VU University Medical Center, Amsterdam, Netherlands;* [2]*VU University Medical Center, Internal Medicine, Amsterdam, Netherlands;* [3]*VU University Medical Center, Radiology & Nuclear Medicine, Amsterdam, Netherlands*

Background: Anticancer drugs can be labeled with positron emitters to study in vivo pharmacokinetics. The development of radiolabeled anticancer drugs will be illustrated by validation studies of carbon-11 labeled docetaxel ([^{11}C]docetaxel) in lung cancer patients.
Methods and Results: Biodistribution and actual human radiation dosimetry of [^{11}C]docetaxel was determined in 7 patients with solid tumors (van der Veldt et al., 2010). The effective dose of [^{11}C]docetaxel was 4.7 $\mu Sv \cdot MBq^{-1}$, comparable to the estimated effective dose in rats. [^{11}C]docetaxel showed low uptake in human lungs., and therefore could be a useful tracer for tumors in the thoracic region.
Tumor kinetics of [^{11}C]docetaxel were irreversible and could be quantified using Patlak graphical analysis. In tumors, the net rate of influx (Ki) of [^{11}C]docetaxel was variable and strongly related to tumor perfusion,. Also, dexamethasone pretreatment significantly lowered 11C-Docetaxel uptake in human tumors.
The microdosing concept was subsequently validated. (van der Veldt et al., 2013). Docetaxel naive lung cancer patients underwent two [^{11}C]docetaxel PET scans, one after a bolus injection of a tracer dose [^{11}C]docetaxel and another during a combined infusion of [^{11}C]docetaxel and docetaxel ($75\ mg \cdot m^{-2}$). The accumulated amount of docetaxel in tumors was <1% of the total infused dose of docetaxel.
The effects of the anti-angiogenic drug bevacizumab on tumor perfusion and [^{11}C]docetaxel uptake in lung tumors were investigated in non-small cell lung cancer (NSCLC) patients. It is assumed that anti-angiogenic drugs transiently normalize tumor vasculature and contributes to improved delivery of chemotherapy (Jain, 2001). Within five hours, bevacizumab reduced both perfusion and [^{11}C]docetaxel uptake in NSCLC. These effects persisted after four days and were not associated with significant changes in heterogeneity of [^{11}C]docetaxel uptake in tumors (van der Veldt et al., 2012).
Conclusion: PET using radiolabeled anticancer drugs enables assessment of accumulation of drugs in human tumors and may facilitate rational treatment choices that are tailored to improve drug delivery to tumors.
No conflict of interest.

Sunday 29 September 2013

Special Lecture (Sun, 29 Sep, 08:00−08:45)
Vasculogenesis: A new Target to Improve the Radiotherapy of Solid Tumors

90 INVITED

Vasculogenesis: A new target to improve the radiotherapy of solid tumors

M. Brown[1]. [1]*Stanford University Medical Center, Department of Radiation Oncology, Stanford, USA*

Radiotherapy, and other cytotoxic agents, kills both the tumor cells and the stromal cells of the tumor including the endothelial cells of the tumor vasculature. Thus, for the tumor to recur from surviving cancer cells, the vasculature must be restored following therapy. A variety of studies have shown that tumor blood vessels can derive from two sources: From angiogenesis, the sprouting of endothelial cells from nearby blood vessels, and from vasculogenesis, the formation of blood vessels by circulating cells. For most tumors following therapy angiogenesis is the most important process for the formation of these vessels. However, in the case of radiation, and with some anti-angiogenic or anti-vascular therapies, angiogenesis is abrogated (in the case of irradiation by the killing of the endothelial cells) thereby forcing the tumor to use vasculogenesis to restore the vasculature.

We have tested the hypothesis that the radiation response of tumors can be increased by blocking vasculogenesis using two human tumors (FaDu head and neck tumors and the U251 glioblastoma) transplanted into nude mice as well as an autochthonous tumor developing in the brains of rats treated while *in utero* with a single injection of the carcinogen ethylnitrosourea (ENU). We show that an essential contributor to vasculogenesis in irradiated tumors are CD11b+ myelomonocytic cells expressing MMP-9. These are recruited to the irradiated tumors by stromal cell-derived factor-1 (SDF-1, or CXCL12) induced by increased levels of HIF-1 in the irradiated tumors. Importantly, a variety of ways of blocking this process (neutralizing antibodies to CD11b, inhibition of the interaction of SDF-1 with CXCR4 and with CXCR7, antibodies against CXCR4, and inhibition of HIF-1) render tumors less able, or unable, to recur following irradiation. This is particularly the case with the rat autochthonous brain tumors. The SDF-1 inhibitor NOX-A12, while having no affect alone, dramatically improves the survival time of rats given whole brain irradiation.

However, though these CD11b myelomonocytes are essential for vasculogenesis, they are not sufficient, and we show using a dual color parabiosis system that circulating endothelial progenitor cells (EPCs) (defined as CD117+, VEGFR2+, and CD45−) migrate into the tumor after irradiation to restore the vasculature. We also show that blocking vasculogenesis does not increase the radiation damage to normal skin. In fact there is evidence both from our studies and those of others that this can be radioprotective of normal tissues.

Thus blocking circulating normal cells (monocytes/macrophages and EPCs) that can reconstitute the tumor vasculature after irradiation can have a major positive impact on the response of solid tumors to irradiation and potentially represents a new paradigm for the treatment of such tumors.

No conflict of interest.

Scientific Symposium (Sun, 29 Sep, 09:00−11:00)
Palliative Care in 2014

91 INVITED

Physicians and nurses experiences with continuous palliative sedation

S.J. Swart[1], J.A.C. Rietjens[1], C. Van Zuylen[2], R.S.G.M. Perez[3], J.J.M. Van Delden[4], A. Van der Heide[1]. [1]*Erasmus MC, Department of Public Health, Rotterdam, Netherlands;* [2]*Erasmus MC, Department of Medical Oncology, Rotterdam, Netherlands;* [3]*VU Medical Center, Department of Anesthesiology, Amsterdam, Netherlands;* [4]*Utrecht University Hospital, Health Sciences and Primary Care, Utrecht, Netherlands*

Background: Palliative sedation, a medical intervention aimed at relieving intractable suffering at the end of life by inducing decreased awareness of symptoms, has become a substantial practice in Dutch end of life care. In 2001, continuous deep sedation was used in 5.6% of dying patients. Since then, this figure rose from 8.2% in 2005 to 12.3% in 2010. In 2005 the Royal Dutch Medical Association launched a national guideline.

Material and Methods: Quantitative questionnaire and additional qualitative interview, inquiring about the last patient for whom Continuous Palliative Sedation until death (CPS) had been used. We studied CPS-practices of physicians and nurses in general practice, nursing homes and hospitals after introduction of the national guideline.

Results: We found that next to dyspnoea, pain and delirium, physical exhaustion and existential suffering were reported as refractory symptoms being decisive for starting CPS. Nurses more often than physicians indicated that patients were anxious prior to the start of continuous sedation and they more often mentioned pain as the decisive indication for starting CPS. Nurses less often felt pressure from patients or relatives to start CPS. A qualitative analysis regarding the considerations concerning the indication for CPS revealed that CPS is not only provided in situations in which *one* symptom was decisive. CPS may also be used to address a 'refractory state' resulting from an accumulation of physical and non-physical symptoms. Furthermore, physicians followed two different approaches towards the depth of CPS. Physicians either aim at deep sedation right from the start, or they start with mild sedation and only deepen it gradually if needed. We found that these approaches are influenced by preferences of patients and relatives, e.g. patients' and relatives' fear of awaking from sedation may affect the dosage of sedatives administered.

Conclusion: Different experiences of physicians and nurses with CPS in clinical practice may be a reflection of their different roles. Whereas in guidelines, proportional sedation is typically understood as sedation in which the dose of sedatives is individually titrated to the relief of distress caused by refractory symptoms, our study shows that in practice proportionality seems to be understood as a multidimensional notion to which preferences of patients and relatives also contribute.

No conflict of interest.

92 INVITED

Define future palliative care − should it form part of rehabilitation?

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The place of rehabilitation in cancer and survivorship as an initiative to promote quality of life is well established. With people surviving longer with their disease and a strategic shift in the understanding and practice of palliative care, there has also been increasing evidence that rehabilitation has a place in the vernacular of contemporary palliative care. A core message in relation to palliative care rehabilitation is that it should meet patient goals, be provided by a multidisciplinary team and be cognisant of the core issues of independence and functional mobility.

In this presentation, the place of rehabilitation as a defined outcome of palliative care will be discussed. The evidence-base for palliative care rehabilitation will be presented as well as the challenges that the development of such initiatives poses for clinical practice. A consideration of the changing dynamic of palliative care will be offered and how the construct of rehabilitation may need further refinement to meet the needs of the population of patients who may require palliative care in the future.

No conflict of interest.

93 INVITED

Xerostomia in palliative care: The "orphan" symptom

A. Charalambous[1]. [1]*Cyprus University of Technology, Nursing Department School of Health Sciences, Limassol, Cyprus*

Background: Xerostomia is the subjective sensation of dryness of the mouth caused or not by function lowering of salivary glands, with decrease of saliva quality or quantity.

The prevalence of xerostomia has been variously reported as ranging from 60% to 80% in patients with advanced cancer and patients at the end-of-life. The aim of this presentation is to illuminate the impact of xerostomia on the patients' lives and present the available strategies for its comprehensive management.

Material and Methods: A comprehensive review of the relevant literature through electronic databases (Cochrane, MEDLINE, EMBASE) with selective keywords.

Results: Xerostomia is a persistent and severe symptom that is difficult to manage and it is associated with a significant degree of morbidity in patients with advanced cancer. It can have a transient or permanent effect and can lead to several complications in the oral and esophageal regions. These include dental caries, mouth infections, taste alterations, bad breath, swallowing difficulties along with alternation in speech formation and voice function. Patients report that xerostomia can negatively affect their daily living exacerbating their suffering. The available pharmaceutical agents have limited contribution to the relief of dry mouth and are often accompanied with severe side effects (i.e. pilocarpine). The evidence for the effectiveness of other agents (i.e. sugar-free chewing gum) used to treat xerostomia is poor and often conflicting.

Conclusions: Xerostomia although a non-life threatening symptom it can have a profound effect on the patient's life. Xerostomia is mainly considered as a symptom with effect on the physical body however this review has revealed social as well as psychological effects on the lives of the patients and their families. There is no strong evidence from this review that any topical therapy is effective for relieving xerostomia.
No conflict of interest.

94 INVITED

Competence for nurses in palliative care in Denmark

M. Bentzen[1]. [1]*Sankt Lukas Hospice, Hellerup, Denmark*

Background: Surveys carried out by the Danish Knowledge Center for Palliative Care (PAVI) confirm a large variation in education standards in palliative care and medicine in nursing competences across Denmark.
Objective: To ensure that palliative patients have equal access to high quality care the Danish Multi-Disciplinary Cancer Group for Palliative Care (DMCG-PAL) prepared standardised recommendation for Nurses in Palliative Care − at an Undergraduate and Postgraduate Level in order to provide opportunities for nurses to obtain and develop a standardised set of skills in palliative care.
Design and Setting: The standardised curriculum of required skills was created, based on a range of national and international palliative care training curricula. The CanMEDS-7-roles Framework has been adapted to the nursing profession. The required skills have been separated into 4 domains: empirical, ethical, personal and psychosocial. The learning outcomes (knowledge, skills and attitudes) were specified in three levels in order to show the progression from undergraduate to postgraduate level of nursing training. The suggested standardised curriculum has been circulated amongst clinical and educational professional groups in Denmark.
Main outcome measures: The standardised curriculum provides a framework for current and future training of nurses in palliative care and creates a foundation for development and evaluation of professionals skills.
Results: 'National recommendations of Competencies for nurses in Palliative Care' was compiled and published in december 2012 with financial support from the Danish Nursing Organisation.
Conclusion: Nursing training in Denmark has been offered a standardised curriculum of required competences in palliative care.
Acknowledgements: The authors are grateful to the the Danish Multi-Disciplinary Cancer Group for Palliative Care and Danish Nursing organisation for their financial support og this project.
No conflict of interest.

Society Session (Sun, 29 Sep, 09:00−11:00)
European Society of Breast Cancer Specialists (EUSOMA) − Ensuring Quality in Breast Care

95 INVITED

The requirements of a specialist breast center: EUSOMA updated recommendations

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Background: The European Society of Breast Cancer Specialists (EUSOMA) is a multidisciplinary society particularly dedicated to the harmonisation of breast cancer care in Europe according to the highest available standards with a multidisciplinary approach and a rigorous quality control.
In 2000 EUSOMA published the recommendations on "The requirements of a specialist breast unit". The document followed what requested by the EBCC1 consensus statement, that all women have access to fully equipped multidisciplinary breast clinics.
The document has been accepted and recognised as a benchmark for the set up of a breast unit.
Material and Methods: EUSOMA has decided to up-date and revise its paper, following the advances in diagnosis and treatment and evidence based changes in practice occurred in the recent years and the experience deriving from voluntary certification process. It has been updated by consensus between a multidisciplinary expert group.
The paper defines the organisational model for a Breast Centre (BC), the minimum standards for the resources, expertise and data audit required to ensure high quality care.
Results: The basic criteria to be considered for the set up of a BC are being an integrated breast centre, dealing with a sufficient number of cases to allow effective working and continuing expertise/care, dedicated specialists working with a multidisciplinary approach, providing all services throughout the patients pathway in the centre, data collection and audit.
It is important that the BC guarantees the concept of continuity of care also in patients with advanced/metastatic disease offering treatments according to multidisciplinary competencies and ensuring a high quality palliative care service.
The BC must ensure to the patients all the support and expertise that may be needed not only through expertise of the BC team members but also consulting all those other experts that may be necessary on a case to case basis, referring the patient to the specific health care giver depending on the problem.
The role of breast care nurses guarantees the support to the patients during their whole pathway from diagnosis to follow up to offer practical advice, emotional support, further explanation with regard to treatment plan and information on side effects, etc.
Conclusions: The constant monitoring of the quality is essential in patient care, through auditing the unit's performance with internal and external audit aiming at improving organization, performance and outcomes.
No conflict of interest.

96 INVITED

Auditing quality of care in a Breast Center

Abstract not received.

97 INVITED

Quality indicators in breast cancer: The EUSOMA database experience

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Background: The European Society of Breast Cancer Specialists (EUSOMA) aims to promote multidisciplinary research and collaboration between scientists and professionals interested in the management of breast cancer. The goal is to improve the quality of breast cancer diagnosis and treatment across the EU, interacting with the appropriate local, national and international authorities as well as fostering training programs.
Material and Methods: With regard to Quality Control EUSOMA published a consensus document identifying quality indicators (QIs) in breast cancer care ranging from diagnosis to local and adjuvant treatment and follow up. To monitor the breast units' performance, EUSOMA has developed eusomaDB, i.e. a central data warehouse of prospectively collected information which includes individual records of primary breast cancer cases diagnosed and treated by those certified European breast units which have provided data according to the society requirements.
Results: eusomaDB is accessible on the web to all registered users. It was started in 2006 and includes about 65,000 cases, diagnosed between 2000 and 2013, entered by the nearly 50 breast units from 7 European countries (Germany, Switzerland, Belgium, The Netherlands, Austria, Spain and Italy) and transferred from 16 different databases. The data record is represented by 108 variables, including patient and tumour characteristics, information about preoperative work-up, multidisciplinary management and follow-up. Records hold no personal identifiers. Data transfer from each unit is performed yearly through an online application and represents a requirement to obtain and to continue to hold certification.
The web system offers analysis functions, including the calculation of 20 EUSOMA QIs. Most QIs show improvement overtime. Besides quality assurance and certification, eusomaDB is used for audit and research. All breast units contributing information into the database convene yearly in a meeting which is finalised to improve the completeness and quality of the data and to discuss research proposals.
Conclusions: Two papers on mastectomy trends have been published using data from the eusomaDB. Current research projects include breast cancer management by age, appropriateness of use of the sentinel lymph node technique, histopathology and biological characterisation of micro-invasive cancer, and the influence of certification in improving quality of breast cancer care.
No conflict of interest.

98 INVITED

European performance on EUSOMA quality indicators

Abstract not received.

99 INVITED

A parallel European objective: Guidelines for quality assurance in Breast Cancer Care and a voluntary accreditation scheme for Breast Cancer Services

D. Lerda[1], S. Deandrea[1], C. Freeman[1], J. Lopez-Alcalde[1], S. Martin[1], C. Nicholl[1], A. Uluturk[1]. [1]*European Commission Joint Research Centre, Institute for Health and Consumer Protection, Ispra (VA), Italy*

A European Parliament resolution (10/04/2008), reiterated by European Council conclusions, called on the European Commission (EC) to "*support the development of European accreditation/certification programmes in cancer screening, diagnosis and treatment based on European quality-assurance guidelines, which could also serve as an example for other areas of health care*". The EC responded by dedicating resources to the development of an EU quality assurance (QA) scheme for breast cancer services and to the updating of the European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis. Throughout 2012, the EC's Joint Research Centre (JRC) conducted bilateral meetings with stakeholders involved earlier in similar projects. It also investigated and compared existing QA schemes in Europe, and organised two European surveys, one on the situation of breast cancer services and one on use of the European QA Guidelines. Two workshops were organised at the beginning of 2013, one for experts and one for countries' delegates, with the purpose of reaching consensus on the overall concept of the scheme and of its reference documents, e.g. the new edition of the European QA Guidelines. As regards the inputs for the project and definition of boundary conditions:

– QA scheme needs to be modular and flexible in order to adapt to all organisational settings;
– linking of recommendations to evidence and an easier utilisation and maintenance (e.g. via an improved structure of guidelines and use of target languages) are needed for the guidelines;
– a fit-for-purpose proposal for the European QA scheme should avoid duplication of effort and guarantee that every aspect of quality and safety is covered;
– the feed-back from participants into the two workshops focused on the urgency for updating the European QA Guidelines and on the need for respecting guidelines and schemes already in place at national level.

The Commission will proceed with a consensus-seeking process for identifying the optimal way forward for this important EU initiative. Whereas the JRC will coordinate and steer the project, all stakeholders will be involved and consulted at all stages.
The project will be based on the need for harmonising benchmarking for breast cancer care across Europe; this means linking evidence-based guidelines based those QA requirements which are considered essential due to their high impact on population-based outcomes without neglecting quality-of-life aspects.
No conflict of interest.

Society Session (Sun, 29 Sep, 09:00−11:00)
European Society for Therapeutic Radiology and Oncology (ESTRO)

100 INVITED

Radiotherapy in rectal cancer − What have we learnt?

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Background: In patients with resectable rectal carcinoma, radiotherapy (RT) has been used with surgery to decrease local recurrence rates, improve survival, increase sphincter preservation and, most recently, preserve the organ.
Methods: A systematic approach to the literature was used.
Results: Preoperative (preop) RT at moderate doses decreases local failure rates by 50−70% whether combined with surgery not optimized or optimized to achieve lateral clearance. Postoperative RT at higher doses is less efficient, even if combined with chemotherapy (CRT). The preop RT can be given with low morbidity, provided the treatment technique is optimised; if not, unacceptable adverse effects have been seen. Since RT adds morbidity, it must be given when the absolute gains are sufficiently large to counterbalance the negative consequences.
Although the balance between positive and negative effects, including financial costs, from RT with optimized surgery is not precisely known, we have learnt to discuss in multidisciplinary team meetings in risk groups, very early, early, intermediate or locally advanced, the "good, bad and ugly concept". There is a gain from preop RT also in early tumours operated by the best surgeons, but it is likely too small (from 3−4% down to 1−2%) considering the late toxicity. In intermediate tumours, where the risk of local failure even after excellent surgery is higher (8−15%), preop RT is motivated since it decreases the risk to 3−7%. In locally advanced tumours (cT3 mrf+ or cT4), chemotherapy adds to the efficacy of RT (decreases local failure rates from 25−30% to 10−15%), and is recommended even if it increases acute and late toxicity. 5x5 Gy is as efficient as 45−50 Gy with chemotherapy, less toxic and more convenient and cost-effective in intermediate rectal cancers.
Survival is only slightly improved after preop (C)RT. Preop (C)RT does not increase anal sphincter preservation, but may in responsive tumours allow a 'wait-and-see' policy (organ preservation). Although this undoubtedly happens in some patients, the negative impact on those who do not respond so well is not discussed.
Conclusions: The locoregional problem in rectal cancer has been solved, albeit not universally. Quality assurance and control programmes are fundamental for success. Novel ways to integrate the different therapy modalities must be explored also to improve survival.
No conflict of interest.

101 INVITED

The science, art and joy of teaching medicine: Reflection on a 25-year personal journey

R. Chhem[1]. [1]*International Atomic Energy Agency (IAEA), Division of Human Health, Vienna, Austria*

In theory, most academic physicians are required to provide clinical services, to teach and to conduct research. The respective amount of time spent working in each of these three areas varies widely. For most physicians, the clinical workload is the major duty. Additionally, productive research activities determine a physician's career progression because research are valued so highly in academic settings. Research performance provides physicians with academic prestige. In contrast, teaching − a less glamorous activity − is undervalued by institutions, and poorly supported in part because its outcomes are difficult to measure.
While physicians claim to practice medicine based on evidence, few realize that teaching also needs to be based on evidence in order to provide diverse students with the best conditions for learning to support the achievement of educational goals.
Based on these premises, I would like to share with the audience my reflections on my transformation from a young teacher of diagnostic radiology into a global promoter for effective medical education that uses scientific methods in all stages of teaching − from the design to implementation and evaluation of curriculum. Is teaching a science or an art? To quote one educationalist: "Good teaching cannot be reduced to a technique. Good teaching comes from the identity and integrity of the teacher" (Palmer P.J.) in his book entitled *The courage to teach: Exploring the inner landscape of a teacher's life*. It is in this spirit that I would like to tell the story of my life as a teacher, and to share with the audience the science and art of teaching medicine and the joy it brings to me.
No conflict of interest.

102 INVITED

Multimodality imaging in head and neck cancer

R. Hermans[1]. [1]*UZ Leuven, Department of Radiology, Leuven, Belgium*

CT and MRI are well established methods in the initial diagnostic evaluation of head and neck malignancy, and are also widely used for treatment monitoring and follow-up. MRI is the preferred method for imaging certain tumour sites, such as the nasopharynx, skull base and sinonasal cavities. However, the characterisation of neck lymph nodes remains a difficult issue with anatomy-based imaging methods. High sensitivities and specificities were reported using diffusion-weighted MRI (DWI), better than what is obtainable by CT or conventional MRI. This increased accuracy is mainly due to improved detection of subcentimetric nodal metastases.
Differentiation of treatment induced tissue changes, especially after (chemo) radiotherapy, and persistent or recurrent cancer, is another topic in which DWI may be helpful. Also, studies investigating the role of DWI as prognostic tool during, and very early after treatment, are ongoing. Preliminary results are encouraging, and if confirmed, tailoring treatment according to the very early individual response, as seen on DWI, may become feasible.
For several of these possible applications of DWI in head and neck cancer, currently FDG-PET is being used or advocated. However, FDG is not an entirely specific cancer tracer, and false positive finding are not uncommon. The spatial resolution of PET is relatively low, potentially leading to false negative results. DWI is an interesting alternative, as correlation with anatomical MR images acquired during the same study is possible, allowing precise anatomical localisation of the observed abnormalities. DWI also appears to better discriminate between neoplastic disease and inflammatory changes than PET.

FDG-PET is indicated in case of a clinically unknown cancer, if CT or MRI fail to reveal the primary tumor. Also, FDG-PET can be used to search for distant disease.
No conflict of interest.

103 INVITED
Advances in the adjuvant management of rectal cancer

B. Minsky[1]. [1]*MD Anderson Cancer Center, Houston Texas, USA*

Chemoradiation is the standard treatment for locally advanced, clinically resectable (T3 and/or N+) rectal cancer. When 5-FU is used concurrently with radiation, continuous infusion is the conventional regimen. Two randomized trials confirmed that capecitabine based chemoradiation regimens are equivalent.
Adjuvant preoperative therapy for rectal cancer is delivered by two fractionation schedules: short course radiation and long course chemoradiation. There are 2 randomized trials of short course radiation vs. chemoradiation. Overall, the TROG data suggest a small local control advantage for long course chemoradiation, especially for distal tumors.
Four randomized trials examined the role of adding oxaliplatin to 5-FU or capecitabine based preoperative chemoradiation. Three reported higher acute toxicity and no significant benefit in the pCR rate. The German trial reported the opposite results. The ACCORD 12 trial revealed no improvement with the addition of oxaliplatin in 3-year local control or survival. Targeted biological agents are being added to preoperative chemoradiation regimens. In the adjuvant setting, preliminary results from the EXPERT-C phase II trial (50.4 Gy/CAPOX/Cetuximab) suggest a survival benefit in patients whose tumors were KRAS wild type vs. mutant. Early trials using preoperative chemoradiation with CAPOX + bevacizumab revealed pCR rates of 18−24%. Unfortunately, more recent trials report increased acute toxicity and have been closed early.
Given the improvements in systemic chemotherapy there may be an opportunity to use preoperative radiation more selectively. This approach remains investigational and is being prospective tested in the phase II/III Alliance N1048 trial.
There are four series which advocate the watch and wait approach following preoperative chemoradiation. This approach remains investigational.
The Spanish GCR-3 randomized phase II trial compared neoadjuvant chemotherapy followed by chemoradiation with conventional preoperative chemoradiation followed by surgery and postoperative chemotherapy. The neoadjuvant chemotherapy approach is now the template for all new US NCI rectal trials.
The therapy of rectal cancer continues to evolve. Both diagnostic and therapeutic advances are challenging historical approaches and have opened new directions for the future and are areas of clinical investigation.
No conflict of interest.

104 INVITED
Optimal multidisciplinary treatment of the cancer patient with a focus on surgery/radiation oncology

Abstract not received.

Scientific Symposium (Sun, 29 Sep, 09:00−11:00)
Care of Special Lymphomas − Challenges in the Clinical Routine

107 INVITED
Waldenström's macroglobulinemia

M.A. Dimopoulos[1]. [1]*University of Athens School of Medicine, Department of Clinical Therapeutics, Athens, Greece*

Waldenström's macroglobulinemia (WM) is a rare disorder defined by infiltration of the bone marrow (BM) by lymphoplasmacytic cells which produce a monoclonal immunoglobulin M (IgM). The extent of BM infiltration (or other lymphoid organs) and the quantity and the immunohistochemical properties of the monoclonal IgM determine the spectrum of the clinical and laboratory disorders of WM. Specific criteria for initiating therapy have been proposed and an international prognostic index (ISSWM) for symptomatic patients has been developed in order to improve prognostication and clinical research.
During the last 10 years, our knowledge in the biology of WM has increased. Survival and homing of WM cells largely depends on PI3K/Akt and NF-kappaB signaling. Deregulated miRNAs and upregulated IL6 expression affect the proliferation and growth of WM cells. Cytokines (such as CCL3 and angiopoietins) and mast cells within the BM microenvironment further support WM cell survival. The most exciting recent advance was the identification of a somatic mutation in the MYD88 gene in ~90% of patients with WM, which results in increased downstream signaling through IRAK1, NF-kappaB & STAT3. Importantly, disruption of MYD88 pathway signaling induces apoptosis of WM cells. However, WM remains incurable with a median survival of 5 to 8 years.
Alkylating agents and nucleoside analogues were the backbone of therapy for several decades. Rituximab has minimal toxicity, but, as a monotherapy is associated with modest response rates and a transient increase of serum IgM ("IgM flare") in 30−80% of patients, which may exacerbate IgM-related complications. Combination of rituximab with chemotherapy (such as DRC) improved response rates but complete responses are infrequent. Combinations with more intensive chemotherapy (R-CHOP) or nucleoside analogues (FR or FCR) induce higher response rates but with significant toxicity. Bendamustine with rituximab is a promising combination with less toxicity. Bortezomib, a proteasome inhibitor, can rapidly reduce IgM levels, and has synergistic clinical activity in combination with rituximab and/or steroids. Other monoclonal antibodies, such as alemtuzumab (anti-CD52) and ofatumumab (anti-CD20) are also under clinical investigation. Everolimus (mTORC inhibitor) and perifosine (Akt inhibitor) have shown encouraging results. Ibrutinib, a BTK inhibitor, induced significant response rates in pretreated patients with WM and has been granted a breakthrough therapy designation by the FDA.
No conflict of interest.

108 INVITED
MALT lymphoma

Abstract not received.

109 INVITED
Primary CNS lymphoma

A.J.M. Ferreri[1]. [1]*San Raffaele Scientific Institute, Department of Onco-Hematology, Milan, Italy*

The use of high-dose methotrexate (HD-MTX)-based chemotherapy, followed or not by whole-brain radiotherapy, is the commonest therapeutic approach for primary central nervous system lymphomas (PCNSL). The current therapeutic knowledge in this field comes from single-arm phase-II trials, meta-analyses of published series, large retrospective, multicentre series, and three randomized trials. Numerous methodological pitfalls were highlighted in both prospective and retrospective series, further hampering interpretation of results. Importantly, the first worldwide randomized trial with completed accrual was recently reported [1]. This trial demonstrated that, in patients $\leqslant$75 years old with PCNSL, the addition of HD-cytarabine to HD-MTX results in consistently better outcome and acceptable toxicity over HD-MTX alone. MTX+cytarabine is an active combination that may be considered as the control arm for future randomized trials since it is supported by the best level of evidence available in the field of PCNSL [2]. Despite this benefit, current results in PCNSL patients remain unsatisfactory. Accordingly to the worldwide used therapeutic strategies for aggressive lymphomas, it is unthinkable to treat PCNSL exclusively with antimetabolites and the assessment of other drugs active against other phases of the tumour cell cycle should be considered for future trials. Some alkylating agents (i.e., temozolomide, ifosfamide, thiotepa, nitrosoureas) are interesting candidates since they are able to cross the blood–brain barrier, exhibit anti-lymphoma activity, are active against phase-G0 cells, and increase cytotoxicity of antimetabolites. Rituximab could be another candidate, especially considering its safe profile. Its combination with HD-MTX-based chemotherapy is feasible, but several doubts on its capability to cross the blood–brain barrier exist. High-dose chemotherapy supported by ASCT has produced encouraging results in PCNSL. However, this strategy seems feasible in young and fit patients, which excludes one third of PCNSL patients. Interestingly, some authors recently suggested that this strategy could replace consolidation radiotherapy, which deserves to be assessed in a future randomized trial. It is clear that a more effective international multidisciplinary collaboration is needed in the fight against PCNSL. Evaluation of single agents in phase II trials on patients with failed PCNSL, and definition and assessment of treatment-related neurotoxicity in prospective trials should be strongly encouraged.
No conflict of interest.

110 INVITED
Treatment of post-transplantation lymphoproliferative disorders

R. Trappe[1]. [1]*UKSH Campus Kiel, Kiel, Germany*

Post-transplantation lymphoproliferative disorders (PTLD) are the second most frequent malignancies after solid organ transplantation and cover a wide spectrum ranging from polyclonal early lesions to monomorphic lymphoma. Available treatment modalities include immunosuppression

reduction, immunotherapy with anti-B cell monoclonal antibodies, chemotherapy, antiviral therapy, cytotoxic T-cell therapy as well as surgery and irradiation. The prospective trial of immunosuppression reduction (IR) showed an overall response rate (ORR) of 6% while the combined ORR for all first-line rituximab monotherapy trials is 55% (95% CI: 45−65%) with a median OS of 2.4 years. Allogeneic EBV-specific T-cells resulted in 64% ORR and a median OS >2 years in EBV-associated PTLD. The PTLD-1 trial, which is the largest prospective trial in PTLD so far, evaluated sequential treatment with rituximab and CHOP in patients unresponsive to IR and has produced better response rates and overall survival than any other prospective trial so far (ORR: 90%, median OS: 6.2 years). As sequential treatment with rituximab followed by CHOP is superior to rituximab monotherapy plus chemotherapy at relapse, it should be applied first-line to all patients not responding to immunosuppression reduction. Outside clinical trials, we currently regard sequential therapy with rituximab and CHOP chemotherapy as standard evidence-based treatment for CD20-positive PTLD. Based on the result of the PTLD-1 trial showing that the response to rituximab at interim staging predicts OS in sequential treatment, risk stratification according to the response to rituximab currently is evaluated by the European PTLD Network. In risk stratified sequential treatment patients achieving a complete remission after rituximab monotherapy (low risk) continue with four 3-weekly courses of rituximab monotherapy while patients in PR, SD or PD at interim staging (high risk) are followed by four cycles of R-CHOP-21 (PTLD-1/3 trial). Interim results will be presented and demonstrate similar efficacy, but less toxicity. While CD20-positive PTLD accounts for only around 75% of PTLD cases, we will also summarize our approach to other PTLD subtypes like plasmacytoma-like PTLD and plasmablastic PTLD, and to primary-CNS PTLD based on the available retrospective data and our experience.

Conflict of interest: *Advisory board: Roche, Takeda. Corporate-sponsored research: Roche, AMGEN, Mundipharma, CSL Behring, Novartis*

Society Session (Sun, 29 Sep, 09:00−11:00)
European Association of Nuclear Medicine (EANM) − Diagnostic Imaging and Therapy in Prostate Cancer

111 INVITED

Prostate cancer: State of the art and future perspective in diagnosis and therapy

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Prostate cancer treatment schemes can be distinguished by 4 clinical stages: 1. Primary tumor, 2. PSA recurrent disease after first line local treatment, 3. Metastatic hormone naive and 4. Castrate Resistant disease. In diagnosis and treatment of primary tumors the balance of (early) diagnosis and treatment outcome is negative. Currently screening with PSA is not recommended by many guidelines and societies. Although recent improvements in imaging using mpMRI and MRI guided or MRI Ultrasound fused biopsy techniques have improved radiological and histological detection rates of Gleason 4 and 5 disease, any advantage of early treatment over standard clinical care has to been proven. Treatment of localized prostate cancer is highly driven by technology. Outcomes of local treatment using radical surgery, brachytherapy and external beam radiotherapy are clinically equivalent when comparing risk groups. Active surveillance increases as first line treatment in low risk prostate cancer given the low 10 years disease specific mortality rates of 1−2%. In locally advanced disease (T3) the standard of care is radiotherapy plus adjuvant androgen deprivation treatment for 2−3 years based on multiple randomized clinical trials.

In PSA recurrent disease after radical prostatectomy early salvage radiotherapy is standard of care. Randomized trials like Radicals (MRC, UK) are still ongoing to study the optimal timing and the role of adjuvant hormonal treatment in salvage radiotherapy. In PSA recurrent disease after radiotherapy, local salvage treatments like prostatectomy, cryoablation, HIFU, laser and brachytherapy are used but with limited long term follow up and all with moderate to severe toxicity. In future more focal treatment would be possible using image guided ablation reducing toxicity.

In metastatic hormone naive prostate cancer the corner stone of treatment is androgen deprivation treatment. However, in non symptomatic man the start of treatment can be delayed, reducing the morbidity and loss of quality of life without any effect on disease specific mortality. Improvements in reduction of toxicity by using intermitted treatment schemes were reported from several randomized trials but efficacy could not be proven in all cohorts of metastatic prostate cancer.

In the final stage of CRPC the increase in active drugs has never been so high as in the last decade. With docetaxel as standard first line chemotherapy, new drugs like abiraterone, cabazitaxel, enzalutamide and sipuleucel-t have been registered form CRPC in the last years. It is clear that within the coming years more new compound will de available and so he need for personalized treatment is there. Having in vivo information about changes in the tumor characteristics during treatment using bioimaging would be one of the rate limiting steps. At present targeted imaging of for instance the androgen receptor is studied as an early response tool.

No conflict of interest.

112 INVITED

Nuclear imaging in urology: From anatomic and functional to molecular imaging

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In recent years molecular imaging is acquiring importance for the evaluation of cancer patients, being complementary to conventional imaging methods as CT, MR and US. Among molecular imaging procedures, PET is the most diffuse and rapidly growing, and at present it is routinely used in patients affected by a large variety of malignant neoplastic diseases, as well as in other diseases. The usefulness of PET relies on its capability of investigating molecular processes by means of specific radiotracers, with the most employed being 18F-FDG. Despite FDG scans represent more than 90% of all PET scans, other positron emitter tracers are available and other tracers have been developed to study other metabolic pathways.

In the field of Urology, Choline PET/CT has been successfully used for studying prostate cancer, using either 11C-Choline or 18F-Choline. Choline PET has been successfully used mainly with the aim of identifying prostate cancer recurrence; however Choline PET/CT has also been suggested for diagnosis, staging and therapy planning in prostate cancer. The usefulness of Choline PET is based on its capability of localizing focal areas of increased metabolism as result of presence of malignancy; such information are often more accurate than those provided by conventional anatomic imaging. Also Choline PET/CT enables to non invasively study the whole body, and a number of investigations are currently evaluating the clinical role of Choline PET.

The real frontier research in this field is the development of other tracers, aimed to identify the tracers best suited for evaluating a specific functional pathway, thus acting like metabolic probes. Many other radiotracers have already been tested in humans, and are currently under study to evaluate the diagnostic accuracy. Among these radiopharmaceuticals there are metabolic tracers, such as syntetic aminoacid (FACBC); receptor tracers such as GRP receptors (BOM) and hormonal receptors (FDHT); and PSMA specific tracers. It is clear that the future of PET holds great promises of further growth, and will likely continue to increase its impact on clinical and experimental medical science.

No conflict of interest.

113 INVITED

Role of bone scan in prostatic cancer in the era of choline PET

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Introduction: In Western Europe and North America, prostate cancer is the most common tumour in men. The incidence of bone metastatic involvement depends on tumour stage and histology. In advanced disease, bone involvement occurs in 65−75% of patients and reflect prognosis [1]. The initial localisation of metastases in the skeleton has a relatively better prognosis in comparison with visceral metastases. The early detection of bone and bone marrow metastases allows a more adapted therapeutic management and a subsequent reduction in morbidity.

Nuclear bone imaging is performed with radiopharmaceuticals which uptake is directly related to blood flow and osteoblastic activity. The most widely used is 99mTechnetium-hydroxymethylene diphosphonate (Tc-HMDP). Image acquisition requires gamma camera for 2D whole body bone scan (WBBS) or partial 3D Single Photon Emission Computed Tomography (SPECT) imaging, which is generally fused with multislice CT (SPECT-CT). A more recent option is 18F-Fluoride (FNa) and Positon Emission Tomograph (PET) bound with multislice CT to obtain whole body 3D fusion imaging (PET-CT).

Bone metastases arising from prostate cancer may also be detected by PET-CT using 18F-Fluoro-Choline (FCH), a lipid component analogue of cell membrane. This radiopharmaceutical is accumulated, by choline metabolism alteration, in several cancer tissues and is manly interesting in non-aggressive forms of cancer [2].

Results: *Bone scan vs 18FNa*: Both FNa and 99mTc-HMDP are able to show the osteoblastic reaction in sclerotic lesions, present in 85% of prostate bone metastases. In case of mixed lesions, bone peripheral reaction seems more evident in FNa imaging. Indeed, PET-CT has a better spatial resolution than SPECT-CT, therefore a better detection and analysis of small lesion. Obviously, CT images add sensitivity (in case of pure lytic lesion with no osteoblastic reaction) and specificity (in case of equivocal bone uptake) to functional imaging.
For these reasons, FNa PET/CT is more sensitive and more specific than WBBS or bone scan SPECT-CT in prostate bone metastases detection.
Nuclear bone imaging vs 18F-Choline: It is important to notice that the radiopharmaceuticals didn't show the same bone involvement. FCH is a direct image of prostate metastasis (eventually localized on bone marrow), while both Tc-HMDP and FNa show only osteoblastic reaction. A very dense sclerotic lesion (easily depicted on CT) or a metastasis depressed after treatment may show no FCH uptake, due to a low cellularity, but still a high bone uptake. Similarly, FNa and Tc-HMDP may show false positive results in case of benign bone pathologies [2].
Overall, bone seeking radiopharmaceuticals methods may result more sensitive but are less specific than FCH imaging in prostate bone metastases detection.
Conclusion: 18F-Choline PET-CT utilization as alternative or complement to nuclear bone imaging in detection of prostate bone metastases should still be defined.
No conflict of interest.

Society Session (Sun, 29 Sep, 09:00−11:00)
European School of Oncology (ESO) − The Importance of Management Skills in Running Oncology Services

114 INVITED

Organizing cancer services: Hierarchies, markets or networks? A personal review

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Cancer services represent a major subsystem of the health care system in terms of resource levels, the number of people affected and political visibility. Yet while narratives of health system reform are often visible at a macro level, their implications for cancer services may be opaque. So how should cancer services be best organized?
This paper offers a social science perspective, specifically from the analysis of health care organizations. It is a personal review which draws on some literature on health care organizations and applies it to the domain of cancer services (e.g. managed cancer networks in the UK).
Hierarchies, markets and networks are introduced as three different ways of organizing health care. Their implication for the organization of cancer services are worked through, with brief examples given. Strengths and weaknesses of each mode are identified, and the question of possible hybrids raised.
No conflict of interest.

115 INVITED

Leadership and management skills for oncologists in the complexity of the European health systems

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In this session we'll address four issues of paramount importance for oncologists in leadership positions or willing to assume leadership roles.
What is leadership? Why is an essentially ambiguous concept? Here we look at whether it is possible to pin down what leadership really is. Especially when we refer to medical leadership.
Can we develop leaders who are not self-serving? This session focuses on how leaders are developed. We ask whether it is possible to develop servant leaders who are able to put others first.
Do the characteristics of leaders make a difference? In this part we examine how personal and demographic characteristics might influence leaders' decision-making in healthcare settings, and we also look at what motivates leaders.
Why are leaders reluctant to lead? Here we explore the increasingly recognised phenomena of reluctant leadership. We examine why in healthcare there exists both a reluctance to take on leadership roles, and a reluctance to be led.
No conflict of interest.

116 INVITED

Development of management skills from an oncologist's perspective

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Background: The increasing emphasis on patient-centered care requires the integration of disease-management abilities with "people-oriented" skills, including communication and management. Hospital-specific management practices are strongly related to a hospital's quality of patient care and productivity outcomes (Management in Healthcare Report, 2010). However, when surveyed, only 20% of oncologists felt sufficiently well trained in management skills (Ramirez AJ. Br J Cancer. 1995). Therefore, development of these abilities is an unmet need in medical oncology.
Material and Methods: The available literature on this topic was reviewed to illustrate the relevance of management skills in running an oncology unit. The current knowledge of this topic among oncologists was explored. Additionally, the different strategies presently available to improve the development of management skills were researched and analyzed.
Results: Management skills (including technical, human and conceptual) are critical and should be emphasized to a greater extent in medical oncology training programs. There is a significant lack of knowledge about this topic in the medical oncology community. Ad-hoc courses are currently being developed and conducted in different academic institutions within Europe and the United States. Medical oncology trainees and staff should be exposed to these skills and acquire a baseline knowledge and understanding.
Conclusions: The new scenario in health care requires an active participation of the physicians in hospital-specific management practices. The advancement of academic programs to train doctors in this particular field remains critical and should be emphasized by European Academic Institutions.
No conflict of interest.

117 INVITED

Practical aspects in managing daily interaction between the institute (general management priorities) and the medical department objectives and priorities

D. De Valeriola[1]. [1]*Institut Jules Bordet-Centre des Tumeurs de l'Université Libre de Bruxelles, General Medical Direction, Brussels, Belgium*

Managing daily interactions between the head office and the medical departments of a comprehensive cancer center is a complex task due to the diversity of professionals involved, the increasing requirement for care coordination among all health care providers to ensure an efficient multidisciplinary approach, the need of a good integration of research, innovation and education into care, the positive impact of a rapid transfer of lab discoveries to the bedside.
It is also somewhat difficult to ensure that the goals of a medical department in research, care and education will converge and that the available ressources of the institution will be used to realize in a good balance the objectives of these 3 main missions.
Maintaining a good equilibrium between, on one hand, the self-fulfillment of the professionals, the freedom necessary at the medical department level to progress in adequacy with the medical and scientific advances and to improve creativity in research and, on the other hand, the respect of equity and esteem between employees but also the important constraints related to financial, legal and regulatory aspects, is a daily challenge.
One of the key issue is certainly to ensure that all the employees know, understand and are involved in the vision and the mission of the organisation of the institution and are able to work together on ensuring that this vision and mission is communicated and implemented.
Communication and evaluation of the performance of the processes are important tools to use.
Tirelessly, re-centering the goals of all the professionals onto the patient and relatives's needs is certainly the key of success.
The presentation will tackle some practical tools that may be used to improve the convergence between the priorities of the institution and the, potentially different, objectives of the medical departments.
No conflict of interest.

Society Session (Sun, 29 Sep, 09:00−11:00)
European Society of Oncology Pharmacy (ESOP)

118 INVITED

Patient adherence to oral anticancer drugs

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Background: Patient adherence to oral therapy is an emerging issue in cancer treatment. Non-adherence to anticancer drugs is a growing concern because of the increasing number of novel oral targeted therapies. Suboptimal adherence to a regimen may lead to ineffective outcomes of treatment, drug resistance, altered response to the therapy or result in disease progression or constitute a potential risk of toxicity and waste of resources.
Furthermore, high rates of non-adherence to oral anticancer drugs have been reported in some publications. Methods for measuring adherence, which differ greatly in published literature, include self-reporting, pill counts, microelectronic monitoring systems (MEMS), prescription database analysis, and the assessment of serum or urine drug levels.
Objectives: Since measurements of patient medication adherence and use of interventions to improve adherence are rare in routine clinical practice, the aim is to investigate cancer patients' attitude, adherence and practices with their oral anticancer agents.
Methods: A systematic literature review was conducted to gain insight into determinants and associated factors of non-adherence in patients taking oral anticancer therapy. Data regarding all the cancer patients treated with oral anticancer agents will be collected from national prescription database and analyzed retrospectively. Patients will be asked to participate in the survey during their visits to the pharmacists or physicians to obtain their oral anticancer medication.
Expected results: Non-adherence and non-persistence to oral anticancer drug therapy are complex phenomena. Since a large number of patients will be taken into account, we will be able to provide information on adherence to anticancer agents at our institute. Monitoring adherence to oral cancer therapies is not a recent approach, but presents an increasing challenge as additional oral therapies enter the marketplace. Oncology pharmacists are uniquely positioned to promote patient adherence to oral cancer therapies by ensuring that patients understand the goals of treatment and identifying or resolving underlying barriers to adherence.
No conflict of interest.

119 INVITED

Drug interactions in cancer treatment: Identify them before they do

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Background: Cancer patients are prescribed numerous medications, including anticancer drugs, drugs for supportive care and comorbidities. Anticancer drugs are considered high risk drugs and drug interactions may have important implications for patient safety. Potential drug interactions should be detected early in order to prevent their manifestation. The presented study evaluates the management of drug interactions with anticancer drug therapy in a routine clinical practice.
Materials and Methods: The study was designed as a retrospective study and reviewed drug interactions in patients where anticancer drug therapy was initiated between the years 2010 and 2013 at the University Clinic Golnik. As part of routine clinical practice, before the initiation of a new anticancer drug, all included patients were visited by a pharmacist, who obtained a comprehensive drug history and searched for potential drug interactions. Drug interactions judged to be clinically important were discussed with the treating physician. As part of the study, patients' medical records were reviewed and drug interactions were reassessed using three different databases. The clinical importance of detected interventions was rated by an expert panel of pharmacists and oncologists.
Results: Our study included over 500 patients, most of which were treated for lung cancer. As the data are still being analysed, their collection revealed that some clinically important drug interactions were easily avoidable by changing patient's chronic therapy whereas this was not possible in other instances. For example, often, therapy with the tyrosine kinase inhibitor (TKI) erlotinib or gefitinib was planned in a patient prescribed with a proton pump inhibitor (PPI): the concurrent treatment may reduce TKI bioavailability and impair TKI treatment outcomes. Luckily, in most cases, PPIs treatment could be stopped to avoid the interaction. On the other side, sometimes, the interacting drug in patient's chronic therapy, e.g. amiodarone, could not be stopped, and a non-interacting anticancer drug, e.g. gemcitabine, had to be chosen over an interacting one, e.g. vinorelbine, as the interaction may lead to increased exposure to vinorelbine and toxicities.
Conclusions: Pharmacist-led review of drug interactions when starting a new anticancer drug may help prevent potentially dangerous drug interactions.
No conflict of interest.

120 INVITED

Medication reconciliation process in oncology patients

A.R. Rubio Salvador[1], J.I. Chacón López-Muñiz[2], J.M. Martínez Sesmero[1], P.A. Bonal López[3], F.J. Rodríguez García[4], C. Cornejo Castro[2], M.A. Cruz Mora[2], P. Moya Gómez[1]. [1]*Hospital Virgen de la Salud, Pharmacy, Toledo, Spain;* [2]*Hospital Virgen de la Salud, Oncology, Toledo, Spain;* [3]*Hospital Virgen de la Salud, Informatics, Toledo, Spain;* [4]*Toledosoft, Informatics, Toledo, Spain*

Background: A common element among the wide variety of onco-haematological malignancies diagnoses is the management of the complex information related to these patients, in which, due to the characteristics of the disease and the drugs used to treat it (most of them with a narrow therapeutic index) it is necessary to closely monitor the clinical and pharmacotherapeutic history in order to control drug interactions, toxicities and side effects, which may compromise the therapeutic success if not handled properly.
In our environment the information generated in the care of these patients in this setting is managed by two different computerized physician order entry system (CPOE) depending on where the patient is being attended:

a. In the hospital, the CPOE is ONCOBASS®. It has been in operation for 6 years, and includes the design, preparation and administration of all chemotherapy courses prescribed by oncologists/haematologists.
b. In the Primary Care setting, the CPOE is TURRIANO®, where the Primary Care physicians register all drugs prescribed to treat any pathological condition in cancer patients (related or not with their main process).

The main objective of this project is to implement a communication tool between the two CPOE: ONCOBASS® and TURRIANO® in order to coordinate all relevant drug information of oncology patients in different health system levels through a medication reconciliation process inside a complete Medication Prevention Error Program.
Material and Methods: We pretend to extend and integrate the pharmacotherapy management of these patients into the Primary Care system, allowing oncologists/haematologists to get access to online data about any drug prescribed by General Practitioners (GP). This online information includes alarms about interactions and incompatibilities between the drugs prescribed by the specialist and those used by the GP. For this objective, a multidisciplinary team has been created to define the tools necessary to communicate with TURRIANO® to implement them and to follow up the project:

- doctors (oncologists, haematologists) are responsible for selecting clinical data relevant to share with GP in order to control medications prescribed for managing adverse effects of chemotherapy drugs.
- pharmacists are responsible for selecting target drugs to be followed up to avoid relevant interactions and for medication reconciliation.
- nurses are responsible for registering any over-the-counter medication taken by patients that are not registered in any of both electronic system.
- Informatics expert to develop the informatics tools necessary for integration of both systems.

Conclusions: With this project we expect to implement a Complete Medication Reconciliation Process across the continuum of care in cancer patients attended in our area within a general Medication Error Prevention standard of care.
We hope to present preliminary results of the project during the European Cancer Congress 2013.
No conflict of interest.

121 INVITED

Pharmacokinetic reasoning − Pemetrexed distribution into third space fluid

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Dosing of drugs is an art and a science. Scientific based dosing is based on pharmacokinetics and knowledge on the positive and negative effects of the drug. The evaluation of dose strength, dose interval and eventually dosing length is based on measurement of drug concentration over time in the blood, the body or in the urine. The relation of drug concentration over time is expressed by simple mathematical expressions as well as the effect magnitude over time or related to drug concentration. The different relations

are expressed in a series of technical terms such as bio-availability, volume of distribution, elimination rate, ED_{50} and clearance assuming that the processes of pharmacokinetics and pharmacodynamics are linear and non-saturated.
The technical terms form a language for expert pharmacokineticists to talk and understand pharmacokinetics and to use for dose suggestions. For others in the beginning they have a high degree of abstraction. The relation to normal physiology and to pathophysiology as well as drug induced changes is difficult to see and to use. Therefore it is essential to point out that pharmacokinetics has its base in physiology and quantitative drug characteristics.
This is a knowledge base that has been termed Pharmacokinetic reasoning (Holford and Karlsson, 2007). The concept of Pharmacokinetic reasoning is stated as follows: *From pharmacokinetic parameters and the relation to the pharmacodynamics understand the physiology for drug disposition in other terms and to get understanding on its mechanism of action and an integration of PK-PD into biological meaning giving basis for execution of trials and for safety sciences.*
Pharmacokinetic reasoning opens up a mechanism-based pharmaco-kinetic-pharmacodynamic domain making possible the elucidation of normal physiology or patophysiology; understanding the site of action of the drug; understanding the mechanism of action of the drug and to separate physiologic changes from the effect of the drug.
Methotrexate is a cytotoxic drug with relative good hydrophylic properties. In high dose significant amounts are distributed to third space fluids like pleura that is withdrawn from following doses of methotrexate in patients wih NSCLC. There have been questions whether the same procedure was neccessary for the analogue drug pemetrexed used for similar indications. Pharmacokinetic reasoning made the conclusion that this probably was not demanded which had to be followed by a clinical pharmacokinetic study in a group of NSCLC patients where samples from pleura were taken once from each but at variable time. The pleura concentrations were low.
No conflict of interest.

Keynote Lecture (Sun, 29 Sep, 11:30−12:15)
Mouse Hospital and the Co-Clinical Trial Project

122 INVITED

The mouse hospital and the co-clinical trial project

P. Pandolfi[1]. [1]*Beth Israel Deaconess Medical Center, Medicine/CLS 401, Boston, USA*

Tremendous advances in technology have allowed us to gain powerful insights into the molecular and genetic drivers of cancer. The rate at which this knowledge has been translated into effective therapeutics, however, has often been pitifully slow. To facilitate this process, we have launched a new platform and initiative, both nationally and internationally, that we refer to as “The Co-Clinical Project”. Its major goal is to accelerate the stratification of patients based on molecular and genetic criteria, and the identification of mechanisms of acquired resistance to specific treatments towards the development of novel therapies that overcome such resistances. This is achieved through integrated analyses of data obtained from preclinical trials performed in the “Mouse Hospital” in genetically engineered mouse models (GEMMs) of human cancer, as well as mouse models orthotopically transplanted with primary human cancers, and run in parallel and synchronicity with experimental clinical trials as well as existing standard-of-care treatments in human patients ongoing in the “Human Hospital” (hence the term “Co-Clinical”).
No conflict of interest.

Special Session (Sun, 29 Sep, 13:15−14:15)
Management of Bladder Cancer

123 INVITED

Surgical status of lymphadenectomy

A. Stenzl[1]. [1]*University of Tuebingen, Department for Urology, Tübingen, Germany*

The role of lymphadenectomy for staging and possibly for a perioperative therapeutic consequence in addition to surgical treatment of the bladder tumour itself has been under discussion for several decades. In the largest series with a long term follow-up exceeding 10 years (e.g. Stein et al, J Clin Oncol. 19: 666, 2001, Monoharan et al, BJU Int. 104:1227, 2009) a disease specific survival of up to 30% at ten years in surgically treated bladder cancer patients with positive nodes has been demonstrated.
From an anatomical standpoint we differentiate between limited, standard, extended, and superextended lymphadenectomy, depending on the cranial limits (obturator fossa, iliac bifurcation, aortic bifurcation, branching of the inferior mesenteric artery, resp.). To date there are indications but no prove that cranial extension of the lymphadenectomy per se may improve survival (Stenzl et al, Eur Urol. 2011 Jun;59:1009).
There are currently 2 ongoing randomized phase III trials which try to answer whether extended lymphadenectomy improves survival compared to standard lymphadenectomy (German AUO trial, US SWOG1011 trial). Results will be available in 2015 and 2020, resp.
The minimum number of removed lymph nodes between 10−20 has been used as a surrogate marker for the quality and extension of lymphadenectomy in bladder cancer treatment (May et al, Ann Surg Oncol. 2011 Jul;18(7):2018). However, the dissection template as well as the way the nodes are worked up in pathology are equally if not more important. Furthermore patients constitution will also lead to different numbers of nodes within the same template.
Recent studies have shown that serum markers such as C-reactive protein (CRP) in combination with T-stage, lymph node density and resection margin (à TNR-C score) may have some prognostic value and may lead thus to a more extensive lymphadenectomy (Gakis et al, BJU Int. 2011 Dec; 108(11): 1800).
No conflict of interest.

124 INVITED

Is organ preservation for muscle invasive bladder cancer viable?

N.D. James[1]. [1]*University of Birmingham, School of Cancer Sciences, Birmingham, United Kingdom*

Prevailing orthodoxy is that cystectomy is the gold standard for invasive bladder cancer. This view is not underpinned by any randomized trials comparing different primary modes of therapy but rather by indirect comparisons of large surgical and radiotherapy series. Scrutiny of these results actually suggests very similar long term survival rates and population-based studies do not appear to show any survival differences linked to mode of treatment. Furthermore, most large surgical series have median ages in the mid-sixties, well below the (rising) disease population median, suggesting the results may well not be applicable to many or even most patients with invasive bladder cancer. Salvage cystectomy remains an option for local radiotherapy failure and appears to carry similar prognosis. Recent publications using synchronous chemo-radiation both from the USA and UK show excellent rates of bladder preservation and good long-term functional outcomes with little or no risk of treatment related death. As bladder cancer is a smoking related disease with a peak age of incidence in the mid-70s, adherence to the dogma that surgery is the treatment of choice needs re-evaluation when safe, lower morbidity alternatives are available. In particular, in older age groups, risks associated with surgery rise, especially in the presence of co-morbidities such as obesity, diabetes, respiratory and cardiovascular problems which may be associated with long term smoking and inactivity. Data from trials such as BC2001 and BCON show that chemo-radiation remains safe even in patients in their 80s. The role of bladder preservation as a primary therapy, especially for older patients rather than as a niche alternative to surgery in younger patients needs urgent re-evaluation by the uro-oncology community.
No conflict of interest.

125 INVITED

Biomarkers for neoadjuvant chemotherapy in bladder cancer

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Neoadjuvant chemotherapy followed by cystectomy improves survival compared to surgery alone. To prevent overtreatment is of outmost importance to define molecular predictors of response for patient selection. We present the currently available data outlining a variety of potential markers to aid for a personalized decision making process. Apart from p53, other markers of cell cycle regulation and apoptosis as p21WAF1/CIP1 (p21) gene, Bcl-2, mdm-2 and pRB have also been related to survival. The clinical relevance of EGFR and HER2 expression has also been investigated with no success. Regarding Ki67, overexpressing tumors may potentially benefit from neoadjuvant therapy and conversely overexpression of VEGF and bFGF have been linked to resistance to cisplatin-induced apoptosis. The role of multidrug resistance gene 1 (MDR1) and ERCC1 support that enhanced DNA repair in the tumor decreases the benefit of platinum-based treatment. A 20 gene expression model has shown to predict lymph node involvement, helping on decision making. A gene expression profiling has been proposed as predictive for response to neoadjuvant chemotherapy.
Conclusion: Predictive markers will eventually aid in the selection of patients that most likely benefit from preoperative treatment. In the coming

Table (abstract 125).

Biomarker	Predictive value	Biomarker status good outcome	Results	Ref.
p53	Controversial	Non overexpression	Related with higher RR to Neoadjuvant MVAC Related to better DFS and OS to RT-Cisplatin	[2]
		Not related with higher RR to Neoadjuvant MVAC Not related to better OS to RT-Cisplatin	[1], [3]	
p21 and p53	Prognostic value	Non overexpression	Related to better DFS or OS to RT-Cisplatin	[2]
pRB	No	Non overexpression	Not related to better DFS or OS to RT-Cisplatin	[2]
Bcl2	Yes, not validated	Non overexpression	Related with better OS in cisplatin and radiotherapy treated patients	[4]
Mdm-2	No	Non overexpression	Not related with pathologic downstaging after neoadjuvant MVAC	[5]
Ki67	No	Overexpression	Trend to better PFS and OS after neoadjuvant MVAC	[6]
XAF-1	Yes, not validated	High mRNA expression	Related with higher RR and PFS after neoadjuvant GC	[7]
VEGF	Prognostic value	Low expression	Related with better DFS after neoadjuvant MVAC	[8], [9]
Her2	Yes, not validated	Non overepression	Related with higher CRR after RT-Cisplatin	[10]
BCRA1	Yes, not validated	Low mRNA expression	Related with higher RR after neoadjuvant Cisplatin regimen	[25]
ERCC-1	Yes, not validated (RT-Cisplatin)	Low expression	Related with higher RR after RT-Cisplatin regimen Not related with higher RR after neoadjuvant Cisplatin regimen	[11], [12], [13]
14-gene expression	Yes, Validated	Positive score	Related with higher RR after MVAC	[14], [16]
20-gene expression	Prognostic value, Validated	Cuttoff high/low risk	Related with risk of nodal involvement in neoadjuvat treated patients	[15]

years a panel of markers will become available to achieve the predicted goal. (See table summary.)
No conflict of interest.

Special Session (Sun, 29 Sep, 13:15−14:15)
Aspirin − A Wonder Drug in the Fight Against Cancer?

126 INVITED
Aspirin and GI cancer incidence

Abstract not received.

127 INVITED
Aspirin and cancers other than gastrointestinal ones

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Background: The role of aspirin on neoplasms other than colorectal and upper digestive tract ones is still unclear. As for gastrointestinal cancers, aspirin may have a chemopreventive effect on other neoplasms by inhibiting cyclooxygenase (COX)-2, which has been reported to be abnormally expressed in many cancer cell lines and has been implicated in the process of carcinogenesis, tumor growth, apoptosis, and angiogenesis. Additional mechanisms of the anticarcinogenic effect of aspirin include the induction of apoptosis through COX-independent pathways, the inhibition of NF$\kappa\beta$ factor, and the upregulation of tumor suppression genes.
Material and Methods: We reviewed epidemiological data on aspirin and the risk of lung, breast, and prostate cancer, and provided an up-to-date quantification of the associations using a meta-analytic approach.
Results: At least 20 epidemiological studies on approximately 16,000 cases reported that aspirin is associated with a modest overall reduction (around 10%) of lung cancer risk. The inverse association, however, seems restricted to case-control studies. Moreover, there is evidence of some publication bias, with several small studies reporting the strongest inverse associations. A modest reduced risk has also been found for breast cancer in over 30 studies on approximately 54,000 cases, with consistent results in case-control and cohort studies. However, some heterogeneity in risk estimates and evidence of publication bias is observed. Moreover, there is no indication of dose and duration-risk relationships. At least 24 studies on more than 37,000 cases indicate that prostate cancer risk is reduced by 10% in aspirin users, with similar risk reductions in case-control and cohort studies, and for less aggressive versus more aggressive cancers. However, as for breast cancer there is no evidence of a relation with frequency, dose, or duration of use. Detection bias is possible since men and women taking aspirin regularly may have had more frequent medical contacts and consequently prostate-specific antigen measurements or mammographies, thus increasing their probability of being diagnosed with prostate or breast cancer.
Conclusions: Regular aspirin use appears to be inversely, but modestly, related to breast and prostate cancer risk. Inference for causality and public health implications are, however, still unclear given the heterogeneity of results, possible bias, and the lack of dose and duration-risk relationships.
No conflict of interest.

128 INVITED
Aspirin in cancer prognosis and pharmacogenetics

C. Ulrich[1]. [1]*German Cancer Research Center, Division of Preventive Oncology, Heidelberg, Germany*

Inflammation has long been recognized as an important contributor to risk of colorectal and other cancers. Although the exact mechanisms that contribute to this process are still unclear, inflammation enables carcinogenesis by contributing to cell proliferation and survival, angiogenesis, and genetic mutations. Use of non-steroidal anti-inflammatory drugs (NSAIDs) is effective in decreasing risk of colorectal and other cancers − in particular, recent studies exemplify that already a low dose of ASS has major potential in the chemoprevention of cancer. In addition, NSAID use appears to improve cancer prognosis. However, there are side effects, such as gastrointestinal upsets and bleeding. This limits the ability to use these agents in cancer prevention among healthy individuals. Interestingly, we have shown that inherited variation in genes that affect NSAID metabolism or efficacy can alter their potential as preventive agents and thus alter each person's individual risk-benefit balance.
NSAID pharmacogenetics can play a role at the level of drug metabolism and excretion, as well as at the level of prostaglandin synthesis. That pathway is the primary target of aspirin/ other NSAIDs and effects are mediated by the inhibition of prostaglandin H synthases (also termed COX1 and COX2). We have shown that polymorphisms in NSAID metabolism or prostaglandin synthesis can be important factors determining the efficacy of NSAIDs in cancer prevention, and are likely also determinants of toxicity. Utilizing NSAID pharmacogenetics is a key tool for tailoring the intervention towards individuals most likely to benefit at the lowest possible risk. This knowledge will provide the foundation for a strategy of personalized cancer prevention.
No conflict of interest.

Special Session (Sun, 29 Sep, 13:15−14:15)
Management of Toxicities Related to Chemotherapy and Targeted Therapy

129 INVITED

Pharmacological principles in relation to toxicity

A. Bergman[1]. [1]*Antoni van Leeuwenhoek Ziekenhuis, Medical Oncology, Amsterdam, Netherlands*

Pharmacology, the science of drug actions, studies the pharmacokinetics and pharmacodynamics of therapeutic agents. Pharmacokinetic parameters are the absorbance, metabolism, distribution and excretion of drugs, while pharmacodynamic studies concentrate on the interaction between the drug and its target cells and tissues and the body's response to that interaction. The maximum tolerated dose (MTD) is the highest dose of a drug that can be administered to a patient without unacceptable toxicity. This MTD is established in early clinical trials, which are designed to step wise increase the dose of a new drug until the dose limiting toxicity is reached (Phase 1 trial). The therapeutic activity of the drug at the MTD is studied in subsequent clinical trials (Phase 2 and 3). The therapeutic index (TI) of a drug is a ratio of the therapeutic efficacy and the severity of toxicities. Since anticancer drugs are toxic and have limited activity, the TI for these drugs is generally low. Therefore, registration and treatment of side effects is an important aspect of the work of an oncology care professional. Toxicity of anticancer drugs can often be explained by their mode of action, metabolism and their distribution over fatty and aqueous tissues in the body. Toxicity of drugs with a specific drug target, such as tyrosine kinase inhibitors and monoclonal antibodies, can be related to the functions of their target. Changes in pharmacokinetic or pharmacodynamic parameters might alter the TI. For example, ascites or pleural effusion will disturb clearance of methotrexate, which might result in unpredictable and prolonged toxicity. Impaired kidney functions will decrease elimination and results in increased toxicity of drugs cleared by the kidney (e.g.: Carboplatinum), impaired liver functions might result in decreased activity of drugs that require enzymatic conversion in the liver from a prodrug into an active drug (e.g.: capecitabine), while increased toxicity can be expected from drugs that are eliminated by the liver (e.g.: taxanes). Also genetic defects might result in increased toxicity of specific drugs. Dihydropyrimidine dehydrogenase (DPD) and UGT1A1 are essential for capecitabine/5-Fluorouracil and irinotecan elimination, respectively. Genetic deficiency of these enzymes is related to increased toxicity. In conclusion, pharmacokinetic and pharmacodynamic properties of anticancer drugs should always be considered prior to prescription.
No conflict of interest.

130 INVITED

Caring for patients with cardiotoxicity

S. Atay[1]. [1]*Hacettepe University, Oncology Hospital, Ankara, Turkey*

Cardiotoxicity is one of the most significant adverse effects of cancer treatment, and is responsible for considerable morbidity and mortality. The most frequent clinical manifestation of cardiotoxicity is asymptomatic or symptomatic left ventricular dysfunction. It may be induced not only by conventional cancer therapy, like anthracyclines, but also new antitumoral targeted therapy such as trastuzumab.
Incidence: From 5% to 65% of treated cases, and has been noted in 3−5% of patients when trastuzumab was administered as a single agent and in up to 64% of patients receiving the drug in combination with anthracyclines.
Risk factors: Most frequently associated with cardiotoxicity are anthracyclines, taxanes, alkylating agents and trastuzumab. The most important risk factor is cumulative dose of doxorubicin. In contrast to anthracyclines, trastuzumab toxicity does not appear to be dose related. Risk factors for developing trastuzumab cardiotoxicity are not clear. Age, obesity and hypertension are known risk factors for cardiac dysfunction.
Prevention strategies: Cardioprotective strategies protocols should be developed for patients undergoing treatment. Although cardiotoxic effects of cancer treatment occur infrequently, early detection and toxicity requires cardiac monitoring. Unfortunately, no proven strategies are available. The American Heart Association recommended close monitoring of cardiac function during anthracycline treatment but does not specify how often or by which means.
Many factors can increase the risk of cardiac toxicity in patients receiving cancer therapy, and nurses should be aware of them. Rigorous assessment of patients before treatment and careful monitoring during and after treatment can help to minimize risk and identify early signs of cardiac dysfunction. Nurses can help to minimize these risk factors by educating patients about the importance of quitting smoking, increasing physical activity, and limiting alcohol intake.
Nurses also can minimize the risk of cardiac toxicity by understanding the types and doses of chemotherapy or targeted therapy that patients have received previously, and whether patients have received radiation therapy to the chest. Knowledge about patients' previous exposure to chemotherapy could help nurses alleviate potential risks associated with treatment administered in the metastatic setting.
Management: No specific evidence-based guidelines exist for the management of chemotherapy-induced cardiac dysfunction. The Heart Failure Society of America's practice guidelines state that before treatment, interventions should be employed to control the following cardiovascular risk factors: body weight, hypertension, hyperglycemia, smoking, and alcohol consumption. Clinical studies have demonstrated the benefit of ACE inhibitors and beta blockers in patients with chemotherapy induced cardiac dysfunction.
No conflict of interest.

131 INVITED

Caring for patients with skin toxicity

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Cancer becomes a chronic disease with long term treatments associated with new and long terms toxicities.
Cancer professionals discovered new skin toxicities related to targeted therapies. New symptoms with new physiopathology . . . what challenges for nursing in cancer care!
Skin toxicity is one of the common ones, with wide consequences: symptoms by themselves, their management, but also issues about body image and social interactions. We are not focused on prevention for the moment, but this should be an aim.
We will discuss and share about these challenges, and propositions in nursing care.
No conflict of interest.

Special Session (Sun, 29 Sep, 13:15−14:15)
Matching p-values to Clinical Needs: Statistical Significance vs Clinical Relevance

132 INVITED

Payers perspective

K. De Nys[1]. [1]*University Hospitals of Leuven, Head Clinical Trial Center Chairman Belgian Federal Commissie voor Tegemoetkoming Geneesmiddelen/Commission de Remboursement des Médicaments (CTG/CRM), Leuven, Belgium*

Payers are facing challenging times. Not only the economic crisis but also the aging population, suffering from various chronic diseases, and the high prices of new drugs increase the pressure on drug reimbursement systems. Moreover and especially in the oncology area, launch volumes are expected to increase when considering the current pipeline[1]. With the sustainability of health care systems at stake, most parties involved realize that a change of mentality, not only in drug development plans, but also in the pricing and reimbursement policies imposes. From a payers perspective, some suggestions can be made.
At the registration level, adding values such as clinical relevance to the classical registration parameters could be considered, as relatively little attention seems to have been paid to the availability of (good) alternative treatment options until recently[2]. In order to better define the best Standard of Care, academic head-to-head trials comparing available treatments, objective registers or trials challenging the optimal dose or duration of treatment offer an important added value to the registration trials, and should therefore be promoted. In the set-up of such trials, participation of the reimbursement systems, defining the current gaps and the research questions, is absolutely necessary.
Reimbursement systems need guidelines, which should be − at least partly − based on the results of these academic studies. The scope of those guidelines can be international especially in the field of the mentioned scientific assessments, but since reimbursement decisions are taken on the national level, national guidelines adapted to the local situation can be helpful. Organizations editing these guidelines should be as independent as possible and free of
No conflict of interest.

133 INVITED

Matching p-values to clinical needs: Practitioner's perspective

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Background: The size of clinical trials in advanced solid tumors has become larger and larger in the last decade. As a consequence, statistical significance is achieved with smaller and smaller absolute and relative treatment effects. The relevance of statistically significant differences has increasingly been challenged whenever the treatment effect is small. There is thus the need to identify the minimum clinically worthwhile effect (MCWE) to pursue in randomized clinical trials. There are 3 major dimensions to characterize the MCWE: the endpoints used, the way to measure them and the threshold values to define the MCWE. In general, depending on the prognosis and the setting of the disease, there is agreement on the fact that OS or PFS are the endpoints to be used in advanced solid cancers.
Methods: Therefore we have concentrated our analysis on the identification of the parameters to be used and on the definition of their threshold levels for MCWE. Starting from 4 premises (1 the incremental nature of cancer treatment advances; 2 the prognostic heterogeneity of the conditions investigated in clinical trials; 3 the search for a compromise between what is relevant and what is feasible; 4 the need to express the benefit in a language understandable by patients), we have identified two conditions satisfying the MCWE in conceptually different ways: small benefit for many (SMALL) and large benefit for few (LARGE). SMALL may be measured both in terms of HR and median gain, whereas LARGE may be more appropriately measured by proportional and or absolute increase in 1, 2, 3 year OS.
Results and Conclusions: We have thus postulated threshold values for MCWE as a function of toxicity and prognosis for each of these 4 parameters and challenged these postulated values with the actual results of 50 trials on 39,426 patients in 13 cancer types on 19 new drugs. This model allows to preliminarily conclude that a) SMALL is more frequently achieved than LARGE, b) the threshold values for MCWE are more frequently obtained for HR than in terms easily understandable by patients (absolute median gains and absolute % increase of OS at 1, 2, 3 years), and c) the chances of obtaining MCWE by these parameters are similar in conditions of poorer or better prognosis (more or less than 12 months).
No conflict of interest.

134 INVITED

Patient perspective

Abstract not received.

Special Session (Sun, 29 Sep, 13:15−14:15) **How Should Complex Treatments in Radiation Therapy be Monitored to Guarantee Quality?**

135 INVITED

In vivo dosimetry

L. McDermott[1]. [1]*University Medical Center Utrecht, Radiation Department, Utrecht, Netherlands*

Patients should receive "treatment (that) is individualised for the specific patient's cancer, taking account of the patient's personal circumstances", according to ESTRO's Vision for 2020. This should go for quality assurance (QA) too. In vivo dosimetry is a patient specific QA procedure, and the only way to ensure the treatment went as intended. For this discussion, we define in vivo dosimetry as a measure of the dose delivered inside the patient during treatment time. The location of the dose in question is important, and not the location of the detector. Compared to pre-treatment dose verification, in vivo can be too late to prevent an erroneous treatment. On the other side, errors can (as reported) occur during treatment that are a missed in pre-treatment checks.
Whether errors that occur are systematic (repeated for many patients/fractions) or unique to one instance, treatment providers want to know when they happen − to assess consequences and prevent re-occurrance. Complete in vivo dosimetry is a measure of the sum of any errors that occurred in the entire chain of planning, data transfer, functioning of the linac, patient set-up and patient displacement. Some like to grade these sources of error in terms of high and low level etc, but in the end, the only interesting information is the similarity between the intended and actual dose. The question is then: is it worth measuring the dose in vivo, if the rest of the treatment chain is in good working order? The answer depends on whether the in vivo dose *can* be measured accurately, quickly, at all points of interest and for all simple or complicated treatments. The past decade has proven this to be not only possible, but has provided years of successful clinical experience that says 'yes it can'. A department can know and respond to errors instantly, as well as collect data indicating how well they are treating large patient groups over long periods.
The problems are not academic but pragmatic − mainly being the lack of any commercially developed solutions. It is not a high enough priority for vendors, who claim the demand from customers has not been sufficiently high. This discussion will address the issue of whether the focus of QA should simply lie with equipment, without the bother of patient-specific in vivo dosimetry. Or perhaps in vivo dosimetry can really guarantee high quality for all current and future RT treatments, and is indeed a worthwhile investment.
No conflict of interest.

136 INVITED

A comprehensive QA programme of treatment unit and treatment planning systems would make pre-treatment verifications redundant

D. Verellen[1], M. De Ridder[1]. [1]*UZ Brussel, Oncologisch Centrum, Brussels, Belgium*

Modern radiation oncology is a well-established, cost-effective and essential component in the curative and palliative treatment of malignancy. The challenge of individualized treatment optimization continuously drives research and technology, yet we should be careful not to get trapped in the "Cargo Cult Science" as described by Richard Feynman. In an attempt of avoiding a blind gallop towards increasingly more precise means of tumour localization and delivery this perspective on challenges in quality will contemplate 3 topics: (a) Due to the cutting edge technology, one might argue that radiation oncology, long considered to be a physical intervention, is now more accurately conceptualized as a biologic intervention with profound effects at the cellular and molecular level. The big challenge is to bring this into daily clinical routine in a safe an consistent way. (b) As systems become more automated and complex the potentials for failure become less intuitively obvious and we need more process-oriented rather than device oriented Quality Assurance to ensure patient safety. Moreover, it suffices no longer to prove we can irradiate phantoms with high precision, patients demand prove of the true delivered dose in their particular case. Again, this implies comprehensive Quality Assurance programs. (c) Scientific and technological progress comes at a significant cost, and many concerns exist regarding the value of that progress. Within these difficult economic times, health care politicians face the difficult challenge to create a furtive soil (e.g. supporting adequate reimbursement) allowing progress through efficacy and driven by outcomes. There is also a danger in that too much focus on sophisticated expensive technology may create a double layer health care system where not all patients have access to the best of care. Ideally, efforts in development should also aim at harmonizing the quality of care throughout Europe and the rest of the world. One might argue that a large part of the financial resources goes to treatments that show limited benefit for the patient and we need new financing mechanisms such as Coverage with Evidence Development. The latter, again, will need feedback from appropriate Quality Assurance programs.
No conflict of interest.

Special Session (Sun, 29 Sep, 13:15−14:15) **Centralisation of Complex Cancer Surgery: Do Outcomes Improve?**

137 INVITED

UK perspective

Abstract not received.

138 INVITED

Swedish perspective

P. Naredi[1]. [1]*Sahlgrenska University Hospital, Department of Surgery Institute of Surgical Sciences Sahlgrenska Academy, Göteborg, Sweden*

In Sweden all complex cancer surgery is provided by hospitals in the public health care system. These are governed by county or regional politicians and at national governmental level only supervision and recommendations can be given. Over the last decade the trend has been towards voluntary centralisation of complex cancer surgery. During the same period traditional outcome measures as postoperative morbidity and mortality and long-term survival have improved for most cancer diagnosis. Whether centralisation of complex cancer surgery has a major role in the improvement is debatable.

For many cancer diagnosis we have national population-based quality registries and historically these were initiated by professionals and managed by regional oncology centers. The data generated have been used by national networking groups to discuss what needed to be done to improve cancer care and to design clinical trials. While there is clear evidence that targeted quality indicators have been improved by these measures there is less evidence that centralisation to date has been of similar importance.
Smaller units have to large extent stopped doing complex cancer surgery. For some diagnosis like pancreatic and esophageal cancer the centralisation is at regional level while e.g. rectal or gastric cancer also is commonly performed at county hospital level. The national cancer plan and collaboration between six Regional cancer centres has initiated projects with the intention to centralise complex cancer surgery to high volume centres. Key arguments are not mainly focused at the improvement of the surgical procedure but more handling postoperative complications and fascilitating an optimal multidisciplinary diagnostic and treatment process for the patient.
No conflict of interest.

139 INVITED
Dutch perspective

Abstract not received.

Special Session (Sun, 29 Sep, 13:15−14:15)
Epigenetics in Cancer

140 INVITED
Epigenetic therapies in haematologic and solid malignancies

Abstract not received.

141 INVITED
Reprogramming the cancer phenotype by epigenetic drugs

J. Issa[1]. [1]*Fels Institute Temple University, Philadelphia, USA*

The epigenome is reset during embryogenesis and matures around the end of development. Large scale genomic studies have now shown considerable proliferation dependent epigenome changes in aging cells and in cancer cells (DNA methylation instability, chromatin instability). Epigenetic instability creates gene expression variation that serves as an enabler of Darwinian evolution at the tissue level, leading to disease formation (e.g. cancer), but also to selectable phenotypes such as drug resistance. Consequently, epigenetic reprogramming has been investigated for prevention and treatment of cancer. In hematologic malignancies, reprogramming by DNA methylation inhibitors has gained acceptance as effective therapy for myeloid leukemias, and drugs for other epigenetic targets are rapidly proceeding towards clinical trials. The hypomethylating drugs azacitidine and decitabine induce clinically meaningful remissions or improvements in 30−60% of patients with leukemias and prolong survival compared to standard approaches including chemotherapy. Both drugs are approved in the for the treatment of advanced and/or symptomatic MDS and AML. Histone deacetylase inhibitors belong to another class of epigenetic modifying agents which also has clinical activity in MDS and AML, though primarily when used in combination with hypomethylators. Clinical observations (delayed responses that are optimal at low doses) and laboratory studies (correlations between sustained hypomethylation, gene activation and response) both suggest that responses are mediated by epigenetic mechanisms. Current studies are investigating more potent DNA hypomethylators such as SGI-110, combination epigenetic therapy, translation of the hematologic malignancies experience to solid tumors, incorporation of epigenetic drugs with standard cytotoxics and a search for drugs that reprogram the epigenome through alternate mechanisms.
Conflict of interest: *Advisory board: Astex, Janssen. Corporate-sponsored research: Astex*

142 INVITED
How to overcome resistance to HDAC inhibitors?

S.E. Bates[1], A.R. Chakraborty[1], A. Basseville[1], V.L. Luchenko[1], R. Frye[1], Z. Zhan[1], R.L. Piekarz[2], R.W. Robey[1]. [1]*National Cancer Institute, Center for Cancer Research, Bethesda, USA;* [2]*National Cancer Institute, Cancer Therapy Evaluation Program, Bethesda, USA*

Histone deacetylase inhibitors (HDIs) have demonstrated activity in cutaneous and peripheral T-cell lymphomas and two have received regulatory approval for these indications in the United States. Histone deacetylases are found in both the cytoplasm and nucleus and are involved in the regulation of multiple cellular processes, most notably the deacetylation of nucleosomal histone proteins, which results in transcriptional silencing. Three families of HDAC enzymes have been described, with the HDIs exhibiting differences in potency of inhibition. Romidepsin and entinostat are potent inhibitors of class I HDACs, while vorinostat, belinostat, and panobinostat are inhibitors of both class I and II HDACs. In the clinic, T-cell lymphoma responses to romidepsin and vorinostat are observed in about a third of patients treated. Responses can be durable but the median time to disease progression is under a year − defining both intrinsic and acquired resistance in T-cell lymphoma. HDI resistance is also widely observed in solid tumors, despite widely documented activity in *in vitro* studies. Mechanisms of resistance have not been clearly delineated but are likely multi-factorial. With the HDAC enzymes as molecular targets, HDIs can be considered targeted therapies, but they differ from other classes of targeted therapy in that the HDAC targets to date have not been shown to be mutated or to be isolated oncogenic drivers in cancer. Accordingly, resistance mechanisms observed with the tyrosine kinase inhibitors (TKIs), such as target resistance mutations or bypass signaling, have not been described. To date, resistance mechanisms reported in various laboratory models include persistent activation of the STAT signaling pathway (with clinical data as well for vorinostat), activation of NF-kB and increased Bcl-2, reduced expression of pro-apoptotic Bim, activated MAPK signaling and in the case of romidepsin overexpression of the drug efflux transporter P-glycoprotein. Our laboratory data demonstrate that downregulation of Bim via activation of MEK is important in T-cell lymphoma resistance to romidepsin. Preliminary results in clinical samples show a wide variation in Bim levels and correlations with outcome are ongoing. Various reports, and data from our group in CTCL and other models, have shown that cells can be sensitized to HDAC inhibition via concurrent treatment with MEK inhibitors, PI3K inhibitors, CHK1/2 inhibitors, and knockdown or inhibition of anti-apoptotic proteins such as Bcl-2. Thus, it appears a key mechanism of HDI resistance is an increase in pro-survival signaling coupled with failed activation of apoptosis − highlighting potential strategies for development of combination therapy in the clinic.
Conflict of interest: *Corporate-sponsored research: This research was supported, in part, by a cooperative research and development agreement between the NCI and Celgene Corporation*

Special Session (Sun, 29 Sep, 13:15−14:15)
Tumour Response Assessment

143 INVITED
Anatomic and functional imaging

D.M. Koh[1]. [1]*Royal Marsden Hospital, Dept. of Diagnostic Radiology, Sutton, United Kingdom*

Anatomic imaging using computed tomography (CT) and magnetic resonance imaging (MRI) remains the cornerstone for tumour response assessment in clinical practice. The Response Criteria In Solid Tumours (RECIST) version 1.1 is widely adopted in clinical trials, although bidimensional tumour size measurement criteria (e.g World Health Organization Criteria; MacDonald Criteria) are sometimes utilized. The assumption that effective therapy results in tumour shrinkage underpins the use of anatomic imaging for tumour response assessment; this observation being true for a range of effective treatment.
However, there are increasing examples of drug that can result in patient benefit without reducing tumour dimensions. This poses a real challenge for evaluating the therapeutic efficacy of such drugs that are already licensed for clinical use; and even more pertinently, raises questions as to how best to measure the therapeutic efficacy of many new drugs in the development pipeline, whose actions are targeted towards specific cellular or metabolic pathways, which may not result in profound cell death and thus tumour size regression. Furthermore, there are “blind spots” in the existing tumour response assessment criteria (e.g. there are still no validated response criteria for bone disease).
Functional imaging CT, MRI and molecular imaging are seen as techniques that can improve tumour response assessment. These techniques reflect changes in specific aspects of the tumour pathophysiology and allow quantitative measurement to be made. There are a range of functional imaging techniques, which enables us to probe, reflect and quantify tumour vascularity, cellularity, metabolism, hypoxia and internal heterogeneity. The parameters derived have been shown to change (often early) in response to drugs that modulate these tumour properties.
However, as many of these techniques are complex to perform, translating functional imaging measurements into robust multi-centre techniques has been challenging. Nevertheless, multicentre studies employing some

of these techniques (e.g. dynamic contrast enhanced MRI; diffusion-weighted MRI) have shown good to moderate measurement reproducibility and acceptable inter-scanner variance. With technological convergence between imaging platforms, it is likely that these techniques will be realized in future clinical practice.
No conflict of interest.

144 INVITED
Data warehouse and uncertainties in response measurements

S. Litière[1], J. Bogaerts[1], L. Seymour[2], E. De Vries[3]. [1]*EORTC Headquarters, Statistical Department, Brussels, Belgium;* [2]*NCIC Clinical Trials Group, Investigational New Drug Program & Audit and Monitoring Group, Kingston, Canada;* [3]*University Medical Center Groningen, Department of Medical Oncology, Groningen, Netherlands*

To evaluate response and/or progression based on RECIST in clinical trials, detailed information is collected on the extent of disease at the start of the study and how disease evolves on treatment. Therefore clinical trial data based on RECIST-like criteria contain a wealth of longitudinal information on objectively measured tumor lesions. Previous analyses have shown that the contribution of tumor growth based on objective tumor measurements may not add much to the predictive capacity of a model for overall survival which already includes factors for tumor shrinkage and progression of non-target disease (Litière et al. J Clin Oncol 30, 2012 (suppl; abstr 10602)). One possible explanation may be the variability associated with these tumor measurements. Different sources could be identified, including measurement error, differing behavior of lesions within a patient as a response to treatment, heterogeneity between patients' measurement profiles, ... The data warehouse used for RECIST 1.1, including 16 randomized clinical trials across various tumor types (breast, colorectal, lung cancer), is a unique source to investigate this variability. Therefore, we will report on some of these results and how they may affect ongoing efforts to improve RECIST.
No conflict of interest.

145 INVITED
Imaging and beyond: What is needed in drug development?

L. Seymour[1]. [1]*Cancer Centre of Southeastern Ontario, Kingston − Ontario, Canada*

The development of cancer therapeutics is dogged by high late-stage failures, resulting in enormous costs, wasted resources, and lost opportunities. Although late-stage failures are the most costly, failures even in phase I are significant, as the selection of that agent may result in another potentially effective drug being abandoned. Failures, while expected, need to be identified at the earliest possible phase; robust methods, including imaging, are needed to improve decision making. Critical is the 'pharmacological audit trail' demonstrating: expression of the relevant target (e.g. her-2), evidence of drug penetration, effect on the target and the pathway, biologic effect and anticancer effect both pre-clinically and in humans.
Reliable processes are needed to ensure optimal decision making, including candidate selection, no-go decisions on proceeding to later development, and importantly, but often undervalued, the selection of an optimal tolerable dose and schedule. Adaptive trial designs have been proposed using efficacy, toxicity and pharmacokinetics, but have been hard to conduct because of the difficulty of evaluating response early. In later phases of development, surrogates of clinically meaningful anti-cancer effects that do not require long, large and costly trials, with overall survival endpoints often complicated by the use of salvage therapies, are highly desirable. These methods would ideally be usable in small trials and be reliable with good predictive value.
Imaging techniques can be harnessed in many of these areas and can be used to molecularly characterize tumours, evaluate metabolism, perfusion, hypoxia, cell proliferation, characterize pharmacokinetics and pharmacodynamics, drug distribution and kinetics, interaction of the drug with the target, as well as follow treatment effects.
Although progress is being made, further improvements are needed including in availability, cost, speed, validation and consistency. In addition, even in clinical practice, existing techniques and methods may be difficult to reliably interpret such as the evaluation of bone metastases, immunotherapeutics, and in certain tumour types such as prostate and pancreatic cancer, brain and hematologic malignancies, and mesothelioma, among others.
Pooled databases, even from negative trials, are needed to robustly evaluate imaging techniques. Data sharing initiatives such as the RECIST warehouse are imperative.
No conflict of interest.

Special Session (Sun, 29 Sep, 13:15−14:15)
How to be a Happy Oncologist

146 INVITED
Quality of life of young oncologists

P. Blanchard[1]. [1]*Institut Gustave Roussy, Villejuif, France*

Numerous multi-institutional studies have shown that medical students have a lower mental quality of life than similarly aged individuals in the general population and that burnout is highly prevalent in this population, reaching 76% in a study among residents in a US internal Medicine program. A meta-analysis of observational studies as shown that depression and anxiety rates were high among US and Canadian medical students, with levels of overall psychological distress consistently higher than in the general population and age-matched peers by the later years of training, the rate being even higher when considering only female students. Besides burnout has a detrimental effect on the physician's quality of life, is associated with an increased risk of suicidal ideation and has been linked to poorer quality of care, increased medical errors and lawsuits, decreased empathy, job withdrawal and absenteeism. Factors usually associated with burnout are insufficient personal or vacation time, a sense of failure, unrealistic expectations of patients, cognitive or ethical dissonance, repeated losses and grieving or problems concerning managed care.
However the prevalence and causes of burnout and low quality of life have rarely been studied specifically in an oncology resident population. In a recent French nationwide cross-sectional study among oncology residents (hematology, medical oncology, radiation oncology), burnout prevalence was 44% and was not significantly different between the three specialties. Burnout was higher among residents who did not feel adequately rewarded for their work. Burnout was associated with a lower perception of one's general health status and the desire to quit Medicine or to change specialty. The aims of this talk are to quickly introduce the concepts of burnout and quality of life, and then to focus on studies evaluating these items among oncology physicians (surgeons, medical oncologists and radiation oncologists) and when available oncology residents. Factors associated with burnout will be analyzed in order to discuss areas for future improvement.
No conflict of interest.

147 INVITED
Why choose oncology? How to identify goals/aims/barriers towards professional fulfilment for young oncologists

P. Dubsky[1]. [1]*Medical University of Vienna, Surgery, Wien, Austria*

Oncology has a potential for both professional fulfillment and total personal burn-out.
What are some of the factors leading to "happiness"? and at the same time- What can go wrong?
"Happiness" is a highly subjective feeling- and this presentation will remain unabashedly so. Motifs behind becoming and staying an oncologist will be presented. Medical education, job training, academic training and mentorship are important factors to stay healthy and happy. Science and research are no longer first steps in an early career. Both private and public settings to practice oncology can be rewarding- both can also be highly frustrating. Oncology is a rare profession that enables you to experience and help others at a time of existential need. At the same time getting paid for a job that is much more than a profession is important for sustained practice.
No conflict of interest.

148 INVITED
Managing burnout in oncology − special focus on young oncologists

L. Fallowfield[1]. [1]*University of Sussex, Brighton East Sussex, United Kingdom*

Medicine is a well-respected, well- paid and rewarding job but mental health problems are common, suicide has been reported as twice as high as in the general population. Alcoholism and deaths from cirrhotic liver disease is greater than in many other professional groups and divorce rates are also high. Burnout − a syndrome of emotional exhaustion, depersonalization and reduced professional accomplishment has been shown in many studies of oncologists in the US and Europe. Examining the reasons for these alarming findings is important, not only to protect young oncologists from experiencing a similar fate, but also for the well-being of their patients, their professional colleagues and their own personal relationships. Good stress and challenges leave individuals fulfilled with a sense of achievement that is validating for oneself and for others. Bad chronic and prolonged stress

is physically and emotionally debilitating and damaging for all. In this talk some top tips and suggestions will be given that will hopefully help towards making your career one that leaves you burnished not burned out!
No conflict of interest.

Special Session (Sun, 29 Sep, 13:15−14:15)
New Insights into Biology of Brain Tumours

149 INVITED

Histones and paediatric high-grade gliomas

Abstract not received.

150 INVITED

Recent insights into the biology of low-grade gliomas

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Background: Low-grade gliomas (LGGs) together account for around a third of all brain tumors in children. This catch-all term, however, masks a significant amount of underlying histological and biological heterogeneity, with many morphologically-defined entities that can show substantial overlap in their microscopic appearance and genetic alterations. It is also now clear that many of these entities are either unique to childhood, or are clearly distinct from their adult counterpart. The pace of progress in LGG research, however, has previously been hampered by delayed application of the latest methodologies in contrast to malignant entities such as medulloblastoma, and also by a paucity of cellular or *in vivo* models. Fortunately, both of these limitations are now beginning to be addressed.
Summary: This presentation aims to provide an overview of the most important findings from several recent genomics and functional biology studies focused on LGG. For example, whole-genome sequencing and high-resolution copy-number profiling have revealed novel alterations in *FGFR1* and *NTRK2* in pilocytic astrocytomas (Zhang J *et al*. Nat Genet 2013; Jones DTW *et al*. Nat Genet 2013), as well as structural rearrangements of *MYB*/*MYBL1* in other LGGs (Zhang J *et al*. Nat Genet 2013; Ramkissoon LA *et al*. PNAS 2013). Important functional investigations have also shed light on possible mechanisms of resistance to BRAF inhibitors in tumors harboring *BRAF* fusion genes (Sievert AJ *et al*. PNAS 2013), or elucidated cell type-specific responses to oncogenic stimuli and cooperating pathways in a new mouse model of LGG (Kaul A *et al*., Genes Dev 2012).
These studies and others from several international groups have provided very welcome new insights into the pathogenic diversity of LGG. They have also opened novel avenues for further research into mechanisms of tumorigenesis involving *BRAF* as well as new targets, providing reasons for cautious optimism about the translational prospects for these results in the not too distant future.
No conflict of interest.

151 INVITED

Biomarkers in ependymoma

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Ependymoma is the third most common malignant brain tumor in children. They exist also in aldults but spatial distribution, genomic alterations and gene expression profiles are different. Ependymomas consist in different categories of glial neoplasms with specific biological characteristics. Their behaviour is associated with clinical characteristics such as age and location. Recent microarray studies have been able to identify subclasses of ependymomas. These classifications are either based on chromosomal imbalances or gene expression profiling; none however has managed to integrate the complex genetic changes simultaneously. The grouping and the number of subclasses vary between studies and consensus has still to be reached before they can be implemented in routine. Conversely, only limited amount of data has been generated with respect to specific biological drivers in these tumors. Notch pathway, including some of its effectors such as tenascin-C or activators such as YAP1, has been shown to be altered by different studies and could be one of these. *EPHB2* has been associated with a given subclass of supratentorial ependymomas. Despite the limitation of our knowledge about ependymoma oncogenesis, several prognostic markers have been identified. A European endeavour, called BIOMECA, is underway to test and validate existing and new biomarkers within the framework of the new SIOPE ependymoma cooperative trial. Amongst these biomarkers, gain of 1q25 has been confirmed as a poor prognostic markers in large studies with homogeneously treated patients populations included in prospective trials. Tenascin-C expression on IHC appears to be as well a marker of poor prognosis, especially in young children. The assessment of these biomarkers need thereafter to be standardized with robust procedures that can be widely applied in Europe. More biomarkers are needed to describe properly the biological landscape of this tumor type in order to guide therapies and to develop targeted approaches.
No conflict of interest.

Scientific Symposium (Sun, 29 Sep, 15:00−17:00)
Technical and Biological Developments in Breast Radiotherapy

152 INVITED

Impact of radiotherapy on loco-regional control

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The Oxford overview established that postoperative radiotherapy (RT) improves loco-regional control and survival in early breast cancer both after mastectomy and breast conserving surgery (BCS). After BCS adjuvant RT roughly halves the risk of first recurrence. For patients at low risk of local recurrence, it is still uncertain whether there is a subset from whom RT may be safely omitted. Selection based on molecular subtype might provide a more reliable way of identifying benefit from RT. There is limited literature on such correlations. To date molecular classification cannot reliably differentiate those at higher or lower risk of local recurrence after RT. After mastectomy in the DBCG 82b and 82c trials (Kyndi et al, 2008) adjuvant RT significantly reduces LRR in luminal hormone receptor (HR) positive/HER2 negative tumours (3% RT+, 32% RT-), HR positive, HER2 positive (3% RT+, 48% RT-) and triple negative cancer (15% RT+, 32% RT-). No reduction in LRR was seen from PMRT in HER negative, HER2 positive patients, perhaps reflecting the impact of Trastuzumab on local control. Analysis of TRANS SUPREMO in the BIG 2−04 MRC/EORTC SUPREMO trial should provide prospective data on molecular subtypes and risk of LRR +/− RT. The role of axillary RT in patients with a positive sentinel node biopsy (SNB) remains controversial. Interpretation of the ACOSOG Z11 trial which showed no statistically significant difference in regional recurrence or DFS from axillary dissection vs no additional treatment is difficult due to the lack of adequate RT QA and failure to meet its target accrual. There is limited literature on the role of loco-regional radiotherapy in the context of neoadjuvant systemic therapy. Potentially the response to neoadjuvant chemotherapy measured at definitive surgery as residual tumour burden might individualise the need for locoregional therapy to the breast/chest wall and axilla (Smith, 2012). The role of axillary RT in this setting is under study in the recently launched NSABP-RTOG 9353 trial. The Alliance Cooperative Group trial is comparing axillary clearance and axillary RT in patients with residual nodal disease on SNB after neoadjuvant chemotherapy in T1−3, NI patients.
No conflict of interest.

153 INVITED

Image-guided radiation therapy

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Background: Radiation therapy (RT) has demonstrated clear clinical benefits for all patients treated with breast conserving therapy (BCT) and for patients with risk factors after radical mastectomy. However, part of this gain can be lost by non breast related mortality, especially due to increased late cardiovascular damage. Especially with locoregional RT, it can be difficult to avoid cardiac dose exposure. Therefore, efforts to reduce the dose to organs at risk are of high clinical relevance. One of these is reducing the margin from clinical to planning target volume (CTV-PTV), needed to compensate for set-up and movement uncertainty.
Material and Methods: We systematically investigated and compared the set-up accuracy, breath-hold stability and reproducibility of our image-guidance procedure for left-sided breast cancer patients treated with 3D-CRT in voluntary moderate deep inspiration breath hold (vmDIBH). Set-up data from 20 patients were used. Before each treatment fraction, patients

were positioned using skin tattoos. Subsequently, a set of anterior-posterior (AP) and left-right (LR) megavolt images were acquired in vmDIBH. Bony structures and soft tissues were matched followed by set-up corrections using shifts to the treatment couch. For verification purposes we made a set of images of the mediolateral (ML) and lateromedial (LM) tangential fields in vmDIBH just before delivery of each of the tangential fields. Breath-hold reproducibility during each treatment fraction was determined from the difference in the thorax-wall position between ML and LM fields delivery in each fraction. Finally, images of the ML and LM treatment fields were acquired in "cine acquisition mode". The difference between the maximum and minimum thorax-wall position within one field is used as an indication of the vmDIBH stability. Geometrical variability values were expressed in terms of group mean (μ), systematic (Σ), and random (σ) errors. Using a standard margin formula, we estimated the required CTV-PTV margin to account for geometrical uncertainties.
Results: The largest measured residual set-up errors (μ, Σ, σ) after on-line set-up correction were in the AP direction (μ = 1.8 mm, Σ = 1.4 mm, σ = 1.9 mm). The required margins to account for these errors were 4.1 mm and 3.3 mm in the AP and LR directions, respectively. The intra-beam thorax-wall position variability was 0.8 ± 0.5 mm. The breath-hold reproducibility (population averaged $\pm$ SD) was 0.3 ± 0.9 mm.
Conclusions: Using on-line daily setup correction, the measured residual setup uncertainties combined with the intra-beam thorax-wall position variability and the breath-hold reproducibility justifies a total CTV-PTV margin of 5 mm. In clinical practice, we now use daily on-line setup correction using AP and LR setup images, combined with a ML verification image once a week.
No conflict of interest.

154 INVITED
The long and short of radiation fractionation

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There is level I evidence that breast cancer is, on average, as sensitive to fraction size as the dose-limiting normal tissues, a conclusion based on 10-year follow up of 7,000 patients entered in randomised clinical trials. Subgroups based on patient age, breast size, tumour grade, receptor status, node status, surgery, lymphatic radiotherapy and systemic therapies can only be fully represented in overviews involving tens of thousands of patients, but the analyses conducted on current data sets are reassuring. Where the heart is concerned, there is no lower dose threshold for major cardiac events, so the priority is to protect the heart whatever fractionation is used. Whichever values of α/β are assumed to describe the fractionation sensitivity of brachial plexus, 40 Gy in 15 fractions delivers a dose intensity lower than 50 Gy in 25 fractions. Current 15-fraction schedules are standard of care for local-regional radiotherapy in the UK, but 15- or 16-fraction regimens are unlikely to represent the lower limit for whole or partial breast external beam radiotherapy. Based on first analysis of the UK FAST trial comparing two 5-fraction schedules of whole breast radiotherapy delivered over 5 weeks against 25-fractions of 2.0 Gy, the current UK phase 3 FAST Forward trial (n = 4000) tests two 5-fraction regimens of local-regional radiotherapy delivered in 1 week against a control regimen of 40 Gy in 15 fractions. Hypofractionation trials provide the evidence base for synchronous boost techniques delivered using intensity modulated radiotherapy, approaches that are also under evaluation in current randomised trials.
No conflict of interest.

155 INVITED
Intra-operative radiotherapy A (ELIOT)

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Electron Intra Operative Radiation Therapy (ELIOT) has been extensively tested in Milan since 1999. After a pilot trial, a randomized study has been carried out from 2000 to 2007. Aims of the study was to compare patients submitted to a 21 Gy single-fraction treatment targeted at the tumour bed only, given at the time of the quadrantectomy, versus standard post-operative WBI after the same BCS. Eligible patients were women with early invasive ductal or lobular breast cancer with a maximum diameter up to 25 mm if they were aged between 48 and 75 years old and suitable for BCS. The study protocol was approved by the institutional ethical committee and a written informed consent was obtained from eligible patients. The primary endpoint was the incidence of local relapse, including ipsilateral breast cancer. Secondary endpoints included overall survival, incidence of axillary or distant metastasis, contralateral breast cancer, and other primary cancers. A total of 1305 breast cancer patients were randomized before surgery in the study (654 in the WBI arm and 651 in the ELIOT arm). Due to ineligibility, 119 patients were excluded and a total of 1186 patients were available for analysis (601 and 585 in the 2 arms). The analysis is based on effective treatment received and not an intention-to-treat. The two treatment groups were perfectly comparable at baseline. All the events are reported at the 5-year follow-up. An excess of "true local relapses" (WBI = 5/ELIOT = 23), "ipsilateral breast cancer" (0/14, respectively) and "axillary/regional lymphonode metastases" (2/9, respectively) in the ELIOT group were observed. An excess of controlateral breast cancer, but without significant statistical difference, was observed in the conventional arm, 1.7% versus 0.8%. If we consider the cumulative incidence of new cancers not related to the recurrence in index quadrant (ipsilateral and contralateral second cancer) we observed a rate of 1.7 in the WBI arm, and 2.9 in the ELIOT arm. We found a low rate of local relapse in women with small tumor ($\leqslant$1 cm), grade 1 tumor and luminal A tumor. Among 200 patients with small ($\leqslant$1 cm) luminal A breast cancer we observed only one local relapse in the WBI group versus 2 in the ELIOT group (log-rank p = 0.55). Among 986 patients with either large (>1 cm) or non luminal A breast cancer we observed 4 local relapses in the WBI group versus 35 in the ELIOT group (log-rank p < 0.0001). In order to assess some subgroups of patients to be selected for ELIOT treatment without statistical differences with the conventional arm, we stratified the patients according to the ASTRO criteria. We had 129 patients in the "suitable" group, 270 in the "cautionary", and 184 in the "unsuitable" group. In the low risk group no statistical differences have been observed between the two arms. No differences were observed in death rate and overall survival. The actuarial 10-year overall survival rates were 92.0 and 89.8, respectively (P = 0.69). This study contributes to identify properly selected patients for PBI.
No conflict of interest.

156 INVITED
Intra-operative radiotherapy B (TARGIT)

Abstract not received.

Scientific Symposium (Sun, 29 Sep, 14:45−16:45)
Joint ECCO/ASCO Session − Improvements and Outcomes in Breast Cancer Care

157 INVITED
EUSOMA

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EUSOMA, The European Society of Breast Cancer Specialists, is a multidisciplinary society of experts dedicated to breast cancer care.
The Society aims to promote scientific research and increase contacts between scientists and health professionals interested in the management of breast cancer. Eventually, the final target is to harmonise, at the highest achievable level, the quality of breast cancer diagnosis and treatment across the EU, interacting with the appropriate local, national and international authorities as well as fostering training programs for young health professionals.
To achieve these goals EUSOMA publishes peer-reviewed recommendations on the different aspect in breast cancer care and promotes voluntary certification of specialist breast units.
The First European Breast Cancer Conference (EBCC) demanded that all women in the EU have access to fully equipped, multi-professional breast services, and that a quality assurance program has to became mandatory; EUSOMA published a position paper on "The requirements of a specialist breast unit" which has been widely accepted and recognised as a benchmark to set up dedicated breast teams.
The requirements underlying the set up of breast units are summarised as a) being a single integrated unit, b) dealing with a sufficient number of cases such to allow effective working and continuing expertise/care by c) dedicated breast specialists in all the required disciplines working within a multidisciplinary approach, providing care and support throughout the patient's journey, from early diagnosis, local and adjuvant treatment and patient support, to the management of advanced disease and palliative care, data collection and audit.
With regard to Quality Control EUSOMA published a paper identifying quality indicators (QIs) in breast cancer care from diagnosis to local and adjuvant treatment and follow up.
To monitor the breast units' performance with respect to the QIs, EUSOMA has developed a database, i.e. a central data warehouse of prospectively collected information which includes individual records of primary breast cancer cases diagnosed and treated by those certified European breast units which have provided data according to the society requirements.

The database is accessible on the web to all registered users; started in 2006 it includes about 65.000 cases, entered by the nearly 50 breast units from 7 European countries. It collects 108 variables for each individual patient, including patient and tumour characteristics, information on preoperative workup, multidisciplinary management and follow-up data. The web system offers analysis functions, including the calculation of the 20 EUSOMA QIs. Besides quality assurance and certification, the EUSOMA database is used for audit and research. All breast units contributing information into the EUSOMA data base convene yearly in a meeting which is finalised to improve the completeness and quality of the data and to discuss research proposals.
No conflict of interest.

158 INVITED

EURECCA Breast: European Breast Audit

G. Liefers[1], On behalf of the EURECCA Breast group. [1]*Leiden University Medical Centrum, Surgery, Leiden, Netherlands*

Comparing patterns of care for breast cancer internationally: an overview and future perspectives for EURECCA − EUropean REgistration of Cancer CAre.
In the past few years, several observational studies have been published addressing variations in patterns of care for breast cancer between countries. Studying several different patient populations; all researchers came to the same conclusion: despite national and international treatment guidelines, wide variations in patterns of care are observed between different European countries, but also on a global scale. However, the few studies that analyzed patient outcome in relation to different treatment approaches did not show an effect of different patterns of care on survival of breast cancer patients, in particular among the elderly. Consequently, it is questionable if different patterns of care have a major impact on breast cancer specific outcomes, and probably in the future we can add other, patient specific, outcome measures to survival or breast cancer specific outcomes. The aim of the EURECCA Breast project is to audit breast cancer care in Europe, to define best practice for breast cancer patients using large observational studies.
In this presentation, the first analyses of the EURECCA-breast group will be shared. For this purpose we collected already existing retrospective data from several European countries to assess differences in patterns of care, impact on survival, differences in quality of databases and gaps in the existing data.
No conflict of interest.

159 INVITED

ASCO's CancerLinQ and breast cancer outcomes

A.P. Abernethy[1]. [1]*Duke University Medical Center Center for Lear, Durham, USA*

The proliferation of scientific results and novel treatments is a growing challenge for oncology professionals as we enter the era of highly personalized cancer care. Patients are increasingly presenting cancers narrowly defined by molecular characteristics, often making the best course of treatment unclear. Oncologists need real-time decision support to help them provide the most effective treatments tailored to a patients' unique biology and tumors. Further, we need data systems that capture adequate information to monitor clinical impact, providing summaries of the relationship between treatments and outcomes including treatment response, toxicity, survival and quality of life. Big data, bioinformatics, clinical informatics, electronic health records, patient reported outcomes, data warehouses, machine learning, mobile health solutions, and precision analytics are health information technology tools that support personalized cancer care through discovery and healthcare optimization; leveraged thoughtfully, they are also fundamental tools for clinical decision support at the point of care. When data are interoperable and can flow across these systems, then they become available in real-time in support of the clinical task; data can be banked and reused to support discovery of personalized interventions, monitoring of quality of personalized care provided, and comparative effectiveness research. Thus, a (rapid) learning health system evolves − where clinical care and research are better approximated through data and information flow. This is the vision of ASCO's CancerLinQ™ − a knowledge-generating computer network that will unlock and analyze cancer care data from every possible source and feed up-to-the-minute conclusions and guidance back to physicians and patients, ultimately generating a learning health system for cancer. CancerLinQ incorporates a growing number of open-source applications; features include real-time data collection from electronic health records and other sources; clinical decision support; and data mining and visualization. A breast cancer-specific prototype has been developed linking information about clinical care, analytics to determine outcomes, and real-time decision support.
No conflict of interest.

160 INVITED

CancerLinQ: A practitioner's perspective

C. Penley[1]. [1]*Tennessee Oncology Centennial Medical Center, Nashville TN, USA*

CancerLinQ: A Community Oncology Perspective.
In late summer 2012, the American Society of Clinical Oncology (ASCO) announced the development of a prototype of a rapid learning system for oncology called CancerLinQ. The project proposed to assimilate and aggregate de-identified breast cancer data regarding patients receiving care in multiple settings, with the intent of analyzing the data and learning from it, and ultimately improving the quality of care delivered. Many practices were invited to participate in the development of the prototype. The prototype set out to accomplish 5 key goals:
1. Identify technology and other challenges to building they system
2. Demonstrate ability to aggregate data from any source in any format and make it available for multiple reporting systems
3. Demonstrate ability to provide real time quality measurement and reporting
4. Demonstrate ability to provide real time Clinical Decision Support
5. Demonstrate a willingness for oncologists to share data for quality improvement purposes.

Tennessee Oncology (TO) is a large community oncology practice located in middle and eastern Tennessee, in the Southeastern United States. TO is composed of fifty five hematologists and oncologists who work in multiple communities in this region. TO has a robust internal quality improvement program, and participates in (and is certified by) ASCO's Quality Oncology Practice Initiative (QOPI). The practice has an internal information technology department, and uses a commercially available electronic health record. When invited to participate in the development of the CancerLinQ prototype, TO leadership readily accepted.
In collaboration with information technology staff at ASCO, an automated data query was developed and tested. Ultimately, TO contributed de-identified data regarding more than 12,000 individual breast cancer patients. The speaker will discuss the importance of CancerLinQ from the perspective of a community oncologist, and will describe the logistics of participation.
Conflict of interest: *Board of directors: Conquer Cancer Foundation*

Scientific Symposium (Sun, 29 Sep, 14:45−16:45)
New Challenges in Metastatic Renal Cancer Cells: Identifying What is Worth Pursuing

161 INVITED

Identifying biomarkers in RCC

T. Eisen[1]. [1]*Addenbrooke's Hospital, Cambridge, United Kingdom*

At the time of writing, the only validated prognostic biomarkers are simple clinical measures such as performance status, LDH, calcium level, neutrophil level and so forth.
Anti-angiogenic treatments work at least temporarily in the majority of patients with clear-cell renal cell carcinoma. Even today, we have relatively few data relating to non-clear cell carcinoma efficacy, let alone biomarkers in that setting. Attempts to predict the impact of tyrosine kinase inhibitors have been made using imaging techniques, including DC-MRI and Doppler ultrasound, and genetic biomarkers usually using a candidate approach of VEGF or VEGF receptor SNPs. Similarly, mutations in pTEN and other pI3K signalling pathway molecules have been investigated to try to select for mTOR benefit. None of these are ready for routine practice. More recently, pharmacokinetic approaches looking at drug level concentrations have shown significant promise. Unfortunately PK approaches are relatively unattractive to drug companies who fear that it will complicate the treatment paradigm and make their product less attractive.
T-cell checkpoint modulators have well-defined mechanisms of action, which can be probed to search for predictive biomarkers. Interestingly, one such biomarker, the expression of PDL1, appears to be both a poor prognostic factor and a positive predictive factor. These observations are based on small scale data and must be viewed with considerable caution at present.
What biomarkers might be useful in the more distant future? Renal cell cancer is a tumour type where a successful adjuvant therapy could have a major role to play, given the epidemiology of the disease. Unfortunately, adjuvant trials take an extremely long time to conduct, limiting the rate of progress and the interest in this form of therapy. A biomarker which could act as a molecular surrogate of progressive disease might accelerate progress in these trials significantly. I will mention ctDNA work we are

conducting in Cambridge and our plans to incorporate this work in adjuvant therapy designs.
No conflict of interest.

162 INVITED
Immune therapy in renal cancer: Not such an ugly duckling?

P. Mulders[1]. [1]*Radboud University Medical Centre Nijmegen, Department of Urology, Nijmegen, Netherlands*

Kidney cancer is a disease that can be cured by only surgery. When metastasized the prognosis is poor. The introduction of new targetted has improved survival with a medium duration of 2 years. However with these new agents cure can not be obtained, and toxicities are class specific and considerable. Improvements have also be obtained with a better selection of patients. The improvements were already obtained during the immunotherapy era, with increased knowlegde of prognostic factors. Also the tendency towards more specific immunotherpy has gained its effect with less toxicities. Especially in the time that many new agents are introduced there is an interest in agents that can cure metastatic renal cell carcinoma with less toxicity. The challenge is in the best timing an sequence of agents, including immunotherapeutic approached. These items will be discussed.
No conflict of interest.

163 INVITED
The mechanism of resistance to targeted therapy

T. Powles[1]. [1]*Barts Cancer Institute, London Cancer, London, United Kingdom*

The introduction of VEFG targeted therapy and mTOR inhibitors have significantly improved the outcomes of patients with metastatic clear cell renal cancer (mRCC). Unfortunately resistance develops, limiting the use of these agents to finite periods of time. This onset of this resistance is unpredictable for both classes of agents. There is molecular and functional imaging data to suggest dynamic changes occur with therapy, which may part explain the difficulies is unlocking the key to resistance in mRCC.
The majority of research in this area has been with the VEGF targeted therapies, such as sunitinib. A small proportion of patients obtain no clinical benefit with these agents, which is known as inherent resistance. The molecular mechanism associated with inherent resistance is inconclusive. The remaining patients initially achieve clinical benefit with sunitinib, followed by treatment failure after approximately 1 year. The molecular mechanism underlying this acquired resistance is also unknown, but is likely to be multifactorial. While it is apparent that adequate VEGF targeting is important in maintaining response, VEGF independent factors such as FGF-2 or MET may also contribute to treatment failure. Further research in this area is required. The mechanisms of resistance to mTOR inhibitors are even less explored. Mutation to the PI3K pathway is under investigation, but results are awaited.
There are a number of logistic and scientific factors hampering progress in this area. These include a lack of adequately collected tissue and a scarcity of sequential tissue, which may be required to indentify the mechanisms of acquired resistance. Other factors such as tumor heterogeneity increase the complexity of this field further. Overall the current data is only able to speculate rather than map out clear pathways of resistance and further work is required.
Conflict of interest: *Advisory board: Pfizer, GSK, Novartis, Astellas, Bayer. Corporate-sponsored research: Pfizer, GSK, Novartis,AZ*

164 INVITED
The role of novel and established imaging modalities in predicting outcomes in clear cell renal cancer

L.S. Fournier[1], S. Oudard[2], C.A. Cuénod[1]. [1]*Université Paris-Descartes INSERM, Radiology, Paris, France;* [2]*Université Paris-Descartes INSERM, Oncology, Paris, France*

Oncologists need fast and reliable tools for evaluating efficacy when treating a patient. New challenges for imaging treatment response are emerging as patients with renal cell carcinoma (RCC) receive targeted therapies stabilizing rather than curing them, or repeated focal therapies inducing changes in lesion morphology but not size.
Current imaging methods of response assessment in RCC will be reviewed, with focus on the prediction of patient outcome, for which no biomarker has been validated to date.
Morphological methods can be based solely on size such as RECIST (Response Evaluation Criteria In Solid Tumours), which is the most often used by convention, though never validated in this setting. Other size-based criteria have been proposed, using a new threshold for response set at −10%, chosen based on prediction of outcome. Other criteria use both size and attenuation to evaluate treatment efficacy, such as Choi, modified Choi [4], SACT (size and attenuation CT), and MASS (morphology, attenuation, size and structure). Contradictory results have been obtained using these, and it remains to be determined in which setting they could be of use.
The potential to predict outcome of functional imaging techniques will also be discussed, focusing on evidence obtained to date. Dynamic contrast-enhanced (DCE) techniques, whether using CT, MRI or ultrasound, are very promising, since they quantify tumor microvessels, and seem the most logical to detect the effect of anti-angiogenic therapies. The level of evidence for each of these will be reviewed, as well as the advantages and disadvantages of each technique. Finally, new radiotracer approaches for positron emission tomography will be reviewed, including (18)F-fluoromisonidazole quantifying hypoxia, and the future potential for the new (124)I-girentuximab antibody which seems specific for clear cell renal carcinoma.
Conflict of interest: *Other substantive relationships: Pfizer Oncology (honoraria): LS Fournier*

Scientific Symposium (Sun, 29 Sep, 14:45−16:45) **Exploiting Defective DNA Damage Response Pathways in Tumours**

165 INVITED
Combining radiation therapy with DNA damage response inhibitors

A.J. Chalmers[1], R. Carruthers[1], S. Ahmed[1]. [1]*University of Glasgow, Institute of Cancer Sciences, Glasgow, United Kingdom*

In the context of radical radiotherapy treatments, radiosensitive normal tissues adjacent to tumours frequently prevent the delivery of a curative dose. Attempts to increase tumour responses by combining radiation with sensitising agents have generally been thwarted by similar sensitising effects upon normal tissues. To improve clinical outcomes, radiosensitisers must be tumour specific.
Radiation kills tumour cells primarily by damaging DNA. Many of the proteins and pathways that protect cells by recognising, signalling and repairing this damage have been characterised, and this knowledge has revealed potential targets for radiosensitising drugs. Furthermore, inherent differences between the DNA damage responses of tumour cells and non-malignant cells raise the exciting prospect of achieving tumour-specific potentiation of radiation therapy by pharmacological inhibition of key DNA damage response proteins.
Poly(ADP-ribose) polymerase (PARP) is a DNA damage sensing protein that plays an important role in the base excision repair (BER) pathway. Highly potent and specific inhibitors of PARP have been developed, and early clinical trials have shown that these agents are extremely well tolerated. PARP inhibitors exert modest radiosensitising effects in cellular systems but show therapeutic potential because these effect are observed only in cells that are actively dividing. Most tumours treated by radiation exhibit rapid cellular proliferation rates, in contrast to a number of critical normal tissues such as brain and spinal cord. Hence PARP inhibitors may act as tumour specific radiosensitisers in selected cancer types, and a number of clinical trials are now underway with the aim of verifying this hypothesis.
Cell cycle checkpoints are frequently defective in cancer, with the majority of malignant cells failing to activate the G1-S checkpoint in response to DNA damage. In simple terms, this increases the relative importance of intra-S and G2-M checkpoint responses in protecting malignant cells from the cytotoxic effects of DNA damaging agents such as ionising radiation. Chk1 plays a key role in mediating these protective responses, and pre-clinical studies have shown that inhibition of Chk1 has enormous potential as a tumour-specific route to radiosensitisation.
Other DNA damage response proteins have been investigated as potential targets and it is likely that a range of novel radiosensitising drugs will enter the clinic in the near future. Patient selection and clinical trial design will be key to realising the potential benefits of this exciting approach. By minimising radiation doses to normal tissues, it is hoped that intensity modulated and image guided radiotherapy techniques will facilitate the use of safe and effective radiation/drug combinations in the treatment of cancer patients.
No conflict of interest.

166 INVITED
New DNA repair targets in cancer treatment

T. Helleday[1]. [1]*Karolinska Institutet, Department of Medical Biochemistry and Biophysics, Stockholm, Sweden*

Mutations in DNA repair are sometimes found in cancer, such as mutations in mismatch repair or *BRCA1* or *BRCA2* genes. We previously

demonstrated that PARP inhibitors can selectively kill BRCA2 defective tumours through synthetic lethality.
Here, I describe efforts into translating the synthetic lethal approach into treatment of cancer in the clinic and the challenges. The overall conclusion is that the synthetic lethal approach offers significant advantages, but no real cancer cures and suffer from similar resistance problems as many other targeted therapies.
The earliest anti-cancer treatments identified, ionzing radiation, nitrogen mustard analogues and nucleosides, all share a common mechanism of action, i.e., causing DNA damage to kill cancer cells. Such DNA damaging treatments sometimes offers complete cancer cures, which are rarely seen by more modern anti-cancer treatments that do not cause DNA damage.
Here, I exemplify how DNA repair inhibitors to a novel DNA repair target, MTH1, can be used in a different context, to overload the high level of DNA damage that is present in cancer. This treatment leads to increased overall DNA damage load in cancer and has a potential to be superior to targeting the cancer genotype. This strategy may offer a treatment for a broad spectrum of cancers, regardless of cancer genotype. This exemplifies a novel concept for targeting the cancer phenotype.
No conflict of interest.

167 INVITED

Targeting oncogene-induced replicative stress for cancer therapy

Ó. Fernández-Capetillo[1]. [1]*Spanish National Cancer Research Centre (CNIO), Genomic Instability Group, Madrid, Spain*

Our laboratory has focused much of its research in trying to understand how cells respond to “replicative stress” (RS), a type of DNA damage which arises unavoidably every time that a cell replicates its DNA, and which is mainly prevented by a RS-Response (RSR) coordinated by ATR and Chk1 kinases.
Given that certain oncogenes can generate substantial amounts of RS, we hypothesized that cells carrying these oncogenes might be “addicted” to a proficient RSR. To explore these ideas, we have generated several cellular, animal and chemical tools for the study of ATR function in mammals. These incluce (1) a cell system in which ATR can be selectively activated at will; (2) mice with a reduced or increased RSR, and (3) chemical inhibitors of ATR. Our early works suggested that ATR inhibitors would indeed be particularly deleterious for tumors with high levels of RS, such as those induced by the Myc oncogene. Our ideas and new results in this area will be presented.
No conflict of interest.

168 INVITED

High throughput screening for genetic determinants of radiosensitivity

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The therapeutic window of radiotherapy could be improved if tumour cells could be selectively rendered more sensitive to radiation. Such a strategy depends upon exploiting tumour specific targets, many of which remain to be identified.
The colony forming assay (CFA) is the ‘gold standard’ method for assessing intrinsic radiosensitivity *in vitro*. We have developed a technique to perform high-throughput CFAs in 96 well plates and have recently completed a siRNA screen of approximately 10,000 genes, of which the 793 gene ‘kinase’ section of the library has been examined in detail.
HeLa cells were reverse transfected with 20nM siRNA (Dharmacon ONTARGET*plus*) in 96 well plates. Seventy-two hours post-transfection, cells were lifted and plated into two sets of quadruplicate repeats. One set of repeats was irradiated at 7 Gy using 6MV photons on a Varian Linear Accelerator, and the other set left unirradiated. Plates were incubated for 7−9 days, stained with crystal violet, and the number of colonies counted. For each gene the fraction of cells that survived 7 Gy irradiation was normalised to the survival of non-targeting (NT) siRNA transfected wells on the corresponding plate. A Z-score was calculated using the median of NT wells across all plates.
The kinase screen was performed on two separate occasions and a ranked-product analysis used to identify the top hits from both runs. On the basis of the top candidate genes identified by the primary kinase screen, an 80 gene siRNA library was produced. This secondary library was then screened on three occasions.
This work identified several genes such as ATM, ATR, DNA-PK and CHEK1, which are known to play key roles in tumour cell radiosensitivity. In addition, we identified a number of novel genes whose depletion induced HeLa radiosensitisation in 6-well plate CFAs. These experiments were repeated with separate siRNA (Ambion) to ensure these findings were not the result of off-target effects. Depletion of these genes appeared to cause radiosensitisation in several other tumour cell lines as well.
We are currently investigating the effects of several of these genes in greater detail. Ongoing work will clarify the effects of gene knockdown on radio- and chemosensitivity in several tumour and normal tissue lines. The mechanism by which this knockdown causes these effects is also being examined.
No conflict of interest.

Scientific Symposium (Sun, 29 Sep, 14:45−16:45)
Outcome Measures in Clinical Trial Design?

169 INVITED

What defines a validated biological biomarker? A pharmacodynamics measurement or a patient-reported or -related outcome?

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The development of novel agents for cancer is heavily dependent on so-called biomarkers. There are many definitions of biomarkers, but in essence they describe a biological effect that reflects the effect of an agent on the human body. The ultimate biomarker in cancer is survival. However, in the favored scenario this is a long-term outcome marker, and particularly in the early stages of drug development cannot rely on long-term outcome measures since it would take too long to the next step of development. Therefor in early clinical trials other markers are used to describe short-term outcomes. Only a few of those can be considered as evidence-based as far as the intention to appropriately reflect longer-term outcomes.
The validation mentioned in the title points to the need to provide evidence as best as we can, of the relationship between the early effect marker and survival, in order to be able to adequately rely on the marker in essential decisions to continue or discontinue drug development in early stages.
Extensive clinical research has provided relevant data on the use of biomarkers such as progression free survival, and on anatomical size change (for instance assessed by RECIST) to reflect a drug effect on tumors. All of these have been tested in large data sets, and can be used in a uniform way all over the world. The more recently used markers reflecting several parameters of pharmacokinetic and/or pharmacodynamic effects are frequently based on well-considered assumptions rather than on evidence of outcome. A nice example is the use of molecular imaging. This is certainly a potential future way forward to assess drug effect and try to predict long-term outcome, but the examples of false-positives are many. A more detailed overview will be provided.
Another way of trying to assess drug effects is to use patient reported outcomes. To some extent safety issues but also Quality of LIfe assessment can be considered as such. While safety has been helpful in identifying doses for further studies or halting drug development in specific cases, these outcomes have not been able to predict more long-term outcomes and a successful further drug development.The challenge we are facing is to limit failures in use of biomarkers while, at the same time, identifying and applying meaningful markers of effect in early stages of development. Recommendations for early clinical trials will be discussed.
No conflict of interest.

170 INVITED

What is the best measure for patient benefit?

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Results from well conducted clinical trials form the evidence base for the practice of cancer medicine. As interventions from trials are moved into practice it is important to consider whether the endpoints of trials measure those outcomes that are important to patients in their decisions about treatment. Research into patient choices of treatment and the information needed to make decisions may provide guidance to investigators on the selection of appropriate endpoints for clinical trials.
In a curative or adjuvant setting, patient preference studies evaluate benefit in terms of overall survival (OS) or probability of cure. Very small gains may be acceptable to patients even when treatment leads to substantial toxicity. Thus the appropriate endpoints for curative intent trials are OS or valid surrogates for OS such as disease free or relapse free survival.
In the non-curative setting, studies of patient preferences have considered information on increments in OS, toxicity, symptom benefit (SB) and/or quality of life (QoL). These studies presume that quality and/or quantity of life are the most relevant endpoints for patients in decision making. However, the last few years have seen an increase in the number of randomized controlled trials (RCTs) of new agents in metastatic solid

tumors that utilize progression free survival (PFS) or rates of non-progression (so-called “clinical benefit rates”) as primary efficacy endpoints. Some trials showing an improvement in PFS, without any corresponding OS increase, have led to approval of new drugs and/or changes in standard of care. The justification of investigators for the choice of PFS as a primary endpoint is varied and has included arguments such as: a) Progression is observed earlier than OS, b) PFS may be a valid surrogate for OS, c) Post-progression therapy may obscure OS gains rendering OS an unreliable measure of treatment effect, and, of particular importance to this presentation, d) that delays in progression are meaningful since they are likely associated with QoL improvement or SB. This assignment of meaning to PFS in terms of its surrogacy for improved SB or QoL is concerning since the definitions of progression used in clinical trials are arbitrary and were created with the intent to guide decisions about biological activity of new drugs in early trials, rather than policy decisions on patient care in metastatic disease. There is little research on whether patients understand the meaning of improved PFS, whether it is associated with SB or QoL improvement, and whether PFS improvement *without* SB or OS prolongation would be viewed as beneficial by patients. Thus research on the SB of PFS gains in a variety of tumour types, as well as patient views on the value of this endpoint is needed.
No conflict of interest.

171 INVITED
Technical pitfalls of measuring biological biomarkers

Abstract not received.

172 INVITED
Impact of biomarkers on the value of crossover designs in cancer clinical trials

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The application of a crossover design in randomized cancer clinical trials has frequently been deplored because of the potentially confounding impact of the crossover treatment on the value of overall survival as a primary study endpoint. However, the use of overall survival as the primary endpoint in the era of molecularly targeted cancer therapeutic agents has become increasingly less attractive for patient populations that may be selected for an individual therapy based on the presence in tumor of well-defined biochemical characteristics. Since the effectiveness of targeted agents, as opposed to traditional cytotoxic drugs, may be equivalent in the first- or second line-therapy setting, ethical as well as scientific considerations for the use of such agents may mandate crossover designs to facilitate accrual or to answer specific molecular questions regarding the efficacy of the treatment in predefined patient populations. In studies where drug selection is driven by the presence in the tumor of a particular mutational spectrum, treatment may be specified for not one but a series of therapeutic agents administered in sequence. Progression-free survival would then be measured after each “crossover” at the time of progression; in this case prior therapies may be expected to have only a modest impact on the utility of the each subsequent agent that has been “matched” to the target based on a different molecular characteristic. Furthermore, if the efficacy of the drug in the particular molecular setting is of sufficient magnitude (whether it involves disease stabilization or an objective response), use of a PFS endpoint will be a sufficient measure of efficacy to move the agent toward regulatory approval whether or not a crossover design is employed. As competence in matching specific therapies to selected patient populations improves, the utility of non-survival trial endpoints will steadily be refined, alleviating concerns about crossover designs that were more pertinent in the era of non-specific cytotoxic treatments.
No conflict of interest.

Scientific Symposium (Sun, 29 Sep, 14:45−16:45) **Minimal Metastatic Pancreatic Cancer: Is it a Surgical Disease?**

173 INVITED
Key criteria in imaging

Abstract not received.

174 INVITED
Neoadjuvant therapy in estimating disease aggressiveness?

Abstract not received.

175 INVITED
Minimal metastatic pancreatic cancer: Is it a surgical disease? The value of synchronous resection

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Pancreatic cancer (PDAC) as the fourth leading cause of cancer-related mortality in the Western countries is found to be irresectable by the time of diagnosis in app. 80−85% of all patients due to locally advanced tumors or metastatic disease. Although improved surgical techniques and neoadjuvant treatment have pushed the borders of resectability in locally advanced tumors during the last decade, there is little evidence on the value of surgical therapy in metastastic disease. The largest series available in the literature report on 22 and 29 PDAC patients that underwent metastases resection either syn- or metachronously. Localization of the metastases (liver, peritoneum, interaortocaval lymph nodes) does not seem to have on influence on surgical morbidity and mortality, in both studies these parameters were similar to standard PDAC resections. Regarding oncological outcome, results show one-year survival rates of 40−60% with median survival times between 8 and 27 months. This seems to be superior in patients with lymph node metastases when compared to outcome in peritoneal or liver metastases resection. However, still liver resection of solitary metastases seems to be beneficial for the patients compared to palliative treatment as median survival can be prolonged from 6 to 12 months in this situation. A metaanalysis published in 2008 with an overall number of 103 patients included the above mentioned studies as well as other publications − mainly case reports and small case series - and led to the conclusion that no general recommendation can be given on the basis of the existing data. As the level of evidence has not substantially increased in the meantime, synchronous resection of minimally metastatic disease in PDAC cannot be recommended as an evidence-based approach. It should be attempted in the setting of accidental intraoperative finding of a solitary metastatic lesion, that can be resected without increasing morbidity. In the metachronous setting, indication for a resection is a highly individual decision for selected patients. However, both approaches may provide benefit for the patient and prolong survival, although adequately powered studies on this topic are still lacking.
No conflict of interest.

176 INVITED
Is local control an issue?

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Pancreatic ductal adenocarcinoma is one of the most aggressive cancers, and complete surgical resection is a requirement for a potential cure. However, only approximately 20 % of the patients are operable at the time of diagnosis. The majority of patients are diagnosed with advanced-stage disease, either metastatic (50%) or locally advanced (30%) cancer. Although palliative chemotherapy is the standard of care for patients with metastatic disease, management of locally advanced or minimal metastatic adenocarcinoma is more controversial. Several treatment options, including extended surgical resection, preoperative chemoradiation with subsequent resection, as well as palliative radiotherapy should be considered. Techniques of stereotactic body radiotherapy (SBRT) with movement compensation strategies have shown low rates of adverse effects with good local control in patients with locally advanced pancreatic cancer. However, there is little evidence available to support treatment options. As valid predictive biomarkers for stratification of therapy are not available today, future trials need to define the role of the different treatment options. Also, more effective systemic agents are needed to maximize radiation sensitisation and to treat upfront microscopic extra-pancreatic disease.
No conflict of interest.

Society Session (Sun, 29 Sep, 14:45−16:45) **European Society of Gynaecological Oncology (ESGO)**

177 INVITED
Role of centralisation in outcome of gynecological cancer treatment and organisation of cancer services

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The management of cancers has seen a very significant change in the course of the past 20 years. Arguably one of the most important

developments of the past 20 years has been the development of multidisciplinary management of cancers and the establishment of tumour boards or multidisciplinary team meetings (MDTs) as the standard of care. Previously tumour boards tended to be selectively deployed in some of the specialist cancer centres but these have been rolled out and are now in many countries deployed for the management of all cancers. This overcomes the problems of clinicians working in isolation or maverick clinicians not working to nationally accepted standards of care.
The development of National guidelines by Ministries of Health, professional bodies and scientific societies and organisations has complemented this approach to care. In Gynaecological cancers, cervix and vulval cancers have tended to be managed centrally but for endometrial and ovarian cancers there has been slower adoption of centralised surgical care. radiotherapy services have traditionally been centralised. The delivery of chemotherapy has been more flexible and maybe provided by medical, clinical or gynaecological oncologists according to local prctices. There has been increasing confirmation from a variety of tumour types to show that the use of multidisciplinary meetings improves the quality of care. This includes the involvement of specialist imaging experts who will review the images prior to decisions being made on surgery, the use of specialist histopathologists who reduce the likelihood of misdiagnosis and of course the opportunity for specialist gynaecological surgeons and radiation and medical oncologists to discuss the optimal treatment for each individual case.
There is increasing evidence that the issues of sub-specialisation and greater experience will improve outcome. Evidence to show that the use of tumour boards/NDTs has actually improved outcome is quite difficult but in Scotland (UK) the setting up of managed clinical networks, a vital component of which was the establishment of tumour boards, has indeed shown increased survival and outcome. Part of this may be due to improved staging and accuracy which may lead to an element of stage migration. Nevertheless it does mean that patients have a better chance of being offered the right care. Good examples of this are illustrated in the management of ovarian cancer where the use of the risk of malignancy index and the tumour board discussion will ensure that the patient gets the optimal surgical approach. Patients can now be selected for referral to the specialist gynae-oncology units to undergo more aggressive surgery which has a greater chance of leading to optimal (maximal) debulking. Patients and their families should now feel more confident that their case is being managed in the optimal way. For rare and uncommon cancers there is a stronger feeling that centralised care together with shared management with local clinicians offers a practical way of managing rarer cancers.
No conflict of interest.

178 INVITED

Lifestyle risk factors and prevention of gynaecological cancer

A.J. Nordin[1]. [1]*Queen Elizabeth The Queen Mother Hospital, East Kent Gynaecological Oncology Centre, Margate Kent, United Kingdom*

Whilst we continue to progress the diagnosis & treatment of gynaecological malignancies, there is far greater potential for reducing the mortality through of cancer prevention strategies. Interventions such as screening & vaccination programmes are making a substantial impact, but we have largely ignored the potential for lifestyle modification to lower the risk of gynaecological cancers.
Obesity now contributes as greatly as smoking to cancer-related deaths worldwide. It is estimated that 36,000 cancer cases could be prevented annually by halving the rate of obesity & overweight people in Europe. The risk of endometrial cancer (OR 4.5−6.2), ovarian cancer (OR 1.4), post-menopausal breast cancer (OR 1.3) & adenocarcinoma of the cervix (OR 2.1) are increased with obesity. Most classifications indicate a BMI >25 as overweight, >30 as obesity, and >40 as morbid obesity. In the UKGOSOC audit of 2948 consecutive gynae oncology surgeries, 38% of women had BMI >30 and 9% had BMI >40. The obesity pandemic is responsible for an increasing incidence of endometrial cancer in the developed world. In the UK, the incidence of endometrial cancer has risen from 13.8/100,000 women in 1997 to 19.3 in 2010.
Endometrial cancer risk relates to adult obesity & perimenopausal weight gain, and weight reduction may decrease the risk. Additionally, physical activity protects against ovarian, endometrial and postmenopausal breast cancer, independent of BMI. Diets featuring fruit, vegetables & antioxidants reduce risk whereas high animal fat & energy intakes increase risk. A high glycaemic load diet increases ovarian cancer risk, independent of BMI.
Alcohol intake increases the risk of breast cancer (accounting for 4% of cases) & mucinous ovarian cancer. The increased risk of cervical cancer (OR 2.9) & vaginal cancer (OR 4.6) may reflect associated lifestyle factors (eg promiscuity, smoking, combined oral contraception use).
Exposure to and persistent infection by oncogenic HPV (particularly HPV 16 & 18) is the major risk factor for cervix and vaginal cancer, and 1 in 3 cancers of the vulva. Risk factors include the number of sexual partners, frequency of vaginal intercourse, behaviour of sexual partners, age at first intercourse, multiparity, Chlamydia infection & divorce. Smoking increases the risk of squamous cell carcinoma (OR 2.2). Tobacco carcinogens in high concentrations in cervical mucous promote HPV infection and predispose to carcinogenesis. Smoking also increases the risk of ovarian cancer, particularly mucinous tumours.
Reproductive and contraception behaviours influence the risk of gynaecological malignancies. The combined oral contraceptive has a substantial and long-lasting reduction in the risk of ovarian and endometrial cancer, but may marginally increase the risk of breast cancer during use. Long-term HRT increases breast cancer risk by a similar magnitude to that of a late menopause. Childbearing protects against ovarian, endometrial and breast cancer but increases the risk of cervical cancer.
No conflict of interest.

179 INVITED

Cancer in pregnancy

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Pregnancy associated cancer is defined as cancer diagnosed during pregnancy or within one year after delivery. Invasive primary breast cancer (BCP) is the most common encountered cancer during pregnancy (Amant et al., 2012a).
BCP typically presents as a painless lump palpated by the woman. Breast ultrasonography is safe and differentiates solid and cystic breast masses. The standard examination to obtain a histological diagnosis is a core biopsy under local anaesthesia which can be performed safely during pregnancy. Overall, staging examinations should be performed as far as they alter clinical management and magnetic resonance imaging in combination with sonography.
In general, surgery can be performed safely during any stage of pregnancy. Both mastectomy and breast conserving surgery with axillary or sentinel lymph node dissection can be carried out safely during pregnancy and should follow the same guidelines as for non-pregnant women. Pelvic surgery, either open or laparoscopic, is possible and safe in expert hands during pregnancy.
Standard regimens of chemotherapy can be administered from 14 weeks gestational age onwards. Treatment with trastuzumab in HER2-positive tumours in pregnant women cannot currently be recommended. For hematologic and gynecologic cancers, standard treatment including paclitaxel-carboplatin, ABVD and CHOP are also possible. Despite the dilution of chemotherapy during pregnancy, the data do not show a worse outcome in pregnant women who receive chemotherapy. Therefore, we advocate the same dosages of chemotherapy based on the actual weight and height during pregnancy.
Although there are no guidelines for obstetricians to monitor pregnant patients treated for breast cancer, some recommendations have been suggested (Amant et al., 2012a). It is advisable to perform the prenatal care of women in a high-risk obstetric unit. The timing of delivery should be balanced according to the oncological treatment schedule and the maturation of the foetus. As in non cancer patients, term delivery (>37 weeks) should be aimed for (Van Calsteren et al, 2010; Loibl et al, 2012). Early labour induction results in prematurity and low birth weight that have been identified as contributing factors in the cognitive and emotional development of children (Lohaugen et al., 2010; Tamaru et al., 2011). The mode of delivery should be determined based on obstetrical indications. Only for cervical and vulvar cancer, a caesarean section is advocated.
Based on recent data it appears that fetal exposure to chemotherapy is not associated with increased morbidity at the level of the central nervous system, cardiac, and auditory functions, as well as general health and growth. Importantly, prematurity was frequently encountered, and was associated with impairment in cognitive development (Amant et al., 2012b). Therefore, we believe that perinatologists should be part of the interdisciplinary discussion and that iatrogenic preterm delivery should be avoided as much as possible.
No conflict of interest.

180 INVITED

Psycho-oncology in gynaecological cancer

V. Kesic[1]. [1]*Clinical Center of Serbia, Department of Obstetrics and Gynecology, Belgrade, Serbia*

Treatment of cancer is sometimes prolonged and difficult, however in large number of cases it is also highly successful. Extensive screening programs and early diagnosis of the malignant diseases have contributed to even better survival owing to which, several million of people worldwide are cured or live with the malignant diseases for years.
Gynecological cancer is particularly delicate type of the disease, influencing not only physical capacities, psychological and social life of women, but also

her future reproductive capacities. Therefore, psychological aspect of care of patients with gynecologic cancer is particularly important. It is estimated that one fourth of the patients diagnosed with malignant diseases are also experiencing some form of psychological disorder. Recognition and help in cases of anxiety and depression, which are naturally developing in patients affected with malignant diseases are important parts of treatment aimed at improvement of their quality of life.
Psycho-oncology is a new sub-specialty concerned with psychological responses of patients and their family members to cancer, as well as the factors that may influence the disease. It is dealing with understanding and treatment of psychosocial, emotional, spiritual, existential and practical aspects of the malignant diseases, as well as the aspects related to quality of life during all stages of the disease and survival. The primary objective of the psycho-oncology is to offer an integral approach to all cancer patients. This is an approach focused on the individual as a whole, which addresses a range of highly diverse needs.
Collaboration of different specialities, such as surgery, gynecology, medical oncology, radiotherapy, psychiatry, psychology, palliative management, rehabilitation medicine, epidemiology, immunology, ethics and research is essential in achieving the optimal care for gynecologic cancer patient.
Complete information on all the aspects of the disease, both medical and psycho.sexual may significantly contribute to prevention or alleviation of the psychological problems in the affected women and their family members. Assistance to patients in accepting treatment necessitates absolute sincerity, the most accurate medical information and detailed advice. Effective communication, which includes active listening, expression of empathy, detection and responding to emotional signs and sensitivity toward the experience of the patient affected with a malignant disease lead to improvement of psychological adjustment, compliance with the treatment plan and satisfaction with care. Compliance with certain treatment option and careful monitoring are basic requirements for successful treatment.
No conflict of interest.

181 INVITED
ESGO/ENGOT scientific portfolio

Abstract not received.

Scientific Symposium (Sun, 29 Sep, 14:45−16:45)
Optimal use of Targeted Kinase Inhibitors (TKIs)

182 INVITED
Combination therapy: Is more better?

A.K. Larsen[1], V. Poindessous[1], D. Ouaret[1], A. Bouygues[1], M. Ayadi[1], P. Mésange[1]. [1]*Saint-Antoine Research Center INSERM U938 and Université Pierre & Marie Curie, Cancer Biology & Therapeutics, Paris 12, France*

The development of novel anticancer agents targeting oncogenic signaling pathways represents a major conceptual break-through. However, in many cases the clinical outcome has been less than expected, in part due to the existence of downstream mutations, unsuspected feed-back loops and signaling pathway cross-talk. As a result, much effort is currently focused on targeting of several signaling pathways at the same time or, alternatively, on targeting different steps of the same signaling pathway. Targeted agents have often been added directly to established cytotoxic agents without dose adjustment, sometimes resulting in excessive toxic side effects. One reason for this is that exposure to classical DNA-targeted agents triggers a range of signaling cascades associated with cell cycle control, DNA repair and cellular survival which may interfere with the targeted agents. In this presentation we will discuss the mechanistic basis for combining selected targeted agents with emphasis on EGFR and VEGF(R) pathway cross-talk.
Conflict of interest: *Advisory board: Daiichi. Corporate-sponsored research: Roche, Boehringer Ingelheim. Other substantive relationships: Sanofi-Aventis, educational presentations*

183 INVITED
Role of genomic sequencing in therapeutic decision making with tyrosine kinase inhibitors

E. Voest[1]. [1]*University Medical Center Utrecht, Medical Oncology, Utrecht, Netherlands*

Detailed information on the genetic make up of tumors holds the promise to better select patients for specific treatments. Examples such as trastuzumab for Her2 amplifications in breast cancer and imatinib for BCR-ABL translocations in leukemia have clearly demonstrated the validity of the concept. Further proof came from pivotal studies with drugs such as vemurafenib and crizotinib targeting V600E mutations in melanoma en ALK-EML4 translocations in lung cancer. Unfortunately, the common denominator in these studies is that the spectacular treatment successes are temporary because of the emergence of resistance to these drugs.
With the advances in sequencing technologies it is now possible to generate detailed information on the genomic aberrations in a tumor. Single gene analysis (e.g. BRAF, KRAS) will be replaced by whole exome or even whole genome in the foreseen future. This more complete genetic overview of a tumor allows analysis at the level of pathways rather than at the level of single genes. For example, we could not find a correlation between chemotherapy outcome and specific actionable mutations in the PI3K gene in breast cancer patients. In contrast, there was a strong correlation with response to chemotherapy when mutations in the PI3K pathway used.
These findings shed light on the use of various genetic abnormalities. Oncogene addiction makes tumors vulnerable to a specific targeted treatment, testing for these genes will define the population of patients most likely to respond. However, some forms of oncogene addiction may also depend on the tissue background. Melanoma patients with BRAF mutations respond far better than patients with colorectal cancer with the same BRAF mutation.
Tumor heterogeneity is an important dimension of tumor growth and during treatment clonal outgrowth of resistant populations is likely to occur. (Ultra)Deep sequencing may identify these clones in an early stage and allow an anticipatory treatment approach. Dynamic changes as a result of treatment may activate certain survival pathways to compensate for the The current dogma is that it will be easier to find a predictive genetic profile for drugs with a specific mechanism of action (such as vemurafenib) than for broad spectrum kinase inhibitors (such as sunitinib). However, given the correlation between response to chemotherapy and the PI3K pathways this may be a misconception and these studies should therefore be performed.
In summary, we are entering an era in which large scale genetic testing of tumor and germ line DNA will become part of our regular diagnostic work up of cancer patients. The sequencing itself will not be a major bottle neck. High quality interpretation of the data by bioinformaticians will be key in a successful implementation of DNA guided decision making. However, to define and refine these genetic profiles we need high quality drug-based databases in which clinical outcome is linked with genetic data. For that collaboration is essential.
No conflict of interest.

184 INVITED
The concept of basket trials

J. Baselga[1]. [1]*Memorial Sloan Kettering Cancer Center, Department of Oncology, New York, USA*

Results from the world-wide sequencing effort have revealed a number of specific genomic mutations or molecular alterations are both infrequent in a given tumor type while may be shared by more than one tumor type. In order to methodically characterize whether they are therapeutically actionable in a context dependent fashion we have launched a series of "basket" studies with tyrosine kinase inhibitors. This new type of genotype-focus studies is particularly useful when the cancer type and the mutations are rare. Ideally, these studies enrolled 10−15 subjects per tumor type and also include a miscellaneous category for patients with rare types of cancer in which the mutation of interest was not previously known to exist.
We have launched a number of basket trials including in patients BRAF V600E, PI3KCA, erbB2 mutations, and FGFR family amplifications or other activating alterations. We will present data with the logistical aspects of such trials as well as emerging results from some of these trials.
No conflict of interest information specified.

185 INVITED
Clinical development of TKIs: Learning from our mistakes

S. Sleijfer[1]. [1]*Erasmus University Medical Center, Department of Medical Oncology, Rotterdam, Netherlands*

In recent years several novel targeted kinase inhibitors (TKIs) have rapidly been introduced into the oncology practice following successful studies. In contrast, many other TKIs failed, sometimes already at an early clinical trial stage, others only after completion of large and expensive phase III studies. From both successful and unsuccessful drug development tracks, important lessons for designing new studies can be learned.
Most of the successful TKIs concerned drugs that directly target and inhibit the product of a mutated gene driving a certain subgroup of malignancies. As the mechanism of action of these drugs was known, and therefore the patient population in which these TKIs were likely to exhibit anti-tumor activity could be identified, these TKIs were tested in specifically selected patient groups from start of their clinical development. Successful couples of such drugs and diseases include imatinib in GIST, vemurafenib

in *BRAF*V600E mutated melanoma, and crizotinib in non-small cell lung carcinoma (NSCLC) harboring an *EML-ALK* fusion gene.
An important feature of drugs that ultimately failed or were only approved after a cumbersome and expensive road to registration is that the mechanism of action was unknown prior to starting clinical trials. As a result, predictive profiles were not established, patients likely to respond could not be identified beforehand, and clinical studies were performed in unselected patient populations. Recent examples are IGF-1R antagonists and mTOR inhibitors.
Most important lesson from these studies is the need to reveal the exact mechanism of action of the compound under study and to identify predictive markers before initiating large clinical trials. If unknown, it is questionable whether such drugs should enter a drug development track at all given the valuable resources needed for such trials and the enormous number of alternative drugs that need further testing. If a compound is taken forward into a drug development track despite the fact that no predictive profiles are known, some adaptive designs are possible. In such circumstances, collection of biomaterial is essential to reveal predictive profiles in retrospect such as was done with EGFR-TKIs in NSCLC.
In summary, identification of predictive profiles and robust assays to select the appropriate patient group is essential before starting novel anti-tumor drugs.
No conflict of interest.

Society Session (Sun, 29 Sep, 14:45−16:45)
European Association of Neuro-Oncology (EANO)

186 INVITED
IDH1 and 2 mutations in gliomas from biology to treatment

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IDH1 gene encodes the cytoplasmic isoform of isocitrate dehydrogenase, and is mutated at Arg132 (mostly Arg132His) in 40% of gliomas (5−8% of primary glioblastoma, vs 75% of grade II and 50% of grade III gliomas). Mutations of the analogous amino acid residue (Arg172) of the mitochondrial isoform *IDH2* are less frequent. *IDH1*/*IDH2* mutated tumors have a better outcome, whatever grade considered. Whether *IDH1*/*IDH2* mutation can predict response to treatment in gliomas needs to be further investigated.
The mutation causes the loss of the isocitrate dehydrogenase function and the gain of an α-ketoglutarate reductase function leading to the cellular accumulation of D-2-hydroxyglutarate (D-2HG) that represents a diagnostic marker (this change is almost specific for gliomas) and prognostic (mutated gliomas have longer survival) of interest. Interestingly, D-2HG can be detected using proton magnetic resonance spectroscopy.
The accumulation of D-2HG, which acts mostly as an inhibitor of alpha-ketoglutarate dependent dioxygenase, results in a wide range of cellular changes including profound modulation of epigenome, with CpG island hypermethylation and histone methylation, and inhibition of terminal differentiation. Strikingly *IDH1*/*IDH2* mutations is a constant feature in 1p19q codeleted gliomas, and suggest a critical role in oligodendrogliomagenesis (in association with *hTERT* and *CIC* mutation) that need to be elucidated.
The mutated neoenzyme is an attractive target for futures therapies: specific inhibitors for IDH1 and IDH2 have been shown to reverse the epigenetic changes induced by the mutation, and to inhibit the growth of the mutated, but not wild type tumors on xenograft models, opening new perspective for glioma treatments.
No conflict of interest.

187 INVITED
Neuroimaging after antiangiogenic agents: What have we learnt?

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High response rates (RR) in two uncontrolled phase II studies were the basis for approval of the vascular endothelial growth factor (VEGF) antibody bevacizumab (BEV) for patients with recurrent glioblastoma in the USA. The acceptance of RR as a denominator for clinical relevance poses increasing weight on magnetic resonance imaging (MRI) as surrogate marker for treatment efficacy. As the accepted mode of action of anti-VEGF/VEGF receptor (VEGFR) compounds includes stabilization of the blood–brain-barrier, it may well be that some responses are in fact due to a decrease contrast enhancement and edema without real antitumor effect. In addition to this phenomenon of pseudoresponse induced by BEV and other agents, there is a lot of discussion on the radiochemotherapy-associated MRI-effect called pseudoprogression. Pseudoprogression is increasing enhancement in the T1-wheighted MRI in the irradiation volume, mainly with no or little clinical symptoms and a resolution over time without changing management. It may prevent to call the correct time point of progression and also changing management in patients that may not be really progressive.
Two further challenges for modern neuroimaging are: the assessment of non-enhancing T2/FLAIR abnormalities, which may reflect invasive tumor and contribute to (neurocognitive) morbidity. Secondly, imaging should be developed to help delineating patients getting benefit from antiglioma therapies, including but not limited to BEV.
A series of well-designed, though retrospective translational imaging studies and new phase III data assist in answering or at least following on these questions. These data suggest that RR cannot be taken as a surrogate for progression-free (PFS) or even overall survival (OS). Further, the data suggest that the application of strict imaging algorithms, but also BEV are reducing the number of pseudoprogressing patients. Further, T2/FLAIR progression remains complicated to quantify, though specific properties of BEV to induce diffuse infiltrative tumors are not demonstrated by case-control series nor the data of the AVAglio trial.
Clearly, the biggest challenge is the provision of imaging parameters helping to predefine patients with likely benefit from a given treatment, specifically antiangiogenic therapy. The development of MRI imaging as a marker for treatment decisions would be a major step ahead in neurooncology.
Conflict of interest: *Advisory board: Roche/Genentech, MSD. Corporate-sponsored research: Boehringer Ingelheim MSD, Eli Lilly*

188 INVITED
Amino acid PET for gliomas

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The signal of amino acid PET which visualizes gliomas is governed by radiotracer influx across the blood–brain barrier (BBB). In tumors with intact BBB (low-grade gliomas) facilitated transport accounts for tracer uptake which is mediated by the L-amino acid transporter 1 (LAT-1). In tumors with BBB breakdown (malignant gliomas) also passive diffusion contributes to tracer uptake which results in 'BBB images' resembling the pattern of contrast enhancement on MRI. In tumors with intact BBB the PET signal is composed by the density and activity of LAT-1, and by the density of capillaries which exhibit LAT-1. Therefore amino acid PET in these tumors can be considered a technique to explore microvessel density.
^{11}C-methyl-methionine (MET) and ^{18}F-fluoro-ethyl-tyrosine (FET) are the most common used amino acids for clinical PET examinations. The intratumoral accumulation of MET/FET can be quantified as the ratio of tumor-to-brain uptake. Uptake ratios for MET range in between 1.0−2.4 for low-grade gliomas, and 2.0−3.8 for malignant gliomas. Of note MET uptake is also increased in the infiltration area of malignant gliomas. According to the specificity of PET images in tumors without BBB breakdown MET/FET are well suited to characterize lesions which do not enhance contrast medium on MRI. Apart from information on tumor grade and prognosis, MET/FET PET can be applied to characterize lesions suspective for low-grade glioma if they are not amenable to resection. In this setting the metabolically most active region should be selected for diagnostic biopsy as this region most likely represents the correct tumor grade. In addition MET/FET can be used for early response assessment in low-grade gliomas during chemotherapy. Metabolic (PET) may precede anatomical (MRI) responses by several months. This allows to individually tailor therapy of these tumors. MET/FET has been also applied to differentiate true progression of malignant gliomas from pseudoprogression and radiation necrosis. However, due to BBB breakdown in these conditions the interpretation of PET images remains a matter of debate.
As a perspective amino acid PET may be used to investigate the behaviour of tumor compartments which do not enhance contrast medium on MRI, e.g. during anti-angiogenic therapy of malignant gliomas. Combined with MRI measures of cellularity (diffusion restriction) amino acid PET should enhance our knowledge on response and resistance to anti-angiogenic agents.
No conflict of interest.

189 INVITED
Chemotherapy induced neuropathies − new frontiers

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Modern cancer therapy often involves treatment with chemotherapy. Several drugs as platinum compounds, taxanes, vinka alkaloids, epithelons,

thalidomide and bortezomib cause predominately sensory neuropathies, which are often dose dependent. In addition to the common pattern of cumulative toxicity, also in oxaliplatin and taxanes also acute effects occur, coasting is a featture of platinum drugs and increasingly long term effects in long time survivors are gaining importance.
The mechanisms of the individual drugs toxicity vary and damage to dorsal root ganglions, axons and small fibers has been identified. In addition in acute toxicity damage of ion channels at the neuromuscular transmission site occur. At present prophylactic treatment for CIPN, except suppression of acute oxaliplatin toxicity has not been successful.
CIPN may be overlooked or can be underestimated in clinical setting. The diagnosis is based on toxicity scales, electrophysiology and increasingly patient based assessment of well being and quality of life.
Although the pattern and cumulative toxicity causing CIPN has been identified for most drugs, clinical experience teaches, that patients are subject to individual different susceptibility. Some factors as preexisting neuropathy, pretreatment with other toxic drugs, and drug combinations, sequences of different lines of chemotherapy have been identified, but other factors as possible genetic dispositions are subject to research, as well in acute as in cumulative neurotoxicity.
The term late toxicity defines persistence of neuropathic syndromes far beyond the termination of cancer therapy for several years. The increasing number of long term survivors has revealed that not all CIPNs are reversible. Reports have been published on platinum compounds, taxanes, vinka alkalods and other drugs or combinations. The symptoms can be persistence of neuropathy, neuropathic pain syndromes. unpleasant sensations, Raynaude's syndrome and muscle cramps.
Strategies for the identification of persons at risk for CIPN, preventive strategies, and more effective symptomatic treatment will be needed to lower the burden of disease.
No conflict of interest.

Scientific Symposium (Sun, 29 Sep, 14:45−16:45)
End of Life Care

190 INVITED

What makes the last few months of treatment so expensive?

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Background: We celebrate that more people are reaching the age of peak cancer incidence and surviving cancer, but must determine how to pay for cancer care as well as other chronic and expensive conditions. The last months of life are becoming increasing more expensive due to more resource use including chemotherapy, supportive care, and diagnostic testing near the end of life; more frequent and resource-heavy hospitalizations with more intensive care unit use; increasing patient and societal expectations; failure to elicit choices about advance care planning; poor communication and planning for death; and inability of most health systems and practitioners to monitor and change their performance.
Material and Methods: Literature review and policy analysis.
Results: The cost of cancer treatment is expected to rise at least 2 % annually in most countries and could be substantially more. Some programs that have shown benefit in maintaining the general quality of care while restraining costs include the following: 1. Evidence-based pathways such as those used by U. S. Oncology; 2. Elicitation of advance directives with better planning for the last months of life, including death, to avoid the hospital; 3. Cost control by limitation of prices (NICE; Veterans Administration Medical Centers); 4. Integration of palliative care earlier, with transition to hospice when appropriate; 5. Regionalization and specialization of services, such as specialty pharmacies for expensive oral drugs; 6. Better communication about medically appropriate treatments with decision aids; 7. Better communication in the community including traditional (Gunderson, Wisconsin) and "cloud" solutions (NHS Coordinate my Care); and 8. Better information about actual patterns of care with real-time feedback to practitioners. There is no simple single solution. All alternatives involve changing patterns of care and expectations, and all alternatives involve someone not getting therapy that might be perceived to be useful.
Conclusions: Cancer care is increasingly complex and costly, as are most chronic diseases. Bending the cost curve downwards while maintaining quality will demand more efficient care, reducing care that is expensive but of little "value", putting downward pressure on prices, and monitoring practice in real-time.
No conflict of interest.

191 INVITED

To treat or not to treat at end of life

S. Kaasa[1], M.R. Grønberg[1]. *[1]Norwegian University of Science and Technology, European Palliative Research Centre (PRC), Trondheim, Norway*

To treat in this context is understood as tumor directed treatment, i.e. chemo- and/or radiotherapy. Symptomatic treatment for pain, dyspnea, anxiety, depression etc. should be offered patients throughout the "cancer journey" − from primary diagnosis until end-of-life care − along with palliative care in general.
Tumor directed treatment is basically offered to the patients with the aims to cure, to prolong life, to prevent and/or treat symptoms. If such treatment is offered to patients having short life expectancy aiming at preventing or relieving symptoms, and maybe marginally prolonging life, the patients' burden needs to be carefully evaluated against the treatment benefit.
Studies have demonstrated that 15−45% of the cancer patients received chemotherapy the last 30 days of life − this proportion appears to increase − while 8−19% received radiotherapy the last 30 days of life. It may be argued that chemotherapy and radiotherapy offered to patients at this stage of the disease is futile; maybe with exception for one fraction radiotherapy for painful bone metastasis.
It is documented in clinical studies that a palliative care program offered to the patients early in their disease trajectory as well as information about palliative care may lead to reduced use of chemotherapy, less anxiety and improved survival at end-of-life. Studies also show that patients prefer to die at home; however, extensive use of tumor directed treatment may result in less patients dying at home.
There is a need for increased awareness of indications and timing of offering tumor directed treatment to palliative care cancer patients.
No conflict of interest.

192 INVITED

Psychological and social factors in palliative care

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Psychological and social factors are important outcomes in palliative care, although research in this domain was limited by significant methodological and practical obstacles, including the lack of relevant and validated outcome measures. Further, most psychosocial research in palliative care was conducted near the end of life, even though symptom burden and psychological distress is considerable much earlier in the course of advanced and terminal disease. The creation and validation of measures that assess relevant psychosocial outcomes in palliative care has significantly increased the rigour of clinical studies in this field. These measures have been critical to evaluate the impact of novel psychosocial interventions that have been developed for this population. The preliminary findings from clinical trials of such interventions suggests that they have the potential to diminish psychological distress and to protect psychological well-being prior to and near the end of life. Although many challenges remain in the conduct of psychosocial research in patients with advanced disease, an evidence base to guide psychosocial interventions in palliative care has now emerged.
No conflict of interest.

193 INVITED

Symptom control at the end of life: What about palliative sedation?

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Palliative sedation (PS) is now considered a normal medical procedure and a required therapeutic intervention at the end of life, in selected cases. The experience on palliative sedation is now well established and numerous case series were published which clarified its indications, clinical characteristics and risks. The widest experience in the use of palliative sedation regards the control of untreatable symptoms in the terminal phases of cancer among which the most prevalent are dyspnoea and delirium. Other less frequent conditions, requiring sedation in the terminal phase of cancer, are hemorrhage and vomiting due to GI obstruction; pain alone is hardly ever an indication to PS. When PS is indicated because of the onset of untreatable symptoms, which are the immediate consequence of life threatening conditions, its prompt use can be a priority to allow a confortable death. In these cases PS is usually a time limited procedure, seldom lasting more than 24−48 hours and often less before death. In case of terminal delirium the timing of sedation tends to be longer. More rarely psychological distress or unbearable psychological suffering can be addressed by sedation but these cases require very careful assessment and pose more complex ethical problems. Available guidelines can be used to frame the clinical and ethical principles informing this practice,

including pharmacological protocols and clinical monitoring. The European Association for Palliative Care recommends that sedation is considered for symptoms that are judged untreatable notwithstanding the provision of appropriate specialized palliative care interventions. Usually specialized palliative care input should be sought to appropriately perform PS. Patient and family comunication and team approach are also required. Data from controlled trials and prospective case series shows that palliative sedation, in expert hands, bears low risk of complications and that patients undergoing PS do not have a shorter survival than patients who do not need PS at the end of life.
PS aims at the control of symptoms and not at hastening death; this distinction in the intention qualifies PS as a medical procedure together with the clinical outcome that is a reduced level of consciousness, pharmacological therapy and monitoring requirements and their careful documentation. PS is now an integral part of the armamentarium of palliative care discipline and the lack of appropriate use when indicated should be viewed as an insufficient level of care if not malpractice.
No conflict of interest.

Scientific Symposium (Sun, 29 Sep, 14:45−16:45)
Sequencing Technologies

194 INVITED

Next generation sequencing: Lessons from an ICGC project

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The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC) have among their aims the elucidation of the genomic, transcriptional and epigenetic architecture of cancers, and next-generation sequencing provides one approach to this. In this talk I will describe some of the bioinformatic, computational and statistical issues that arise in such projects. I will touch upon the identification of somatic aberrations, inference about clonal substructure, and tumour heterogeneity. Data from our ICGC Esophageal Adenocarcinoma project will be used to illustrate the methods.
No conflict of interest.

195 INVITED

Novel technologies for deep genome sequencing − target enrichment

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Next Generation Sequencing has the power to exhaustively profile and monitor the transcriptome, methylome or genome of any biological system, including the evolution of tumour progression. Targeted deep resequencing of key components of the genome can help provide enough depth to identify low copy number clones and follow their evolution. The Fluidigm Access Array system enables high throughput PCR amplification of up to 480 target regions, or around 60 target genes based on median exon count. Coupling this with Illumina MiSeq Next Generation Sequencing enables sequencing of up to 300 patients to 100X coverage. We review our first year's experience with this approach on both human and non-human samples. We discuss the advantages and disadvantages in light of our experience with other sequence enrichment strategies, e.g Sure Select and Haloplex.
No conflict of interest.

196 INVITED

The application of massively parallel sequencing technologies in cancer diagnostics

Abstract not received.

197 INVITED

Bioinformatics in genomics

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Deep sequencing is now rapidly being applied within many biomedical domains, presenting challenges at many levels to harvest the analytical precision and genome scale depth inherent in the technology. The large-scale generic mapping of genomic features at many levels in the chromosomal organization enables novel computational approaches. The emerging charting of the three-dimensional organization of the DNA in the nucleus provides even further unprecedented opportunities to understand not least complex diseases such as cancer, provided available analytical strategies of sufficient vigor and flexibility.
The Genomic HyperBrowser framework (http://hyperbrowser.uio.no/) will be presented as one realization of a statistical genomics system to meet the challenge. It embodies rich and flexible statistical testing on a genome-wide scale, permitting rapid solutions in both interactive tabular formats and visualizations, for a multitude of biological examinations.
Methods for analysis of genomic information in a three-dimensional setting have also been developed within the same framework, again providing robust procedures for a number of 3D related questions.
We leverage such solutions in the quest to ascribe importance to the multitude of changes to DNA and chromatin as observed in cancer, not least in the context of personalized medicine.
Conflict of interest: *Ownership: E.H. is a shareholder in PubGene.Inc. Board of directors: E.H. is a board member in PubGene.Inc.*

Society Session (Sun, 29 Sep, 14:45−16:45)
European Association for Cancer Research (EACR) − microRNAs in Cancer

198 INVITED

Long noncoding RNAs required for p53 tumor suppressor activity

R. Agami[1]. [1]*The Netherlands Cancer Institute, Department of Oncology, Amsterdam, Netherlands*

p53 is a transcription factor and tumor suppressor that is very frequently mutated in cancer. Chromatin binding profiles reveal specific interactions of p53 with promoter regions of nearby genes, within genes, but also with remote regions located more than 50 kbps away from any known gene. Interestingly, many of these remote regions possess evolutionary highly conserved p53-binding sites and all known hallmarks of enhancer regions, as well as binding of RNAPII. While p53 binding to promoter regions locally activates expression of one gene, its binding in the context of enhancers may affect several distant genes in tissue dependent manners. Interestingly, several of these p53-enhancer domains produce, in a p53-dependent manner, a unique type of non-coding RNAs termed enhancer RNAs (eRNAs). We show that p53-dependent eRNA production is required for efficient transcriptional enhancement of interacting target genes and induction of a p53-dependent cell-cycle arrest.
No conflict of interest.

199 INVITED

MicroRNAs, EMT and cancer stem cells

T. Brabletz[1]. [1]*Universitätsklinikum Freiburg, Freiburg, Germany*

We have shown, that in particular tumor cells at the invasive front of common adenocarcinomas undergo an epithelial–mesenchymal transition (EMT) and aberrantly express EMT-associated transcriptional repressors, like ZEB1. The amount of such cells strongly correlates with metastasis formation and poor clinical outcome. Strikingly, metastases show again a re-differentiated phenotype, indicating a mesenchymal-epithelial re-transition (MET) and a support a regulatory role of the tumor environment for malignant tumor progression.
We described that the EMT-activator ZEB1 is a crucial promoter of metastasis and demonstrated that ZEB1 inhibits expression of cell polarity factors and the microRNA-200 family, whose members are strong inducers of epithelial differentiation. These results indicate that ZEB1 triggers a microRNA-mediated feedback-loop, which stabilizes EMT and promotes dissemination of cancer cells. Moreover we detected that in addition ZEB1 is necessary for the tumor initiating capacity of pancreatic, breast and colorectal cancer cells. ZEB1 inhibits expression of miR-200c, miR-203 and miR-183, which cooperate to suppress expression of stem cell factors, as demonstrated for the polycomb repressor Bmi1.
We propose that ZEB1 links EMT-activation and stemness-maintenance by suppressing stemness-inhibiting microRNAs and thereby is a promoter of mobile, migrating cancer stem cells. Notably, these cells also acquired a drug-resistance phenotype. Thus, targeting the ZEB1 − miR-200 feedback loop might be a promising treatment option for fatal tumors, such as pancreatic cancer.
No conflict of interest.

200 INVITED

Role of oxidative stress in tumor development and response to treatment

F. Mechta-Grigoriou[1]. [1]*Institut Curie, Paris, France*

The discovery of free radicals -highly unstable molecules present at low levels in our body- has greatly modified our view of certain biological processes. Free radicals are constantly produced in the body by metabolism and cellular respiration; but this physiological production is controlled by efficient “antioxidant” defence systems. Under certain circumstances, imbalance arises, either because of antioxidant deficiency or overproduction of radicals. The excess of derivatives of oxygen (or ROS, reactive oxygen species) becomes toxic for major components of the cell: this reaction is called oxidative stress. We have investigated the role of chronic oxidative stress on tumor development. We have shown that persistent accumulation of ROS (still faint enought for being compatible with cell survival) promotes tumor development. Indeed, accumulation of ROS stabilizes HIF under normoxic conditions and further increases tumor angiogenesis (Gerald D. et al., Cell, 2004). HIF has also been defined as a key regulator of glucose metabolism by regulating insulin secretion (Laurent G. et al., Cell Metabolism, 2008). Interestingly, chronic oxidative stress also deeply modifies other components of the stromal compartment, such as fibroblasts. Indeed, ROS accumulation converts fibroblasts into myofibroblasts and promotes dissemination of metastatic cells into lymph nodes in HER2 breast cancers (Toullec, A., EMBO Molecular Medicine, 2010). Finally, we recently defined a miRNA-dependent stressrelated signature, which has a predictive value for survival of patients suffering from high grade ovarian cancers. miR-141 and miR-200a target p38α and modulate the oxidative stress response. Enhanced expression of these miRNAs mimics p38α deficiency and increases tumor growth in mouse models, but it also improves the response to chemotherapeutic agents. High-grade human ovarian adenocarcinomas that accumulate miR-200a have low concentrations of p38α and an associated oxidative stress signature. The miR200a-dependent stress signature correlates with improved survival of patients in response to treatment. Therefore, the role of miR-200a in stress could be a predictive marker for clinical outcome in ovarian cancer. In addition, although oxidative stress promotes tumor growth, it also sensitizes tumors to treatment, which could account for the limited success of antioxidants in clinical trials (Mateescu, B. et al., Nature Medicine, 2011; Batista, IJBCB, 2013).

No conflict of interest.

201 INVITED

Identification of microRNA functions in cancer using high-throughput screens

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MicroRNAs are important regulators of gene expression in normal development and disease. With the number of human microRNAs approaching 2000 a major quest is to incorporate these into cellular pathways. Whereas a multitude of studies have demonstrated deregulated microRNA expression in human cancers, establishing causal roles for microRNAs in cancer development and maintenance is lagging behind.
High-throughput functional screening for microRNAs affecting cancer-related cellular functions is an efficient first step to identify key microRNAs in a particular pathway. The p53 tumour suppressor acts as a negative regulator of cell proliferation in response to stress and represents the most commonly lost and mutated gene in human cancers. To identify microRNAs affecting the p53 tumour suppressor pathway a library of 500 microRNA precursors were screened. The screen data will be presented focussing on the identification of a potent inhibitor of the MDM2 ubiquitin ligase responsible for functional inhibition of p53.

No conflict of interest.

Scientific Symposium (Sun, 29 Sep, 14:45−16:45) **Treatment of Rhabdomyosarcoma in Children and Adolescents Across the Atlantic: Time for Increasing Joint Initiatives?**

202 INVITED

Reducing radiation therapy for children with rhabdomyosarcoma: Results of the European strategy

O. Oberlin[1]. [1]*Institut Gustave Roussy, Pediatrics, Villejuif, France*

Outcomes of patients with localized RMS although not yet satisfactory, are sufficiently good enough to justify a focus not just on cure but also on the consequences of cure. This focus is reinforced by the proportion of children who are very young and for whom the consequences of local treatment is a particular concern. It is of paramount importance to identify which subset of patients can be spare aspects of treatment which may cause important long-term sequelae.
Since the 80s, the links between the North American and European Soft Tissue Sarcoma groups offered the possibilities of meta-analysis of outcomes for groups of patients treated in different settings.
In 1997, the cooperative groups took as the topic the outcome of children with orbital RMS. Long known to have a favourable outcome, there was concern that the systematic use of radiation therapy, at this site, in young children, created a high risk of important late sequelae Data showed that a subset of patients with orbital RMS could be cured without systematic local therapy, although there was a high relapse rate in those who did not receive radiation therapy as part of primary treatment. The possibility of salvage for some of those who relapsed resulted in overall survival rates being no different whether patients received radiation therapy during primary treatment or not. However, the total burden of treatment (i.e., primary therapy and treatment given for relapse) needs to be taken into account when assessing the implications for late sequelae for all patients.
Similar analyses were performed in other relatively favourable sites of disease including bladder/prostate or vagina/ uterus RMS and produced similar conclusions: delayed selective RT was not disadvantageous in relation to overall survival.
However, the application of a similar strategy for parameningeal RMS was not successful and accounted for the less good overall results of some European studies compared with those undertaken by the North American group.
The challenge of how to spare the sequelae of radiation therapy remains an important issue and work still needs to be done to try and further refine the selection of patients who may have less treatment. Apart from conventional measures of prognosis including site, size, stage, age, pathological subtype and rapidity of chemotherapy response, we hope that in future studies markers of tumour’s biology might help to select these tumours.

No conflict of interest.

203 INVITED

Progress in the treatment of rhabdomyosarcoma: Results of the North American strategy

D. Hawkins[1]. [1]*Seattle Children’s Hospital, Hematology-Oncology, Seattle, USA*

Background: The Children’s Oncology Group (COG) continues the legacy of the Intergroup Rhabdomyosarcoma Study Group to improve the outcome for rhabdomyosarcoma (RMS) using risk stratified clinical trials based upon the expected failure-free survival (FFS).
Materials and Methods: Recent COG RMS trials included ARST0331 for low-risk RMS (defined as embryonal histology, non-metastatic disease, and either favorable site ***or*** unfavorable site with completed resection prior to chemotherapy), ARST0531 for intermediate-risk RMS (defined as embryonal histology, non-metastatic disease, unfavorable site, and unresected ***or*** alveolar RMS without metastatic disease), ARST0431 and ARST08P1 for high risk RMS (defined as any RMS with metastatic disease), and ARST0921 for recurrent RMS.
Results: ARST0331 used a modest cyclophosphamide dose (4.8 g/m^2), with 22 week of therapy for subset 1 (mostly orbital and paratesticular RMS) and 46 weeks of therapy for subset 2 (mostly unresected tumors at favorable sites). For subset 1, the 2 year FFS was excellent (88%); for subset 2, the 2 year FFS was worse than anticipated (68%). ARST0531 was a randomized addition of irinotecan to standard chemotherapy. Secondary aims included evaluation of early radiotherapy, functional response imaging with positron emission tomography (PET), and assessment of *FOXO1* translocations in alveolar RMS. ARST0531 completed enrollment in December 2012 with results pending. ARST0431 used a very intensive seven agent chemotherapy combination for metastatic patients. Compared to historic results, the outcome for patients with embryonal RMS appeared to be improved (3 year FFS: 60%), while there was no improvement for alveolar RMS (3 year FFS: 21%). ARST08P1 uses the same intensive backbone as ARST0431 with the addition of cixutumumab (given weekly) or temozolomide (given with concurrently with irinotecan). ARST0921 uses a vinorelbine/cyclophosphamide backbone with the addition of either bevacizumab or temsirolimus in a selection design to identify the agent of greater interest for future development. Both ATSR08P1 and ARST0921 will reach their accrual goals soon.
Conclusions: The COG RMS risk stratification requires modification to account for changes in outcome for selected low-risk and metastatic embryonal RMS and molecular features. Planned changes include PET as an early surrogate for outcome and incorporation of molecularly targeted agents into frontline therapy.

No conflict of interest.

204 INVITED

Treatment of relapsed rhabdomyosarcoma − Experience of the CWS Study Group

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Despite improved prognosis in patients with RMS, about 30% percent of patients with primary localised tumours who achieved complete remission (CR) relapsed, mainly locoregional (50−60%) and/or metastatic. The relapse rate (RR) did not differ substantially between the consecutive CWS-Studies and was similar to the RR reported by other RMS-Study groups (SIOP-MMT, STS Committee of COG, AIEOP-ICG) showing that no major progress has been achieved in treating patients after recurrence in the last 20 years. The relapse behaviour depends on the histological subtype (alveolar vs. embryonal) and primary tumour site. Alveolar RMS (RMA) relapsed more frequently: 48% of primary non-metastatic RMA relapsed after achievement of CR, majority of them experienced systemic relapse. The most frequent site of systemic relapses (in all RMS) were thorax (ca. 50%) and abdomen (ca.30%). 70−80% of the recurrences occurred $\leqslant$2 years after diagnosis and only 1% later than 4 yrs after diagnosis. Post − relapse overall survival (OS) was 20−30% but varied greatly depending on histology, type of relapse (locoregional vs. combined or metastatic) and time of occurring. Patients with embryonal RMS (RME), local, late (>12 months after diagnosis) recurrence and a still existing option for irradiation (RT) have a survival chance of about 50%. Similarly patients with a relapse to the lung as a solely metastatic site have an OS of ca. 50%. In contrast patients with RMA and metastatic relapse have a very poor prognosis (OS <5%). However, even in this poor prognostic group, survival in the subgroup of individuals with circumscribed recurrences and an option for local therapy was significantly better (ca.50%). Early relapse (<6 months after diagnosis) was associated always with poor prognosis (4 yrs OS of 19% and 4% in RME and RMA respectively). Age, histology, tumour size and site, post-surgical stage and omission of RT were identified in the multivariate analysis as factors associated with an increased relapse risk. Tumour site, an option for RT, time to relapse and type of relapse, were identified as independent factors predicting survival after relapse. Alkylating agents and anthracyclines should be used in patients who did not receive these agents in the first-line therapy. Additionally topoisomerase inhibitors (VP-16, topotecan, irinotecan), cisplatin, carboplatin, vinorelbine are used in relapse treatment. The use of high-dose chemotherapy has not been shown to improve prognosis. Advances in molecular characterization of RMS have identified new therapeutic targets which are being tested in phase I−II studies. The characterization of subgroups with distinctive pattern and risk of relapse can be used to develop risk-adapted, tumour-directed guidance for detection of recurrent disease in RMS and identification of patients for experimental therapeutic approaches.

No conflict of interest.

205 INVITED

Biology-driven strategy for new drug development in rhabdomyosarcoma

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Despite significant improvements in outcome for children and young people with rhabdomyosarcoma (RMS), outcomes remain suboptimal in certain groups, particularly high risk localized disease, metastatic and relapsed disease. In addition to continued improvements in local therapy (surgery and radiotherapy) there exists a need to improve systemic therapy for these groups of RMS. Cytotoxic chemotherapeutic agents remain the gold standard of systemic therapy, with studies in Europe and North America now underway to begin to evaluate the addition of targeted therapies.

Many potential targets have been identified in rhabdomyosarcoma. These include: ALK; MET; FGFRs; HSP90; IGF1R; PDGFR; VEGFR; PI3KCA/mTOR; SPRY1; PTEN; Raf1; Src; G2M kinases; PLK1; NOTCH. In translocation positive alveolar RMS, the PAX3-FOXO1 or PAX7-FOXO1 fusion gene drives a number of downstream effects, although as yet the fusion gene cannot be targeted directly. The biological differences between translocation-positive alveolar RMS and embryonal RMS/translocation-negative alveolar RMS must be recognised in future therapeutic strategies and clinical trials.

Prioritization of known druggable targets with potential therapeutic benefit in RMS is important to aid selection of the most promising agents or combinations of agents for in vitro and in vivo studies with a view to early phase clinical trials in children. In reality, prioritization is complex. Moreover, the number of relevant targeted agents with phase I paediatric data currently available for clinical trials in RMS remains limited.

The European paediatric Soft tissue Sarcoma Group and the Innovative Therapies for Children with Cancer network are collaborating together to introduce targeted agents in RMS. The role of bevacizumab in combination with standard chemotherapy is being evaluated in newly diagnosed metastatic RMS and other soft tissue sarcomas in a randomized phase II study. In the relapse setting a randomized phase II study of vincristine and irinotecan with or without temozolomide seeks to define the chemotherapy backbone to which targeted therapies will be added in future studies.

In the future, more flexible trial designs incorporating predictive and pharmacodynamic biomarkers may facilitate more rapid introduction of new drugs in the phase II setting, give a faster indication of their likely effectiveness and allowing the most promising new drugs to be taken forward in the phase III setting. In addition, transatlantic cooperation in trial design will enable early identification and introduction of those targeted therapies that are of most benefit to RMS patients.

Conflict of interest: *Ownership: F Hoffman La Roche. Advisory board: Steering committee for BERNIE trial, a randomised phase II study of chemotherapy with or without bevacizumab in newly diagnosed rhabdomyosarcoma and non rhabdomyosarcoma soft tissue sarcoma*

Special Session (Sun, 29 Sep, 17:00−18:00)
Concurrent Chemo-Radiotherapy Prediction of Outcome and Toxicity

206 INVITED

Predicting survival outcome for stage III lung cancer

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Although the TNM staging system gives the same survival prognosis for all patients with stage III lung cancer, these patients form a very heterogeneous group, which leads to large differences in survival outcome. These differences can, to some extent, be explained by basic patient, tumor and treatment characteristics.

A short overview will be given of prediction models that have been developed, the factors that have been incorporated and the performance of the models. It will be shown that these models already outperform the prediction of doctors. In addition, the possible impact of new variables, derived from genetic or imaging information, will be discussed. Finally, the importance of collecting and sharing cohort data for modeling will be explained.

No conflict of interest.

207 INVITED

Predicting oesophageal and lung toxicity

J. Belderbos[1], C. Chen[1], M. Kwint[1], W. Uyterlinde[2], J. Nijkamp[1], M. Van den Heuvel[2], M. Van Herk[1], J. Sonke[1]. *[1]The Netherlands Cancer Institute, Radiotherapy, Amsterdam, Netherlands; [2]The Netherlands Cancer Institute, Thoracic Oncology, Amsterdam, Netherlands*

Background: The improved survival in locally advanced non-small cell lung cancer (NSCLC) patients treated with concurrent chemo-radiation (CCRT) comes at a price of increased oesophagus toxicity. Estimation of the probability to develop oesophageal toxicity or lung toxicity after CCRT is crucial. This allows for individual prescription of (adequate) tumour doses based on normal tissue complication probabilities. Several theoretical models have been developed to estimate the risk of radiation pneumonitis based on the planned dose distributions. These models simplify dose-volume histograms to a single parameter like the mean lung dose (MLD) or the volume of lung receiving more than a threshold dose (V_x). For conventional fractionated radiotherapy, both the MLD and the V_{13-20} are used for the prediction of RP. For acute oesophagus toxicity (AET) several dose-volume parameters were reported but for late oesophagus toxicity (LET) like stenosis and fistula, models are lacking.

Material and Methods: The dose-effect relation of AET (185 patients) and LET (171 patients) and dose-volume parameters of the esophagus after Intensity Modulated Radiotherapy up to 66 Gy in 24 fractions and concurrent daily cisplatin for NSCLC patients were investigated. To that

end, the dose distribution were first converted to Normalized Total Doses (NTD) to account for fractionation effects with an α/β-ratio of 10 Gy (AET) or 3 Gy (LET). Clinical parameters, onset and recovery times were analyzed as well.
Results: Radiation pneumonitis grade $\geqslant$3 was scored in 7% of the patients. A total of 22% patients developed AET toxicity and 6% developed grade $\geqslant$3 LET. For prediction of grade $\geqslant$3 AET the equivalent uniform dose (EUD) with n = 0.13 (high dose) was found to be the best predictor. Patients with un-recovered AET had a significantly ($p < 0.001$) higher risk of developing severe LET, compared to patients without or with a recovered AET. Higher grade of AET was also associated with a lower recovery rate. The median time to AET grade 3 was 30 days, with a median duration of 80 days. Prediction of LET $\geqslant$ grade 3 was done using $EUD_{n = 0.03}$, where all severe LET patients had an oesophageal EUD >70 Gy.
Conclusions: In routine clinical practice it is possible to estimate the probability and severity of lung toxicity as well as the occurrence of AET for each individual patient. Both the maximum grade and the recovery rate of AET were significantly associated with severe LET. In clinical practice, oesophageal $EUD_{n = 0.03}$<70 Gy could be a dose constraint to prevent severe LET.
No conflict of interest.

208 INVITED

Resectability after concurrent chemoradiotherapy (CCRT)

P. Van Schil[1]. [1]*Antwerp University Hospital, Departement Thorax- en Vaatheelkunde, Antwerp, Belgium*

Due to a variable degree of fibrosis that occurs after chemoradiation surgical resection may become technically challenging, especially after high-dose concurrent chemoradiation. A distinction has to be made between induction chemoradiotherapy followed by surgical resection and so-called salvage surgery after previous full-dose chemoradiation.
For locally advanced stage IIIA-B non-small cell lung cancer (NSCLC) chemoradiation has become standard treatment but in selected patients induction therapy may be followed by surgical treatment when a downstaging is obtained and a complete resection seems feasible. However, a higher morbidity and mortality have to be anticipated, especially when a pneumonectomy has to be performed. In the Intergroup 0139 trial patients with proven stage IIIA-N2 NSCLC were randomized between full-dose chemoradiotherapy and induction chemoradiation followed by surgery. In the surgical arm mortality after lobectomy was 1% in contrast to 25% after pneumonectomy. In a recent review induction chemoradiation was not found to be superior to induction chemotherapy alone in stage IIIA NSCLC. Superior sulcus or apical chest tumours respond very well to induction chemoradiation and good long-term survival results have been reported. Most severe complications after induction chemoradiation include empyema and bronchopleural fistula which are difficult to treat with still a very high mortality rate and often a prolonged hospitalisation time in surviving patients.
Locoregional recurrence of NSCLC may occur months or years after full-dose chemoradiation given with curative intent. In selected patients salvage surgery is sometimes the only remaining therapeutic option, especially when an infected cavity is present. At the present time only a few reports have appeared in literature but it is obvious that surgical resection in these cases represents a real challenge to thoracic surgeons with an increased morbidity and mortality rate. Such cases should be discussed individually at a multidisciplinary team to determine optimal treatment. These patients should be operated in high-volume institutions with adequate experience, also in postoperative care. As high-dose radiotherapy in combination with chemotherapy is more frequently utilized, thoracic surgeons will increasingly be confronted with salvage surgery in often desperate cases and should be prepared to deal with this new category of patients representing new challenges, as well intraoperatively as postoperatively.
No conflict of interest.

Special Session (Sun, 29 Sep, 17:00–18:00)
New Clinical Opportunities in Targeted Therapies

209 INVITED

Combination modality treatment for brain metastases

G.V. Long[1]. [1]*Melanoma Institute Australia and The University of Sydney, Medical Oncology, Sydney, Australia*

Brain metastases are difficult to manage and carry a poor prognosis regardless of the solid tumour from which they arise. They are frequent in melanoma, a cancer for which there was no systemic therapy that prolonged overall survival until recently. Immunotherapy and targeted therapy (e.g. BRAF inhibitors) prolong survival in patients with metastatic melanoma, and have shown activity in brain metastases. Using melanoma as an example, the approach to the management of brain metastases using systemic and local therapies will be discussed, with a focus on the shift in the treatment paradigm due to highly active systemic therapies. Understanding the patterns of response and relapse to systemic therapies in brain metastases is critical for the planning of treatment with local therapies such as surgery and stereotactic radiosurgery. For example, the BRAF inhibitor dabrafenib reduces the size of brain metastases in most patients with V600 BRAF-mutant melanoma, with a disease control rate of over 80% in the brain. However, relapse is not necessarily in the brain, and although the median duration of response in the brain is over 20 weeks, some patients continue to respond for over a year. Anticipating the duration of response and the type of relapse is important for optimal management and use of local therapies. Most importantly, inclusion of patients with active brain metastases in early-phase drug trials is a priority, and remains a barrier to better outcomes for patients with brain metastases.
Conflict of interest: *Advisory board: GSK, Roche, Novartis, BMS*

210 INVITED

Combination treatment for irresectable melanoma masses

O. Nieweg[1]. [1]*The Netherlands Cancer Institute, Skin and Melanoma Center/Surgery, Amsterdam, Netherlands*

Unresectable melanoma masses are rare, but if they occur they are usually lymph node metastases in the axilla or in the pelvis. Unresectable in-transit metastases are more frequent but their number rather than their size typically prevents resection. Regional drug therapy is the traditional approach if such lesions are situated on a limb. Regional perfusion results in a complete response in some 55% of the patients and a partial response in another 35%. A partial response is usually sufficient to allow excision of the remaining lesions.
An underrated approach is the combination of intravenous dacarbazine and topical dinitrochlorobenzene, an allergenic substance. The complete response rate with this regimen is 25%.
The armamentarium of surgeons is quickly expanding. Electrochemotherapy combines high-intensity electric pulses over the mass with intravenous or intralesional cytotoxic drugs. The electroporation improves drug delivery into the tumor cells. A systematic literature review showed a complete response rate of 57% and a partial response rate of 81%.
Diphencyprone is a topical immunogenic drug with a complete response rate of 14% and partial response rate of 8% in patients with intradermal metastases. The immune-stimulatory imiquimod cream combined with the depigmenting agent monobenzone is another promising approach for dermal metastases and resulted in five partial responses in eight patients at our institution. These treatments can be combined with laser ablation. Rose Bengal (PV-10) works for subcutaneous lesions with a complete response rate of 24% and a partial response rate of 13%.
Oncovex is a vaccine made of an oncolytic Herpes virus. It is administered in the tumor mass where it encodes GM-CSF, which stimulates the immune system. In a phase II trial, 16 percent of patients achieved a complete response and 10 percent achieved a partial response.
The recently approved drug Vemurafenib with its swift response offers an interesting option in patients with the V600E BRAF mutation and quickly growing non-resectable masses. Half of the patients respond, although responses are not durable and rarely complete. However, the speed of the response may offer a time window for resection before the metastasis becomes resistant and starts to grow again. This appears to be good option in patients with inoperable lymph node metastases.
In conclusion, melanomologists have an increasing number of options for combination treatment of unresectable melanoma masses. At this point, there is not a standard regimen.
No conflict of interest.

Special Session (Sun, 29 Sep, 17:00–18:00)
Hope Across Cancer Care

211 INVITED

Portraying hope – a study among woman newly diagnosed with gynecological cancer

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Aim: The aim of the thesis *Portraying hope among women with newly diagnosed gynaecological cancer* is to examine hope experienced the day the woman get diagnosed with cancer. Hope is also closely linked

to hopelessness, and the day you get a cancer diagnose can be a day of emotional chaos and a feeling that one has lost control over life. The feeling of hopelessness can easily appear. However, precisely because hope is a part of life, hope is present, in one form or another.
Background: Helping a patient to find hope in illness and suffering is one of the cornerstones of humanistic-oriented nursing where also dignity, respect, integrity and caring are overarching values. Knowledge of how patients themselves feel hope at the time of diagnosis will enhance the nursing knowledge base and will increase understanding and opportunities for clinical nurses. Cancer is a common and often life-threatening disease and also the word cancer have a stigmatizing meaning. Gynaecological cancer is one of the most frequent cancers among women.
Methods: This qualitative study was carrying out at a surgical unit at a Danish University Hospital, in order to provide a comprehensive understanding of hope. The data collection is based both on interviews and drawings. Fifteen women, all diagnosed with gynaecological cancer, were interviewed the same day they received their diagnosis. Semi-structured interviews were chosen in order to investigate the informants lived experiences of hope. Data was analyzed using a phenomenological and a visual approach.
Results: In this thesis hope as collected in a synthesis showing three sides, an internal, an external and a commotional force are belonging together, and where hopelessness is seen as a dark shadow in a circumference of the triangle shaped design. The findings discovered of the close relationship between hope and hopelessness supports the need for nurses and other health care to supports patients find hope starting from time of diagnosis.
Perspective and Implication: New in this study is to use interviews and drawings in combination and that hoped stimulated by external force loaded from the nature. Drawings and conversations about the drawings gave a deeper understanding of the phenomenon of "experience of hope." This study, which creates new knowledge about patients' experiences of hope in general and describes hope in newly diagnosed gynaecological cancer, are importance for clinical nursing practices. The results may create a platform for discussion between nurses and compared with their own experiences. Perhaps crayons and drawing paper could be included as standard in clinical nursing practices when interview with patients about hope or other existential topics are actual. A combination of interview and drawing could have a therapeutic and explanatory of those involved. Hope could give life force − whether the patient has newly diagnosed or otherwise in need of support and nursing care.
No conflict of interest.

212 INVITED
Nurses' perspective of hope in cancer care

E. Benzein[1]. [1]*Linnaeus University, Kalmar, Sweden*

Background: Nurses who meet patients with cancer in palliative care have a great challenge to create possibilities to facilitate the experience of hope in patients and their families. Nurses need to be aware of the phenomenon *per se* and each patient's potential for experiencing hope. A most important start is that the nurses themselves become aware of their own perceptions of hope related to their patients. Research show however that nurses' experiences are not always in line with the patients' experiences.
Material and Methods: Individual interviews with nurses in oncology care was performed in a previous study (n = 9) and some additional interviews is ongoing. Nurses are asked to narrate their reflections on hope as a phenomenon and their experiences of patients who they consider have had hope and those who had not. Interviews are analyzed by a hermeneutic approach.
Results: The results from the previous study showed that nurses view hope as an inner strengths and energy in their patients. Hope for patients could also be to achieve and experience significant events, often including relatives and friends. The nurses argued it was from relatives and friends the patients got the most important support to experience hope. Being in the home milieu was also a way to support hope. Further, many patients put their faith in various treatments and if nurses support the patients' decisions it is also a source of hope for the patients. The nurses thought that nursing actions could both foster and reduce hope in their patients.
The analysis of additional interviews is ongoing and will be presented at the conference together with a comparison of the experience of hope from the patients' perspective.
Conclusion: Nurses can be important persons for patients with cancer and their families in order to experience hope. By being aware of one's own perceptions of hope nurses can open up space to invite patients and families to narrate their experiences and needs in order to experience hope. The nurse-patient/family relationship should be characterized by a partnership in which hope can be created in a collaborative way.
No conflict of interest.

213 INVITED
When hope is all that is left: Hope and end of life care for cancer patients

H.W.M. Van Laarhoven[1]. [1]*Academic Medical Center, Department of Medical Oncology, Amsterdam, Netherlands*

Hope can be a valuable asset in coping with terminal disease. However, fostering hope in the context of end of life care may be complicated. How can there be hope if life is coming to an end? Hope has been defined as 'a confident yet uncertain expectation of achieving a future good which, to the hoping person, is realistically possible and personally significant'. This definition highlights three important characteristics of hope. It refers to personal significance, a future perspective, and combines confidence with uncertainty. In this presentation we will discuss the relevance of these characteristics for end of life cancer care.
Although the concept hope relates to personal significance, it does not state *what* is personally significant. Hope may refer to hope for cure or prolongation of life, but also to a broader perspective of living life to the fullest.
Hearing that the disease is incurable destroys one's future perspective in a split second. To maintain hope, some kind of future perspective is needed, however short the time ahead may be. The HP's main task is to restore this perspective by discussing different themes, giving patients a new perspective which allows them to live full lives until the end. Such a focus on the future, rather than the past, may be related to reduced levels of distress, even in the last phase of life.
The characteristic of hope combining confidence with uncertainty does not preclude honesty of HPs. In fact, the majority of patients and their caregivers report that they want the HP to be honest when discussing prognosis and end-of-life issues. However, patients may differ in their view what constitutes a honest approach. They may request full disclosure, including statistical information about their life expectancy, while others prefer to remain partly ignorant and receive general information only. In general, highly explicit information combined with the reassurance that patients will receive continued support from their HP in the course of progressive disease, decreases patients' uncertainty and anxiety, while increasing self-efficacy and satisfaction.
No conflict of interest.

Special Session (Sun, 29 Sep, 17:00−18:00)
Is There a Role for Surgery in the Management of HCC?

214 INVITED
Value of liver function tests and volumetry

P. Pessaux[1], L. Soler[1], T. Piardi[1], D. Mutter[1], J. Marescaux[1]. [1]*Nouvel Hôpital Civil, Service de Chirurgie Hépato-biliaire et Pancréatique, Strasbourg, France*

The hepatic functional reserve may be evaluated by the association of the measurement of the volume of the future remnant liver and the assessment of the preoperative liver function. The importance of assessing liver function has been further increased because several aggressive preoperative therapies could alter the liver function and so decrease the postoperative outcomes.
Imaging reconstruction techniques in three dimensions is mandatory to evaluate the total volume of the tumors and the volume of non-tumoral liver. Although the normal liver tolerates removal of up to 60−70% of its volume, the extent to which the liver parenchyma may be resected in patients with Chemotherapy-associated steatohepatitis has not yet been clearly defined. The 3D-CT has been shown to be the most adequate procedure for measurement of liver volumes. When the volume of the future remnant liver seems to be insufficient, portal embolization or two-stage hepatectomy has been recommended in order to improve the safety of the procedure.
Standard liver biochemistry tests have not been shown to be of any predictive value. Other methods have included measurement of uptake of organic anions (such as bromsulphtalein, rose Bengal and indocyanine green (ICG)), the arterial ketone body ratio, redox tolerance test, aminopyralene breath test and the amino acid clearance test. These tests measure different aspect of hepatic function and may not correlate with one another. The ICG clearance test appears to be the best discriminating investigation. Hepatectomy involving resection of up to 60% of the parenchyma can be justified in patients with normal liver function and with ICG retention at 15 minutes value <20%. Minor hepatectomies can be accomplished even if ICG retention at 15 minutes reaches 23 to 25%.

Nuclear imaging with variety of agents has existed for years. Synthetic asialoglycoprotein, galactosyl-neo-glycoalbumin was complexed to 99m-Tc to study hepatocyte binding via asialoglycoprotein receptor. In addition, imaging provided volumetric/anatomic information, as well as a functional assessment.
No conflict of interest.

215 INVITED
Limited vs anatomical resection

Abstract not received.

216 INVITED
Liver transplantation

Abstract not received.

Monday 30 September 2013

Scientific Symposium (Mon, 30 Sep, 09:00−11:00) Metastatic Breast Cancer: From Biology to Therapeutic Strategies

217 INVITED
Dealing with tumour heterogeneity: The exception or the rule?

M. Piccart[1], D. Zardavas[1]. [1]*Institut Jules Bordet, Bruxelles, Belgium*

Breast cancer is a heterogeneous disease, with its diversified clinical and histological aspects having been recognized since a long time. Gene expression profiling analysis studies deepened our understanding of this intertumoural heterogeneity, with different molecular subtypes of breast cancer identified among different patients. Recently, our conceptual view of cancer has been shifted to an ecological perspective, according to which breast cancer progression proceeds in a Darwinian-like branched evolution manner. Powerful next generation sequencing and other high-throughput molecular analysis techniques enable us to interrogate the complex intratumoural heterogeneity of breast cancer, with cancer cells within one tumor of any given patient displaying heterogeneity in a number of their molecular features. This refers to both spatial and temporal heterogeneity, as tumor cells of different topologies or different phases of the life cycle of breast cancer have been shown to display different molecular and phenotypic profiles. Importantly, evidence supports the existence of both genetic and non-genetic heterogeneity, with the existence of subclonal cancer cell populations exhibiting distinct landscapes of genetic and epigenetic aberrations. In the metastatic setting intratumoural heterogeneity is a significant impediment to precision medicine, since to the present day we have been basing our therapeutic strategy upon analysis of the primary tumour. However, as already shown by conventional pathology assessments, discordance in biomarkers dictating the clinical management of breast cancer patients can occur between primary and metastatic tumor lesions. Lastly, data supports that molecularly targeted agents pose a selective evolutionary pressure against breast cancer cells, inducing treatment resistance through the emergence of intratumoural heterogeneity. These aspects render the issue of tumor sampling extremely important, since the genetic and non-genetic landscape of molecular changes in the metastatic lesions should guide treatment decisions. To this end, molecular analysis of plasma-derived biomarkers holds a great promise. Additionally, “warm” autopsy studies can help us reconstruct the evolutionary tree of breast cancer disease. Having entered the era of individualized cancer medicine, the dissection of this tumour heterogeneity is of paramount importance, and this is why the Breast International Group (BIG) is launching an ambitious longitudinal study that will consist in target sequencing (n = 400 genes)of 1000 metastatic lesions together with their respective primaries with clinical follow-up (the “PRISM” project).
Conflict of interest: *Ownership: N/A. Advisory board: Amgen, Astellas, AstraZeneca, Bayer, Invivis, MSD, Novartis, Pfizer, Roche-Genentech, Sanofi-Aventis, Symphogen, Synthon, Verastem. Board of directors: PharmaMar. Corporate-sponsored research: most companies. Other substantive relationships: N/A*

218 INVITED
How to best assess response: New imaging techniques

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Currently, treatment response monitoring in metastatic breast cancer is based on measurement of changes in anatomical sizes. This is in clinical trials with primary endpoint of objective response done according to Response Evaluation Criteria in Solid Tumors (RECIST) and is generally performed every other cycle. This approach provides no insight in changes of molecular characteristics, and assessment of response takes at least weeks before information is obtained. Moreover, bone metastases, being the most common site of distant metastases in breast cancer, are not measurable by RECIST. In the era of targeted medicine, knowledge of specific tumor characteristics becomes more important. A potential way to assess this is by means of molecular imaging. Techniques for molecular imaging include magnetic resonance imaging (MRI), optical imaging, and radionuclide imaging with single photon emission computed tomography (SPECT) or positron emission tomography (PET).
Currently, most know-how is available about PET. Molecular imaging by PET can visualize general tumor processes, such as glucose metabolism with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and DNA synthesis with ^{18}F-Fluorodeoxythymidine (^{18}F-FLT). In addition, an increasing number of more specific targets, such as hormone receptors, growth factor receptors and growth factors can be evaluated. Moreover, PET imaging provides a whole body image, also allowing assessment of heterogeneity between and within lesions.
Optical imaging can be performed to provide real-time visualization of small lesions during surgery, which may aid intra-operative staging and image-guided surgery. We are currently performing a feasibility fluorescence imaging study with the NIFR 800CW-bevacizumab tracer in primary breast cancer. If successful, optical imaging with for example a handheld probe might also be able to support evaluation of drug effects.
Molecular imaging may thus be of value for personalized treatment by providing insight in the expression of drug targets and by intra-operative tumor visualization. Additionally, molecular changes may be observed soon after therapy initiation, which may serve as early predictor of response. In order to define clinical utility of these techniques, including burden for the patient and evaluation of costs, results from (ongoing) clinical trials are required.
Conflict of interest: *Advisory board: Genentech, Roche. Corporate-sponsored research: to the UMCG, Novartis, Genentech, Roche*

219 INVITED
How to best assess response: Blood-based tests

J.Y. Pierga[1], R. Lebofsky[2], F.C. Bidard[1]. [1]*Institut Curie, Department of Medical Oncology, Paris, France;* [2]*Institut Curie, Circulating Biomarkers Lab SIRIC, Paris, France*

Serum markers as carcinoembryonic antigen (CEA) and cancer antigen 15.3 (CA 15−3) have been developed in metastatic breast cancer (MBC) patients as tools for non-invasive assessment of the tumour burden. Quantitative variations are used to assess treatment efficiency. However, the specificity and sensitivity of serum tumour are considered as low and no clear consensus exists on what threshold and/or variation are clinically significant. Additionally, it is not uncommon for a phenomenon of flare of tumour markers to occur in the first 6 weeks of an efficacious therapy. According to ESMO recommendations, a change in tumour markers alone should not be used as the only determinant for treatment decisions. Since a study by Cristofanilli et al. in 2004, the enumeration of circulating tumour cells (CTC) has emerged as a promising biomarker. Although there are numerous methods to detect CTC in the research setting, the CellSearch System is the only test that has repeatedly demonstrated its clinical validity (i.e. association with outcome) in breast cancer. Moreover, we have recently confirmed in a level of evidence 1 study that changes in CTC count after one cycle of chemotherapy were associated with progression-free survival and demonstrated that CTCs, but not serum markers, have an independent prognostic value in multivariate analysis. Current prospective large interventional studies have been specifically designed to demonstrate that CTC enumeration/ characterization may improve the management of MBC patients: STIC CTC METABREAST (France) and Endocrine Therapy Index (USA) assess the CTC-guided hormone therapy vs chemotherapy decision in M1 patients; SWOG0500 (USA) and CirCe01 (France) assess the CTC count changes during treatment in MBC patients. These trials are expected to be the pivotal trials for CTC implementation in the routine management of MBC patients. A third blood-based marker is particularly promising, and is currently under investigation: circulating tumour DNA

(ctDNA). These specific DNA fragments can be detected in the plasma, in general after the genetic alterations harboured by the primary tumour and/or its metastases have been characterized. Several highly sensitive techniques, such as BEAMing, PAP, or digital PCR have been used for the purposes of finding a single ctDNA molecule within a large volume of plasma sample. Recent pioneering study has shown that ctDNA detection is associated with tumour burden. Demonstration that the method can be used to take better care of patients with MBC in a cost-effective manner awaits further studies. Next generation sequencing analysis of ctDNA in plasma could also complement current invasive biopsy approaches to identify mutations associated with acquired drug resistance in advanced disease.
Conflict of interest: *Corporate-sponsored research: Veridex, Roche*

220 INVITED

Personalised drug discovery: An academic experience

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Background: Breast cancer includes a large number of rare genomic segments defined by genomic alteration on targetable genes. The use of multiplex genomic technologies have been proposed in order to optimally drive patients to clinical trials testing targeted therapies. Based on this background, we have developed molecular screening programs that aim at genotyping breast cancer and treat them accordingly.
Patients and methods: The current presentation will update participants on two molecular screening programs: SAFIR01 and MOSCATO, with an emphasis on breast cancer patients. These two programs use array CGH and sequencing (sanger and next generation sequencing) to identify a targetable genomic alteration.
Results: SAFIR01 was a multicentric trial performed in 18 centers that included 423 patients. 48 patients have been treated with a targeted therapy matched on genomic alteration, with evidence on antitumor activity in 28% of them. MOSCATO is a monocentric trial that aims at including 600 patients. Update results will be presented about this trial.
Perspectives: Several additional molecular screening programs are being developed including PRISM program from BIG, PROFILER from Centre Leon Berard. These molecular screening trials aim at identifying rare genomic alterations that are associated with drug sensitivity. The molecular screening programs feed large database that will be used to develop algorithm for individual drug response. The mid-term perspective will be to evaluate, in the context of randomized trials, whether the use of these algorithms improve outcome.
No conflict of interest.

Scientific Symposium (Mon, 30 Sep, 09:00−11:00) **Personalised Treatment in Colorectal Cancer**

221 INVITED

Are predictive/prognostic biomarkers/platforms ready to be placed in adjuvant treatments?

A. Roth[1]. *[1]University Hospital, Oncosurgery, Geneva 14, Switzerland*

Recent improvements in the knowledge of the molecular biology of colon cancer have provided us with new tools, which might enhance our ability to assess the prognosis and the risk of relapse of curatively resected colon cancer. These would allow us to better select patients in the need of adjuvant therapy and avoid over-treatment of tumors with good prognosis. However, despite of the large amount of exciting positive results obtained with molecular markers (mutations,changes in expression or ploidy alterations etc) and with the development of sophisticated signatures based on extensive genomic profiling, many of these potential tools lack formal validation to allow us to apply them safely in daily practice. In the present paper we will detail the present status of this innovative field with special emphasis on the traps we could encounter in case of insufficient validation of the molecular markers/signatures used.
No conflict of interest.

222 INVITED

Selecting for maintenance or stop-and-go strategy in metastatic colorectal cancer

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Survival in metastatic colorectal cancer is improving. Several recent trials have shown a median survival in excess of two years with some patients still alive after 5 years. Continuing first-line toxic chemotherapy for such a long period negatively impacts the quality of life. Furthermore, some drugs, like oxaliplatin, have a cumulative toxicity which occurs before tumor progression. Stopping oxaliplatin after 6 cycles of FOLFOX reduces the neurotoxicity and allows reintroducing later the drug which remains particularly active in case of a long interval between the two periods of treatment. These facts provide a rationale to develop alternative strategies such as oxaliplatin stop and go with maintenance therapy after a few cycles of combination chemotherapy or even a complete stop in chemotherapy followed by reintroduction of oxaliplatin in sensitive patients who did not develop neurotoxicity. Recent trials have given data to support this strategy and have studied maintenance therapy with fluoropyrimidines alone or in combination with bevacizumab, bevacizumab alone or bevacizumab with erlotinib.
Without any patient selection, fluoropyrimidines plus bevacizumab is the most active and recommended maintenance therapy. Fluoropyrimidines alone, 5-fluorouracil or capecitabine, or bevacizumab alone also appear beneficial over a complete stop in therapy. Bevacizumab plus erlotinib is superior to bevacizumab alone regardless of the KRAS status. However, based on retrospective data, a subset of patients with MCRC may benefit from stopping chemotherapy: patients with normal platelet count at baseline and/or patients with normal CEA level after 3 months of oxaliplatin-based chemotherapy. New studies are ongoing or needed to further improve maintenance therapy: maintenance or stop and go after irinotecan-based chemotherapy, capecitabine or erlotinib in combination with bevacizumab, new combinations of chemotherapy such as S1 or TAS 102 and targeted therapies such as regorafenib or others.
No conflict of interest.

223 INVITED

Selecting for anti-EGFR inhibitors in CRC: KRAS and beyond?

Abstract not received.

224 INVITED

Do we have a light for predictive biomarkers with angiogenesis inhibitors or are we still lost in translation?

D. Lambrechts[1]. *[1]University of Leuven, Vesalius Research Center, Leuven, Belgium*

Angiogenesis inhibitors have been established over the past decade as valuable tools to inhibit tumor growth and improve tumor response to chemotherapy. In advanced colorectal cancer, these include the humanized monoclonal antibody against VEGF, bevacizumab, the more recently developed soluble VEGF receptor fusion protein, aflibercept, as well as the multikinase inhibitor of VEGF-receptors and other pro-angiogenic molecules, regorafenib. Although these molecules have changed clinical practice, some patients do not respond or gradually develop resistance, resulting in rather modest gains in terms of overall survival. A major challenge is to develop robust biomarkers that can guide selection of patients for whom bevacizumab therapy is most beneficial. During my presentation, I will highlight recent progress in finding such markers, including the first results from randomized phase III clinical trials evaluating the efficacy of bevacizumab in combination with comprehensive biomarker analyses. In particular, these studies suggest that circulating levels of short vascular endothelial growth factor A (VEGF-A) isoforms, expression of neuropilin-1 and VEGF receptor 1 in tumors or plasma, and genetic variants in VEGFA or its receptors are strong biomarker candidates. The current challenge is to expand this first set of markers and to validate it and implement it into clinical practice. In breast cancer, a first prospective biomarker study known as MERiDiAN, which will treat patients stratified for circulating levels of short VEGF-A isoforms with bevacizumab and paclitaxel, is ongoing and will hopefully provide us with new directions on how to treat patients more efficiently.
Conflict of interest: *Ownership: None. Advisory board: Hoffman-La Roche Sanofi-Aventis Bayer AG. Board of directors: None. Corporate-sponsored research: Hoffman-La Roche Sanofi-Aventis. Other substantive relationships: None*

Scientific Symposium (Mon, 30 Sep, 09:00−11:00)

Treatment Planning of Lung Cancer Using Innovative Therapy

225 INVITED

Latest developments in imaging

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Imaging plays a major role in the entire spectrum of diagnosis and treatment of lung cancer ranging from tumor detection to post-treatment follow-up and surveillance.
This presentation will give an overview over the current perspectives of modern imaging for the purpose of image-guided therapy of lung cancer. This includes image guided radiotherapy, as well as imaging in the context of innovative targeted medical therapy. The presentation will especially focus on new imaging techniques (PET-CT, functional CT, functional MRI) allowing functional tumor characterization and improved patient selection.
No conflict of interest.

226 INVITED

Drug uptake − monitoring and prediction

S. Burgers[1]. [1]*The Netherlands Cancer Institute, Department of Thoracic Oncology, Amsterdam, Netherlands*

The most commonly used and most reliable methods to predict responses of NSCLC to EGFR-tyrosine kinase inhibitors are screens for activating EGFR mutations. Monitoring of TKI- plasma levels is hardly incorporated in daily clinical care. In contrast to the dosing of chemotherapeutics, dosing of small molecules is not adapted to body surface or other individual traits of the patient. And surprisingly, the fixed dose for these drugs seems appropriate for most patients. Nevertheless, monitoring plasma levels of, for instance, erlotinib and its active metabolite *O*-desmethyl erlotinib might be appropriate when tumors do not respond despite the presence of activating mutations, when unexpected side effects arise, or when alternative dosing schedules are used like the weekly high-dose erlotinib schedules used for central nervous system metastases or to overcome acquired resistance mechanisms. Preliminary studies using radiolabeled erlotinib seem to show a correlation between drug uptake and its clinical efficacy.
TKI's induce drastic initial responses in sensitive tumors. However, almost all patients develop drug resistance within a year. Molecular heterogeneity of cancers that appear similar when examined through conventional diagnostics requires new predictive markers to foretell responses to specific therapies. Techniques like patient derived xenografts and short term *ex vivo* tumor cell cultures are used to explore the sensitivity of individual tumors for multiple anti-cancer agents, and have resulted in exciting and promising data. Whether the *ex vivo* techniques represent the *in vivo* tumor characteristics remains to be established, preferentially by translation of the data to the clinic.
No conflict of interest.

227 INVITED

Radiomics: A new paradigm in the analysis of medical imaging data − The example of lung cancer

P. Lambin[1]. [1]*Maastricht University Medical Centre, Maastricht, Netherlands*

"Radiomics" refers to the extraction and analysis of advanced quantitative imaging features in high throughput from medical images, including computed tomography (CT), positron emission tomography (PET) and magnetic resonance imaging (MRI) (Lambin *et al*. EJC 2012; ww.radiomics.org). Importantly, these features are designed to be extracted from standard-of-care images, leading to a very large potential subject pool. Radiomic data are in a mineable form that can be used to build descriptive and predictive models. The core hypothesis of radiomics is that these models, which can include biological or medical data, can provide valuable diagnostic, prognostic or predictive information. Also, relating image features to phenotypes or gene-protein signatures is being investigated. The radiomics enterprise can be divided into four processes, each with its own challenges that need to be overcome: (1) image acquisition and reconstruction, (2) image segmentation and rendering, (3) feature extraction and qualification, (4) bioinformatic analyses. Each step, especially involving large datasets, poses unique challenges. The focus of this presentation will be on the predictive value of CT & FDG-PET radiomics features of non-small cell lung cancer and head and neck cancer, complemented by preclinical tumour data. Finally we will describe the current and potential applications of radiomics to other problems in oncology.
No conflict of interest.

Scientific Symposium (Mon, 30 Sep, 09:00−11:00)

Joint ECCO/JSCO Session: Extended Lymph Adenectomy in GI Cancer

228 INVITED

European view gastric cancer

H. Hartgrink[1]. [1]*Leiden University Medical Centrum, Surgery, Leiden, Netherlands*

The extent of lymphadenectomy is under discussion since Billroth performed the first gastrectomy in 1881. Since then a lot of studies have been performed to find out to what extent a lymph node dissection should be performed. Theoretically, removal of a wider range of lymph nodes by extended lymph node dissection increases the chances for cure. Such resection, however, may be irrelevant if there are no lymph nodes affected or if the cancer has developed into a systemic disease, or if it increases morbidity and mortality substantially.
D2 dissections became standard in the 90's of the last century in East Asian countries. Western countries, however, found that D2 dissections lead to a higher mortality, which offset a possible survival advantage. More recent evaluations, however, show that there is an advantage for D2 dissections even in Western patients. More extended dissections in Japan (i.e. D4) did not further improve survival.
In order to reduce the post-operative mortality, D2 dissections in Europe do not include pancreatico-splenectomy anymore, unless there is direct invasion into these organs. Furthermore registration and centralisation should lead to a further decrease in post-operative morbidity and mortality. Data bases of several European countries are now being combined in the Eurecca upper GI project in order compare protocols, evaluate current treatment and to define future treatment protocols.
Finally more individual techniques of lymph node removal like Image Guided Surgery are explored to optimize the extent of lymph node dissection.
No conflict of interest.

229 INVITED

European view rectal cancer

Abstract not received.

230 INVITED

Optimal nodal dissection for curable advanced gastric cancer

M. Sasako[1], S. Kikuchi[1], M. Takemura[1], T. Oshima[1], N. Kaibe[1], H. Yamashita[1], H. Niwa[1], M. Takii[1]. [1]*Hyogo College of Medicine, Surgery Division, Nishinomiya, Japan*

There are several evidences to support superiority of D2 dissection for curable advanced gastric cancer, although two major European trials failed to prove the benefit in their primary endpoints.
1. Lymphadenectomy for gastric cancer is quite different from that of colonic surgery. In the latter, mesentery can be taken out en-bloc by just ligating and cutting the first trunk of mesentery. In the former exceptionally, the organ has two mesenteries (dorsal and ventral) and the dorsal mesentery incorporate the pancreas body and tail. This means D2 level nodal dissection is special type of dissection, preserving all second branches of the mesentery. In many cases, even in this anatomical disadvantage, complete dissection from the root of first trunk (i.e., celiac artery) and its braches resulted in better survival than D1 dissection.
2. Dutch and MRC D1 versus D2 study were surgical RCTs which have been carried out before each participant learned the technique and post-operative care to a plateau level. Immediate high mortality offsets the benefit of D2 surgery, which was eventually shown after 15 years follow-up by significantly better disease specific survival rate and significantly better local control. High mortality in these studies was attributed to limited experience to cure post-operative surgical complications throughout the study period due to extremely low hospital volume. This was suggested strongly by much lower hospital mortality in Italian study where they carried out a feasibility study of 200 cases among only 8 hospitals and participant had more cases and experience to avoid treatment related death after surgery.
3. A Taiwanese RCT proved the benefit of D2 dissection over D1. Due to high hospital and surgeons' volume, their hospital mortality was zero. This study is the only one which could show statistically significant improved OS after D2 than D1.
4. In the past, many of Western surgeons claimed that gastric cancer with nodal metastasis is already a systemic disease and therefore incurable even by providing a good local control. INT0116 study compared R0 surgery alone versus post-operative chemoradiation treatment, for first,

clearly demonstrated the benefit of good local control for curable gastric cancer.
It is already known that hospital mortality after D2 surgery for gastric cancer can be reduced as low as 3% by good training and having relatively high volume even in Western patients.
Now, not only in Asia but also in the West, both in Europe and USA, D2 is recommended as standard surgery for potentially curable gastric cancer.
No conflict of interest.

231 INVITED

Lateral lymph node dissection for rectal cancer − A Japanese perspective

T. Watanabe[1], T. Akiyoshi[2], K. Sugihara[3]. *[1]The University of Tokyo, Division of Surgery, Tokyo, Japan; [2]Cancer Institute Hospital, Division of Surgery, Tokyo, Japan; [3]Tokyo Medical and Dental University, Division of Surgery, Tokyo, Japan*

In Japan, lateral lymph node dissection has been widely performed to reduce local recurrence after surgery for low rectal cancer. However, in many countries, lateral lymph node metastasis is considered as a systemic disease and lateral lymph node dissection is not performed as a standard therapy. Therefore, we examined whether lateral lymph node metastases are metastatic disease or part of regional lymph node metastases that are amenable to curative resection. We extracted data of all patients with stage I−III low rectal cancer who underwent curative resection from 1978 to 1998 from the Multi-institutional Registry of Large Bowel Cancer in Japan. We compared overall survival (OS) and cancer-specific survival (CSS) between patients with only mesorectal lymph node metastasis (mesorectal-Node group) and lateral lymph node metastasis localized to or extending beyond the internal iliac area (internal-LN group or external-LN group). Among 11,567 patients, lateral lymph node dissection was performed in 5,789 (50%). Mesorectal-Node, internal-LN, and external-LN metastases were present in 3,905 (34%), 411 (3.6%), and 244 (2.1%) patients, respectively. Next, we subdivided the mesorectal-Node group according to the classification by the American Joint Committee on Cancer. Both in 5-year OS and CSS, there were not significant differences between the N2a and internal-LN groups (OS: 45% vs. 45%, *P* =. 9585; CSS: 51% vs. 49%, *P* =. 5742). Furthermore, there were not significant differences between the N2b and external-LPLN groups either (OS: 32% vs. 29%, *P* =. 3342; CSS: 37% vs. 34%, *P* =. 4347). When we compared 5-year OS and CSS between the external-LPLN group and the stage IV patients who underwent curative resection, external-LPLN group showed significantly better 5-year OS and CSS than stage IV patients (OS: 29% vs. 24%, *P* =. 0240; CSS: 34% vs. 27%, *P* =. 0117). These results suggest that lateral lymph node metastasis is not a systemic disease and can be considered as regional lymph node metastasis in low rectal cancer. However, metastasis extending beyond the internal iliac area is associated with poorer survival. From a technical point of view, open surgery is the standard procedure to perform lateral lymph node dissection. In Japan, there are institutions where lateral lymph node dissection is performed laparoscopically. However, it is still not clear whether laparoscopic procedure can achieve the same quality as compared to open surgery in lateral lymph node dissection. On the other hand, recent studies have shown that robotic surgery with enhanced dexterity and stable camera platform may provide a powerful additional tool for optimal management of rectal cancers. We performed rectal cancer surgery in 35 cases including 10 cases with lateral lymph node dissection. In our experience, robotic approach seems to allow better ergonomics and more refined dissection during lateral lymph node dissection. However, further studies are needed to confirm the usefulness of robotic approach both from oncological and functional aspects.
No conflict of interest.

Scientific Symposium (Mon, 30 Sep, 09:00−11:00) **Potential Novel Targets in Gynaecological Cancer**

232 INVITED

Novel membrane receptor inhibitors

A. Leary[1]. *[1]Institute Gustave Roussy, Villejuif, France*

Early trials of membrane receptor inhibitors, such as gefitinib, erlotinib, lapatinib or trastuzumab in unselected patients (pts) with cervical, ovarian or endometrial cancer were negative. However advances in the profiling of gynaecological cancers and new inhibitors targeting c-Met, FGFR, HER3, IGF1R, or the folate receptor offer new hope. Data from the TCGA have made it quite clear that ovarian (OC) and endometrial cancers (EC) are heterogeneous diseases. When considered individually, genomic alterations are rare. However amplifications (A+) and mutations (M+) in membrane receptors are described and associated with specific histological subtypes: HER2 M+ are found in 9% of low grade serous OC while HER2 A+ in 20% of clear cell OC or high grade serous EC. HER3 A+ and EGFR M+ are described in 4−9% of high grade serous OC, c-Met A+ in 20% of clear cell OC, FGFR2 M+ in 15% of endometrioid EC and FGFR-1/3 A+ in a subset of high grade serous EC, while IGF1R is amplified in 5% of high grade serous OC and EC. These data may provide the rationale for an adaptive trial matching pts to inhibitors according to specific genomic alteration. Finally the folate receptor (FR) is ubiquitously expressed in OC and EC and antibodies targeting FR are in phase II/III development. However a number of questions remain unanswered. Early negative trials used receptor inhibitors alone in unselected pts. Response may require an association with chemotherapy. If pt selection is required, what is the appropriate biomarker: receptor protein, mRNA, mutation or amplification? The only response to gefitinib in OC was associated with an EGFR M+, however trastuzumab had no activity in HER2 A+ EC; trials of FGFR inhibitors in FGFR2 M+ EC are ongoing. In addition, ligands may be relevant; preclinical studies suggest that autocrine receptor activation predicts sensitivity to HER inhibition. Dimerization inhibitors have the potential to disrupt more HER-mediated pathways, unfortunately phase II studies of pertuzumab in unselected pts with OC have been disappointing. However a trial of pertuzumab selecting pts on the basis of tumor HER3 mRNA levels as a surrogate for receptor activation is ongoing. Finally, unless the receptor is a true oncogenic driver (such as EGFR M+ in lung cancer), inhibiting the target alone may not translate into tumor shrinkage. However drug-antibody conjugates may be worth investigating in patients selected for receptor overexpression as a means of selective chemotherapy delivery. For example, a phase III trial of the antibody against FR, farletuzumab, in OC was negative, however a phase II trial of EC145, an FR antibody-drug conjugate showed a significant PFS benefit in FR expressing OC. An update on these and other novel membrane receptor inhibitors in gynaecological cancers will be presented.
No conflict of interest.

233 INVITED

Novel agents in overcoming drug resistance

A. Reyners[1], B. Poppema[1], S. De Jong[1], H. Hollema[2], H.W. Nijman[3], E.G.E. De Vries[1]. *[1]University Medical Center Groningen, Medical Oncology, Groningen, Netherlands; [2]University Medical Center Groningen, Pathology, Groningen, Netherlands; [3]University Medical Center Groningen, Gynaecological Oncology, Groningen, Netherlands*

Standard treatment of advanced epithelial ovarian cancer (FIGO stage IIB-IV) consists of surgery and 6 cycles platinum-based chemotherapy. Despite tumor responses of ~80% to this frontline therapy, recurrences are common and result in a 5-year overall survival (OS) rate of ~35%. The addition of other chemotherapeutic drugs and/or targeted therapy to the frontline regimen as well as dose dense or maintenance therapy failed to show therapeutic superiority.
Patients that initially responded well to platinum-based chemotherapy can be re-treated with a platinum-based regimen if the treatment naive interval was $\geqslant$6 months. Prolongation of the platinum-free interval by other drugs has been advocated to allow reintroduction of a platinum-based regimen and thereby increase OS. Data of 2 phase III studies that compare a platinum-based to a non-platinum-based regimen (liposomal doxorubicin and/or trabectedin) in patients with recurrent disease 6−12 months after platinum-based therapy, are awaited to proof this hypothesis. No effective treatment has been established for platinum-refractory disease.
Eventually, most patients will develop platinum-resistant disease and then only ~15% response rate can be achieved with various chemotherapy regimens. Therefore, novel agents are warranted to overcome drug resistance. Combining standard chemotherapy in first or second line with the VEGF-A antibody bevacizumab, prolongs progression-free survival with 4 months without affecting OS.
Recently, more insight has been obtained in the various ovarian cancer subtypes. PARP inhibition resulted in up to 40% responses in patients with BRCA1/2 mutation associated ovarian cancers in phase II studies. The most prevalent histological subtype, the high grade serous, is genomic unstable and associated with various mutations and/or molecular aberrations, whereas only a limited number of driver oncogenes are apparent. This makes the emerging fields of immunotherapy, treatment with antibody drug conjugates and drugs interfering with cell cycle kinases of major interest. Low-grade serous cancer is different, the mitogen-activated protein (MAP) kinase pathway is frequently activated and MEK inhibition showed efficacy. Moreover in about a third of the clear cell and endometroid ovarian cancers the PI3K pathway is activated and therefore a potential drug target.
Conflict of interest: *Advisory board: Roche*

234 INVITED

PARP inhibitors

Abstract not received.

235 INVITED

AKT, mTOR, PI3kinase

Abstract not received.

Scientific Symposium (Mon, 30 Sep, 09:00−11:00) **Technology Issues: Healthcare 2.0**

236 INVITED

E-health is empowered health

L. Engelen[1]. [1]*Radboud University Nijmegen Medical Center, REshape & Innovation Center, Nijmegen, Netherlands*

The “e” of e-health is very popular nowadays. Mostly pointed as electronic health the real value in my perspective is the empowering value of real e-health. For that over the past years I have been renaming e-health in to empowering health.
The lecture will reflect on the current and future developments that will be brought through (exponential) growing technological possibilities. (Monitoring of) health will be consumerized over the next 5−10 years, where devices, applications and services will be developed that will turn the way we will deliver health(care) ‘a bit’ upside down.
Personal Health Records, activity trackers, blood pressure meters, EKG-sleeves, and other (FDA approved) devices that can track 9 vitals signs all priced under $200 will be hitting the market; are we in healthcare ready for that, whether or not the speed of these developments may vary, as the impact will as well, it is going to affect our work. Are we willing to accept that the livespan of inventions might be half the one that we are used to. Accept in terms of actively collaborate to find the true value of this. How do we cope with this in education, training, CME?
That and more, also from the work I am doing at Singularity University, FutureMed Silicon Valley.
No conflict of interest.

237 INVITED

Patients’ experiences in dealing with technology

J. Pelouchova[1]. [1]*Leukemia Patient Advocates Foundation, Prague, Czech Republic*

While the 21st Century represents a decade of targeted therapies in oncology, the focus on e-health is emphasised on the field of patients’ use of technology. The increasing demand for information on cancer is connected to improving treatment outcomes, legislative changes enabling cancer patients to access their medical records and the constant rise of internet connectivity amongs all generations.
These factors contribute to a general need for information concerned with disease related facts, treatment options, navigation to experts in the respective cancer diagnostic area and crucial possibilities regarding medical innovations such as enrollment in clinical trials. Internet as the prime medium of information distribution needs to be used as a reliable source of knowledge as opposed to floods of unsorted and dubious material.
This presentation aims to address vital possibilities and options that can be offered via means of technology to help patients seeking expertise, advice and support and, impacts on the patient-doctor relationship.
Main issues are the navigation of patients towards support groups, online patient discussion forums connecting patients by sharing experiences and methods of patient education. Electronic tools and materials represent a cost-effective information flow with a wide outreach, i.e. educative videos, online surveys or mobile applications for patients and, have proven successful for patients (examples of patient led projects).
No conflict of interest.

238 INVITED

Nurses’ experiences in dealing with technology

R. Fraser[1]. [1]*Patient Order Sets, Research and Development, Toronto, Canada*

Nurses work across the healthcare system in many ways − interacting with patients in acute and community care, as well as working in public health, health administration and as researchers. Nurses’ wide range of involvement with clients and caregivers across the care continuum means they frequently interact with traditional and emerging technologies in healthcare. Healthcare 2.0 technologies offer platforms with entirely new potential that previous technology, time and geography prevented. Therefore, it is critical for nurses to learn the appropriate skills to leverage the expanding possibilities and mitigate risks created by digital tools and social media.
New technology enables new possibilities and can have unintended consequences. As new uses for technologies are explored within healthcare, equal consideration must be made for the potential harm. Nurses must be aware of both the benefits and risk when engaging with digital tools. New opportunities must be balanced with clients’ preferences and their right to access and control their information. As health professionals navigate these challenges, lessons have emerged which need to be shared.
When risk is considered and mitigated, nurses can explore and experiment with new technologies to advance healthcare and the health of patients. Understanding both perspectives will enable nurses to develop new ways to support collaboration, expand research, enhance knowledge translation, and accelerate quality improvement in healthcare. Healthcare 2.0 can surface previously hidden work and connect groups with shared interests. A selection of examples will be used to illustrate ways healthcare providers are working to advance healthcare delivery and patient outcomes.
The objectives of this presentation are to highlight the opportunities of healthcare 2.0, explore the risks, and suggest ways to plan and measure online initiatives. Case studies and examples will be used to illustrate the nurses’ experience with technology.
Conflict of interest: *Advisory board: Connecting Nurses (Supported by Sanofi Aventis Groupe). Board of directors: VON Canada*

Scientific Symposium (Mon, 30 Sep, 09:00−11:00) **Therapeutic Procedures in Liver Metastases: Conventional and Future**

239 INVITED

Therapeutic procedures in liver metastases: SBRT for which patients?

L. Dawson[1]. [1]*University of Toronto, Princess Margaret Hospital, Toronto, Canada*

Background: Resection of liver metastases from colorectal carcinoma (CRC) is associated with 5 year survival rates from 30 to 40%, with the possibility for cure, even in the absence of systemic therapy. This demonstration of a local therapy improving outcomes for ‘oligo-metastatic’ CRC is well accepted. Long term survivors have also been reported following resection of liver metastases from sarcoma, renal cell carcinoma, breast cancer and melanoma. Clinical experience in stereotactic body radiation therapy (SBRT) for CRC and non-CRC liver metastases is rapidly increasing.
Material and Methods: SBRT is an attractive option for patients with liver metastases, due to increased convenience, as well as pre-clinical data demonstrating dose-per-fraction effects (e.g. endothelial and immune effects), with a threshold of approximately 8 Gy. SBRT has been used most often to treat liver metastases <6 cm in maximum diameter, with a range in doses from 30 to 60 Gy in 1 to 6 fractions.
Results: In general, survival rates following SBRT for liver metastases have been better than that expected with systemic therapy alone, and toxicity is uncommon as long as enough uninvolved liver can be spared from radiation therapy (e.g. >700 cc receiving 15 Gy in 3 fractions). The median survival of patients treated with SBRT ranges from 17.6 to 37 months, with the best outcomes seen in more recent series. Local control at one year ranges from 67% to 100%. Median survival from a phase I/II study of 107 patients with bulky metastases (median volume 75 cc) treated with 6 fraction SBRT (median dose 42 Gy) at PMH, Toronto was 18.1 months. Presence of extra-hepatic disease was associated with worse survival. Prognostic factors for improved local control included breast primary site, dose and tumor volume. Some patients with CRC or breast cancer liver metastases have had no progression, with no further therapies at 5 or more years post SBRT. In a pooled analysis of CRC metastases SBRT, dose was the only significant prognostic factor for local control, and extra-hepatic disease and local recurrence were associated with impaired survival. A dose of 48−51 Gy in 3 fractions was estimated to be associated with a one year local control rate of 90%. As outcomes are best following higher dose SBRT, the most suitable patients for SBRT include those with 3 or fewer metastases, <3 cm in maximal diameter, more than 1 cm from luminal gastrointestinal organs. However, long term local control is also possible in patients with 3−5 metastases, >3 cm in maximal diameter. Breast cancer metastases appear more sensitive than CRC metastases.

Conclusions: SBRT is a promising treatment for patients with focal 'oligo' liver metastases. More research is required regarding SBRT specific mechanisms of actions, as well as optimal patient selection.
Conflict of interest: *Corporate-sponsored research: Bayer research grant. Other substantive relationships: Raysearch licensure agreement*

240 INVITED

Gastrointestinal malignancies − noncolorectal cancer: RFA for which patients?

A. Veltri[1], I. Garetto[1], M.A. Satolli[1], C. Gazzera[2], M. Busso[3], F. Solitro[3]. *[1]University of Torino, Department of Oncology, Torino, Italy; [2]University of Torino, Città della Salute e della Scienza, Torino, Italy; [3]University of Torino, A.O.U. San Luigi Gonzaga, Orbassano (TO), Italy*

Background: While RFA has accepted indications for HCC and has demonstrated some usefulness for metastatic colorectal cancer (CRC), there are few studies on hepatic metastases (METS) from non-colorectal (NCRC) gastrointestinal malignancies (GIM).
Material and Methods: We performed a retrospective analysis on 75 patients (46 male; age 30−81 y, av. 64) with 140 METS from NCRC GIM, treated at our institution between 1998 and 2013. They were sub-classified by primary histological types, due to a potentially very different biological behavior. 51 METS were from neuroendocrine tumors (NET), 45 from pancreatic and biliary cancer (PBC), 29 from gastro-esophageal cancer (GEC), and 15 from GIST. The mean tumor size was 25 mm (6−65 mm). 129 treatments were percutaneous, 11 intraoperative.
Adverse events (AE), technique effectiveness (TE) and clinical usefulness were statistically analyzed.
Results: AE rate was 7% (10/140; only 4 major, 3%); a lower mean size seemed to be protective against AE (35 vs. 24 mm, $p = 0.0092$).
During the follow-up (1–134 months, av. 25) a maintained complete ablation (CA) was obtained in 70% of METS (98/140), while 30% showed viable tissue either residual at first follow-up imaging or recurrent after a CA had initially achieved (local tumor progression). Predictors for TE have been diameter $\leqslant$25 mm ($p = 0.0015$; mean diameter of CA vs. non CA, 21 vs. 31 mm, $p < 0.0001$) and the intraoperative approach ($p = 0.0334$).
4 patients were lost at follow-up; 32 patients died, mainly for a systemic progression of the disease. By histological subtypes, 3 and 5-yr overall survival (OS) rates were 100% and 57% for NET, both 28% for PBC, 24% and 8% for GEC, 83% (3-yr only) for GIST. Despite a bad overall prognosis, single vs. multiple METS resulted predicting better 3-yr survival in the GEC group (39 vs. 11%, $p = 0.015$).
Conclusions: Based on our results and literature, RFA of METS is feasible and safe. However, so far RFA should be considered less useful for NCRC as compared with CRC, except for NET, in which loco-regional therapies can both reducing symptoms and prolonging survival. Currently, there is no evidence robust enough to demonstrate which patients could benefit from RFA. Therefore, a patient selection based on a multidisciplinary approach should be recommended, including RFA in a multimodal therapy. In fact, it could be an adjunctive tool in treating METS from NET and GIST and may be used in conjunction with systemic therapy to manage limited PBC and GEC metastatic disease.
No conflict of interest.

241 INVITED

Radioembolization: For which patients?

A. Hendlisz[1], A. Deleporte[1], P. Flamen[2]. *[1]Institut Jules Bordet, Digestive Oncology, Brussels, Belgium; [2]Institut Jules Bordet, Nuclear Medicine, Brussels, Belgium*

^{90}Yttrium-loaded microspheres, used for radioembolization, are registered in the European Union as medical devices, indicated for treatment of liver neoplasms.
This definition is vague and allows many different interpretations.
Radioembolization is a locoregional treatment that has to be compared to other local techniques such as surgery, radiofrequency ablation, stereotactic radiotherapy, chemoembolization, etc.
Radioembolization takes advantage of the anatomical particularity of dual liver blood flow by delivering the therapeutic devices via the hepatic artery, which predominantly brings its blood flow to the liver tumors as opposed to the portal vein irrigating mainly the liver parenchyma.
Radioembolization requires usually a pre-therapeutic simulation with ^{99}Technecium-labelled albumin macro aggregates (99mTc-labeled MAA). This test is commonly used to assess the presence of a hepatopulmonary shunt, precluding the use of radioembolization if superior to 20%. It allows also the prediction of the therapeutic effects by assessing the concordance between lesions mapped out by the baseline imaging (CTScan, magnetic resonance imaging, FDG-PET, . . .) and the lesions showing an uptake of microspheres, visualized by 99mTc-labeled MAA.
As commonly discussed for every loco-regional treatment, the decision-making process of radioembolization should undergo 3 major steps:
1. A multidisciplinary discussion on the medical indication, taking into account the tumoral histology, the general and liver status of the patient, the curative or palliative therapeutic intention, put in perspective with available data in the medical literature.
2. A technical discussion, essentially held between the interventional radiologists and the nuclear medicine specialists, where the liver artery anatomy, existing shunts (pulmonary or others) and the uptake of 99mTc-labeled MAA in the liver lesions are reviewed in order to define the feasibility, the potential toxicity and the foreseen oncological outcome for the patient. This should take place after the simulation.
3. A general discussion in a multidisciplinary setting to discuss and confirm the indication and the treatment before its effective administration.

As a consequence, almost 50% of the patients proposed in our hospital for this therapy are denied radioembolization because of poor indication, excessive toxicity or therapeutic futility. The aim of this talk will be to identify the principles underlying yttrium-90 microsphere therapy for hepatic malignancy, review theoretical indications and help clinicians understand the potential and challenges of this innovative technique.
No conflict of interest.

242 INVITED

HIFU for which patients?

G. Ter Haar[1]. *[1]ICR − Centre for Cancer Therapeutics, Division of Radiotherapy and Imaging, Sutton Surrey, United Kingdom*

High intensity focused ultrasound (HIFU) is a technique which allows selective destruction of tissue at depth by thermal ablation, whilst sparing overlying and surrounding tissues. For most current applications it is delivered using an extracorporeal source. A relatively recent technique, it has been used most extensively for the treatment of uterine fibroids, and (using a trans-rectal route) for the treatment of prostate cancer.
There are limited clinical trials for the application of HIFU to the treatment of primary liver cancer, but to date its use for liver metastases is limited, and reports of its efficacy are largely anecdotal.
HIFU can be delivered entirely non-invasively, and so is suitable for patients who cannot withstand hepatic surgery. In order to reduce organ movement, a light anaesthetic is usually administered, thus allowing control of respiratory motion. Few side effects have been reported, the most serious being minor skin burns that resolve rapidly, without the need for further treatment. Tumours can be targeted trans-costally, although this may restrict the depth at which ablation is achievable, and care must be taken that the energy deposition at the rib surface does not lead to excessive tissue heating. It is important to use an acoustic window at the skin surface that does not include any scar tissue as its high acoustic energy absorption may result in a skin burn.
HIFU has the potential to ablate tumours under real time imaging guidance, and is well tolerated by patients. When appropriately delivered, only tissue in the focal region is exposed, and so repeat treatments can be carried out, in the same, or adjacent targets.
There is a real need for well designed prospective trials of the use of HIFU for the treatment of liver metastases, either on its own, or in conjunction with adjuvant therapies, in order that its true potential can be properly assessed.
No conflict of interest.

Scientific Symposium (Mon, 30 Sep, 09:00−11:00)
Immunology from Bench to Bedside

243 INVITED

Translational biomarkers in immunotherapy

M. Maetens[1], D. Fumagalli[1], C. Sotiriou[1]. *[1]Institut Jules Bordet, Breast Cancer Translational Research Laboratory, Brussels, Belgium*

In the past decade, cancer immunology has emerged as a fundamental aspect of oncology and immunotherapy has become a reality for cancer patients. While immunotherapies are routinely used against tumor types such as melanoma and renal cell carcinoma, increasing evidence suggests that certain subtypes of Breast Cancer (BC) may also be vulnerable to immune approaches. Our group showed that an immune response module, the STAT1 module, was predictive of a better prognosis in TN and HER2+ BC patients, and other investigators showed in the same setting that the overexpression of immune related genes was able to identify subgroups of patients with a better prognosis.
Specific cytotoxic agents were found to induce "immunogenic" cell death that can facilitate host immune tumor elimination and produce better clinical outcomes.

In a neoadjuvant clinical trial (Trial of Principle (TOP) study) in which patients with ER− BCs were treated with anthracycline monotherapy, we showed that high immune module scores were associated with sensitivity to anthracyclines. Similarly, in a recent meta-analysis of 996 patients treated with neoadjuvant chemotherapy (CT), we showed that an immune module, consisting mainly of TH1/interferon response, predicted pathologic complete response (pCR) in all BC subtypes adding prediction to standard clinico-pathologic parameters. The IS seems also pivotal in determining the response to monoclonal antibodies such as trastuzumab, and some evidence indicates a possible role in the response to endocrine treatment. In a recent study, Denkert et al. showed that the percentage of tumor-infiltrating lymphocytes (TILs) was a significant independent parameter for pCR in BC patients treated with anthracycline/taxane neoadjuvant CT. Several subsequent studies showed that besides being a predictive biomarker of CT and trastuzumab efficacy in TN and HER2+ BC, respectively, baseline TILs levels seem to be associated with better survival. Further prospective studies are needed to validate these findings and to better characterize the population of TILs in breast tumors.
The observed correlation of clinical prognosis with PD-L1 expression in multiple cancers suggests that the PD-1/PD-L1 pathway might play a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention. Indeed, recent trials with agents inhibiting programmed cell death-1 (PD-1) or its ligand PD-L1 showed durable tumor regression and stabilization of disease in patients with advanced cancer, providing new hope for the treatment of BC patients.
Conflict of interest: *Advisory board: Novartis, Merck, Nanostring, Roche. Other substantive relationships: C Sotiriou discloses a co-ownership of several patents involving gene expression immune related signatures*

244 INVITED

Engaging in adaptive tumour response in cancer

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Immunotherapeutic strategies that modulate the adaptive immune system to enhance antitumor immunity have demonstrated remarkable recent clinical success. Specifically, targeting the normally negative T cell regulators, cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death-1 receptor (PD-1) with monoclonal antibodies has led to improvements in overall survival and durable tumor responses, respectively. We and others are studying ways to further improve the number of patients who benefit from these treatments by combining these antibodies with conventional cancer treatments and performing biomarker studies to identify patients most likely to benefit. This talk will focus on the preclinical rationale and our ongoing clinical investigations of CTLA-4 blockade in combination with PD-1 blockade, radiotherapy, targeted therapy, and vaccines. We will also discuss our current work investigating the absolute lymphocyte count and the immunosuppressive cell population, myeloid derived suppressor cells, as potential biomarkers for CTLA-4 blocking antibodies and tumor cell membrane expression of PD-L1 as a potential biomarker for antibodies blocking PD-1 and/or PD-L1.
Conflict of interest: *Advisory board: Non-paid advisory board participation for Bristol-Myers Squibb. Corporate-sponsored research: Recipient of research funding from Bristol-Myers Squibb*

245 INVITED

Targeting immune regulator circuits in cancer: New mechanistic insights

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The continual interaction of the immune system with a developing tumor is thought to result in the establishment of a dynamic state of equilibrium. This equilibrium depends on the balance between subsets of effector and regulatory lymphocytes. Whereas the overall mechanisms underpinning this balance remain unknown, we have learned that regulatory T lymphocytes have a great tendency to infiltrate and accumulate in tumors, meanwhile effector T cells fail to efficiently do so. Furthermore, different subtypes of regulatory cells and inhibitory molecules such as CTLA-4 tightly control the few effector T lymphocytes that manage to infiltrate the tumor. The outcome of this balance is critical to survival, and while in a few cases the equilibrium resolves in the elimination of the tumor by the immune system, in many other cases the tumor manages to escape immune control. Remarkably, antibodies against CTLA-4, a key immune modulatory receptor expressed on T cells, efficiently modify this balance, driving effector T cell expansion and increasing the ratio of Teff/Treg within the tumor. Whilst the high Teff/Treg ratio in the tumor directly correlates with tumor destruction in mice and humans, the mechanisms underpinning this phenomena remain unknown. By focusing in the study of effector and regulatory tumor-reactive CD4+ T cells my group is interested in the mechanism underpinning the activity of different immune-modulatory antibodies within the tumor microenvironment, and the potential positive and negative impact that the tumor microenvironment may have in the recruitment, survival and function of different T cell subsets.
No conflict of interest.

246 INVITED

Immunology from bench to bedside

G. Curigliano[1], C. Criscitiello[1], A. Esposito[1], L. Fumagalli[1], L. Gelao[1], M. Locatelli[1], I. Minchella[1], A. Goldhirsch[1]. [1]*European Institute of Oncology, Early Drug Development Division, Milan, Italy*

The basic concept of immunotherapy in cancer is to enable the immune system to identify neoplastic cells and to either prevent carcinogenesis and/or reject transformed cells with a potential for malignant tumour growth. Denkert et al showed that the percentage of tumor-infiltrating lymphocytes (TILs) defined on a hematoxylin-eosin slide was a significant independent parameter for pCR in breast cancer (BC) patients treated with anthracycline/taxane neoadjuvant chemotherapy (CT). Several subsequent studies showed that besides being a predictive biomarker of CT and trastuzumab efficacy in triple negative and HER2+ BC, respectively, baseline TILs levels seem to be associated with better survival in the same two BC subtypes. More prospective studies are needed to validate these findings and to better characterize the population of TILs. Available data suggests that TILs are mainly represented by non-active T cells that can become active after CT induction, but the role of B cells, natural killer (NK), NKT and TReg cells is still unclear. This is of particular relevance now that therapeutic strategies targeting the immune system are emerging. Recently, molecules inhibiting programmed cell death-1 (PD-1) or its ligand PD-L1, which inhibit antitumor immune response, were shown to induce durable tumor regression and stabilization of disease in patients with advanced cancer and give new hope for the treatment of BC patients. A major limitation of the various approaches to turning on an immune response to cancer is that the immune system exerts a major effort to avoid immune over-activation, which could harm healthy tissues. Cancer takes advantage of this ability to hide from the immune system by exploiting a series of immune escape mechanisms that were developed to avoid autoimmunity (mechanisms of tolerance). Among these mechanisms are the hijacking of immune-cell–intrinsic checkpoints that are induced on T-cell activation. Blockade of one of these checkpoints, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or the programmed death 1 (PD-1) receptor, provided the first evidence of activity of an immune-modulation approach in the treatment of a solid tumor. The future frontier in the treatment of cancer requires identification of potential targets in order to personalize therapies. The immune system remembers what it targets, so once the system is correctly activated, it may mediate a durable tumor response.
Andre F, Dieci MV, Dubsky P, Sotiriou C, Curigliano G, Denkert C, Loi S. Molecular pathways: involvement of immune pathways in the therapeutic response and outcome in breast cancer.
Clin Cancer Res. 2013 Jan 1;19(1):28−33.
No conflict of interest.

Scientific Symposium (Mon, 30 Sep, 09:00−11:00)
How Next Generation Sequencing is Changing Therapeutic Decision Making

247 INVITED

Next generation sequencing: Basic principles and applications in the biomarker arena

Abstract not received.

248 INVITED

Massively parallel sequencing analysis of clinical samples: Challenges and opportunities

M. Berger[1]. [1]*Memorial Sloan Kettering Cancer Center, New York NY, USA*

Massively parallel sequencing technology has the potential to transform cancer diagnosis and treatment through the identification of driver genetic alterations that may be suppressed by targeted therapies. Through retrospective analysis of clinical specimens, one can discover genomic biomarkers that correlate with outcomes and therapeutic response. Profiling multiple tumors from individual patients can reveal factors that influence tumor progression and drug resistance. Finally, prospective sequencing of clinical specimens can complement traditional radiology and histology based imaging in the routine diagnosis and treatment of cancer patients.

For increasingly lower costs, one can interrogate all clinically relevant genes for mutations, copy number alterations, and structural rearrangements, with high detection sensitivity in heterogeneous tissue. Advances in exon capture, molecular barcoding, and profiling of formalin-fixed paraffin embedded (FFPE) specimens have further established the clinical potential of next generation sequencing. However, challenges remain in the application of these techniques to the analysis of clinical tumor samples. In addition to the technical challenge of analyzing ever-decreasing amounts of FFPE tissue, one must overcome the biological challenges of aneuploidy and heterogeneity inherent to the genetics of cancer.
In this talk, I will discuss different strategies for sequencing clinical samples, including different sequencing platforms, capture methods, and breadth of testing (i.e. targeted versus comprehensive approaches). I will describe examples in which our group has performed massively parallel sequencing on clinically annotated tumor specimens to identify genomic biomarkers predictive of drug response and resistance. Finally, I will describe additional challenges in the application of these techniques involving bioinformatics, scalability, clinical interpretation, reporting, regulatory compliance, reimbursement, and ethics.
No conflict of interest.

249 INVITED

Massively parallel sequencing for predictors of therapy

M. Ellis[1]. [1]*Washington University in St Louis, Division of OncologyCampus, St Louis, USA*

Next generation sequencing is beginning to suggest new therapeutic approaches that might be more effective for the treatment of breast cancer (Cancer Discovery 2013: 3; 27−34), the most notable of which are HER2 mutations in HER2 non-over-expressed tumors which are the target of an ongoing neuratinib trial (Cancer Discovery 2013: 3; 224 227). Other areas of focus for discovery sequencing in advanced clinical trials include the CDK4/CyclinD pathway and the PI3K pathway. However there are currently no clinically validated predictive biomarkers for the use of CDK4 inhibitors, rapalogs or other PI3 kinase inhibitors so that these agents are being used in a relatively indiscriminate way. The efforts to define predictors based on sequencing DNA is clearly limited by the focus on analysis of paraffin-embedded formalin-fixed primary breast tissue and the retrospective nature of the analysis. It is clear that biopsies of advanced disease before the initiation of treatment and higher quality material would be ideal, but there are ongoing concerns about the feasibility of obtaining this material which is magnified when research questions require serial sampling before and after treatment to study resistance. There is also a more fundamental biological problem. Instead of the one gene one drug paradigm pathway exemplified by our HER2 mutation and neuratinib study, CDK 4/6 inhibitors and PI3 kinase inhibitors target complex multi-gene mutational spectra and we have yet to secure algorithms that can put multiple genes in a pathway into a common predictor.
The use of patient-derived xenografts (PDX) is an alternative system to develop predictors of response based on genome sequencing. PDX models are readily obtainable from HER2− and ER− disease at any stage of presentation, but for ER+ HER2− disease, most models are derived from advanced disease patients. Whole genome sequencing was used to demonstrate that a PDX was excellent genomic replica of the originating basal-like breast cancer (Nature 2010 464:999–1005) and we now have extensive experience of multiple whole genome comparisons between originating tumor/PDX pairs.
We are now initiating a series of “xenograft phase 2 trials” with CDK4/6 inhibitors, PI3 kinase agents and MDM2 inhibitors that are not only designed to study drug efficacy but to develop a more secure diagnostic paradigm for the use of these novel targeted agents through DNA, RNA and protein sequencing approaches. The relatively large yield of tissue in this system facilitates the use of next gene mass spectrometric analysis of phosphoproteomes. This is a logical compliment to DNA and RNA sequencing in our search for predictive markers because perturbations in signaling flux induced by somatic mutations and drugs execute the phenotypes we are interested in.
No conflict of interest.

250 INVITED

The impact of massively parallel sequencing on the classification and prediction of haematological malignancies

T. Haferlach[1]. [1]*MLL Münchner Leukämielabor GmbH, München, Germany*

The diagnosis, characterisation, classification and prognostication of haematological malignancies are changing gears. The description of the diseases are on the way from a phenotype to a molecular genotype. This is paved due to increasing knowledge of the cytogenetic background but even much more due to rapidly emerging molecular techniques. Thus, so called Next Generation Sequencing techniques had revolutionized the field in haematology during the last five years and led to fascinating and important examples first by gene expression profiling nearly ten years ago but finally due to massively parallel sequencing based on amplicon or panel testing, whole exome sequencing or even whole genome sequencing.
Due to this new application not only many new genes have been found to be of importance for the underlying biology of the respective leukemias and lymphomas. But in addition new prognostic markers and even new targets have been defined. This is true for several genes that are involved in DNA methylation, chromatin modification, for cohesin complex genes and also theses of the spliceosome. The landscape of several diseases such as AML and MDS has been highlighted by combination of several techniques, in detail also based on these next generation sequencing approaches. It will be our challenge now to place these new techniques and results on the background of techniques such as morphology, immunophenotyping, cytogenetics, FISH and standard molecular approaches. The final scenario of the diagnosis, classification and prognostication of haematological malignancies will for sure be a mixtum compositum of all these approaches but will be mainly driven by the understanding of the genome of the respective diseases.
Conflict of interest: *Ownership: MLL Munich Leukemia Laboratory. Corporate-sponsored research: Novartis, ROCHE*

Scientific Symposium (Mon, 30 Sep, 09:00−11:00)
Empowering Survivors of Childhood and Adolescent Cancer

251 INVITED

What is the issue? The survivor's view point

A. Brownsdon[1]. [1]*University College London Hospitals, Oncology, London, United Kingdom*

There is a gap in services for survivors of childhood and adolescent cancer particularly for those over 25 years old.
The main gaps in service provision for adult cancer survivors are around education, employment and psychological support. In addition adult and children's services in the UK are funded and managed differently. This can make it hard for survivors to access appropriate care and support especially when transitioning between services.
The specific needs of adult cancer survivors are also different to those of children and adolescents. For example, as adults, survivors of childhood cancer can face societal expectations of independence and an ability to maintain self-sufficiency which cannot always be met. In addition, many adult survivors will be trying to access higher education or employment with the added burden of a cancer history and some may also have families of their own to support.
Adult cancer survivors have repeatedly expressed their need to address issues such as those outlined above. It is important that they feel empowered to make informed decisions about their health and lives in general and that they are supported in making these choices.
Survivors of childhood and adolescent cancer want to receive reliable, personalised information and follow-up care from specialists with expertise about late effects occurring in adult life. Survivors also want to be able to access specialist health services without a GP referral.
In addition, adult survivors would like advice and support regarding access to education and employment as well as information on issues such as life and travel insurance. Survivors have also expressed a need for access to support groups and networks in order to meet others in a similar position and to share experiences.
The National Cancer Survivorship Initiative (NCSI), a part of the National Cancer Reform Strategy for England has helped to recognise some of the needs of adult childhood cancer survivors. This includes the development of models of long-term follow-up care which promote self-management, effective transition between services and service re-entry without referral as well as treatment summaries for survivors. As a result of the NCSI work some of the needs of survivors are being recognised and there are now more specialist long-term follow-up and late effects nurses in more treatment centres than previously.
Despite these changes, there is still a long way to go in terms of addressing the issues faced by adult survivors of childhood cancer. Services need to be developed so that adult survivors can feel empowered to self-manage and make informed, supported decisions about their health in order to lead lives that are as normal and independent as possible.
No conflict of interest.

252 INVITED

Genetic predisposition to late complications after cancer treatment − what do we know?

T. Langer[1], S. Radtke[1], J. Meitert[1], O. Zolk[2]. [1]*University Hospital for Children & Adolescents, Ped. Oncology, Erlangen, Germany;* [2]*Institute for Experim. and Clinical Pharmacology and Toxicology, Pharmacogenetics, Erlangen, Germany*

Modern therapy optimizing protocols raise the survival rates of children with cancer. These patients are exposed to the risk of late effects of their treatment. Adverse effect of the cytostaticum cisplatin is the irreversible hearing impairment of the inner ear. The risk of ototoxicity is associated with polymorphism in candidate genes, i.e. megalin, glutathion-S-transferase, *COMT* and *TPMT*. These results have to be conformed by larger study cohorts with more statistical power. Furthermore methotrexate is an example for a drug with many adverse effects. Based on data from the ALL-BMF 2000 study cohort we showed that the polymorphism c.521C>T in SLCO1B1 is highly significant associated with the MTX-clearance. In a multiple regression model, MTX AUC0−48 h increased by 26% (P=6.8x10−8) per *SLCO1B1* rs4149056 C allele. MTX AUC0−48 h was a significant predictor of overall toxic adverse events during MTX courses (R2=0.043, P=2.9x10−5), whereas the *TYMS* rs34743033 tandem repeat polymorphism was predictive of stomatitis (R2=0.018, P = 0.009), a frequent side effect of high-dose MTX. Multiple Cox regression analysis revealed an association of minimal residual disease (hazard ratio 7.3; P=3.2x10−4) and *MTHFR* rs1801131 (hazard ratio 3.1; P = 0.015) with event-free survival in the ALL-BFM 2000 study population. Studies on pharmacogenetics may identify genetic markers to avoid acute or chronic late effects in future.

No conflict of interest.

253 INVITED

Non-visible subtle long-term complications to treatment − what are they, how do we find them and what do we do?

H.J. Van der Pal[1], L.C.M. Kremer[2]. [1]*AMC, Medical Oncology/Pediatric Oncology, Amsterdam, Netherlands;* [2]*AMC, Pediatric Oncology, Amsterdam, Netherlands*

Major advances in medical and supportive care have contributed to a growing population of childhood cancer survivors (CCS). With 5-year overall survival approaching 80%, most children diagnosed with cancer today are expected to become long-term survivors.

Unfortunately, successful cancer treatment can cause treatment-related health problems, the so-called late adverse effects or chronic health conditions which can emerge even decades after treatment.

Previous studies have soon that approximately 3 out of 4 survivors will experience one or more late effects, which are severe or life-threatening in 25%. Adverse late effects are divers and include the full spectrum of potential health problems. Late effects such as; second malignancies, cardiovascular disease, endocrine disorders, and cognitive and psychosocial problems, often affect quality of life. Asymptomatic late effects precede most symptomatic late effects. By identifying these asymptomatic late effects, treatment can be started early and can possible prevent deterioration or development of a symptomatic late effect. In light of this, long-term risk-based follow-up care of CCS is advocated to facilitate early detection of late effects and timely initiation of interventions to optimize life-long health of survivors.

It is very important to realize that screening for asymptomatic events should only be done based on guidelines. These guidelines should focus on five key issues: (1) Who needs surveillance? (2) At what age or time from exposure should surveillance be initiated? (3) At what frequency should surveillance be performed? (4) What surveillance modality should be used? (5) What effective treatments are available if health problems are identified? Only if possible treatment for asymptomatic late effects could be effective to prevent further deterioration, screening should be recommended. For example serial monitoring of cardiac function in CCS treated with anthracyclines to identify asymptomatic cardiac dysfunction is recommended based on the evidence that early treatment with ACE-inhibitors can prevent deterioration of cardiac function. Furthermore it is essential to weigh the benefits of screening for asymptomatic disease against the harms of finding an asymptomatic but possibly incurable disease.

Since the 1980s pediatric oncology centers have developed programs specifically for CCS. However, relatively few programs are able to provide follow-up into the adult age range.

No conflict of interest.

254 INVITED

Health Passport for risk adapted follow-up: A joint project of the ENCCA and PanCareSurFup EU consortia

R. Haupt[1], M. Ortali[2], S. Caruso[1], F. Bagnasco[1], C. Dellacasa[2], S. Karner[3], L. Kremer[4], A. Kienesberger[3], R. Skinner[5], L. Hjorth[6]. [1]*Giannina Gaslini Children's Hosp., Epidemiology and Biostatistics, Genoa, Italy;* [2]*Consorzio Interuniversitario CINECA, Health Care, Bologna, Italy;* [3]*International Confederation of Childhood Cancer Parents Organizations (ICCCPO), Survivors, Nieuwegein, Netherlands;* [4]*Emma Children's Hospital/Academic Medical Center, Pediatric Oncology, Amsterdam, Netherlands;* [5]*Great North Children's Hospital Royal Victoria Infirmary, Paediatric and Adolescent Haematology and Oncology, Newcastle Upn Tyne, United Kingdom;* [6]*Skåne University Hospital, Pediatric Haematology and Oncology, Lund, Sweden*

Background: Between 300,000 and 500,000 childhood cancer survivors (CCS) are now living in Europe and most of them have reached or are entering adulthood. Cancer or its treatment put survivors at increased risk of developing chronic health conditions that may affect their quality of life. It is important that each CCS is given a document summarizing cancer history and providing recommendations on targeted follow-up based on treatment exposure. This document should be discussed with the family doctor or any other health provider and should empower survivors of taking care of their own health.

Materials and Methods: Within the EU funded European Network for research on Cancer in Children and Adolescents (ENCCA), paediatric oncologists, cancer survivors, and IT experts set up a working group aiming to develop an electronic data base for treatment summary reports available on a secure website or in a document on paper, translated in several European languages. Cancer-specific and treatment data can be downloaded from clinical trials data bases through standard format files or can be imported by the pediatric oncologist or survivors. Recommendations for surveillance, based on the best available evidence, are formulated after extensive literature review and consensus meetings within the EU funded project: PanCareSurFup in collaboration with the International Late Effects of Childhood Cancer Guideline Harmonization Group. Four categories for the strength of recommendations will be used: (1) strong; (2) moderate; (3) weak recommendation "to do"; and (4) a recommendation not to do. The passport provides tailored follow-up to each CCS in order to optimize age-appropriate healthcare.

Results: The Survivorship passport prototype is available and provides information relevant to each individual patient. Data transfer from some clinical trials data bases has shown to be feasible; when needed scientific nomenclature has been "automatically" translated in lay language and changes can be made if needed. Guidelines have already been developed for breast cancer and cardiomyopathy surveillance. Guidelines for gonadal toxicity are in progress and other topics are planned for the next years.

Conclusions: Providing treatment summary and standardized patient-specific follow-up guidelines to every patient at the end of cancer treatment should be considered as a key component that will foster the delivery of high-quality patient care and awareness throughout adulthood.

No conflict of interest.

Keynote Lecture (Mon, 30 Sep, 11:30−12:15)
Improved Cure Through Personalised Radiation Oncology − Basis and Perspectives

255 INVITED

Improved cure through personalised radiation oncology − basis and perspectives

M. Baumann[1]. [1]*Universitätsklinikum Carl Gustav Carus, Klinik und Poliklinik Strahlentherapie, Dresden, Germany*

Radiotherapy has a proven curative potential in many cancer types, due to its high efficacy to inactivate cancer stem cells in the primary tumor and regional metastases as well as its increasing ability to spare normal tissues. Already today radiation treatment planning and delivery is fully individualized based on anatomical imaging, precise space-resoluted radiation dose models, tumor control probability- vs. normal tissue complication-models and clinical parameters. Most of these advances in personalized radiation oncology can be attributed to the revolutionary progress in high-precision radiation delivery and planning technology during the past decades. These have been rapidly translated into clinical practice and allowed the development of novel more efficient clinical strategies. Further rapid technological advances are anticipated for the coming years both in hardware and software development. These

advances will further promote personalized radiation oncology, however this process in the future will be significantly spurred by integrating biological information on the specific tumor and on surrounding normal tissues in the treatment strategy of patients. Because of spatially resoluted information, biological imaging is of particular relevance for advancing biology-driven individualization of radiation oncology, but other predictive and prognostic markers also demonstrate high potential in preclinical and clinical studies. This holds true for stratified selection of the best total dose, dose-distribution and fractionation parameters but also for the combination of radiation with specific drugs. An important feature specific for personalized radiation oncology is that already broad biological stratification of patients in two or few groups can very substantially enhance individualization as this information adds a power-function to the fully anatomically-personalized dose-distributions achieved today. This lecture will review preclinical and clinical examples, including data on bioimaging, demonstrating how systematic integration of technological advances with biological information may improve cure rates through personalized radiation oncology.
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No conflict of interest.

Special Session (Mon, 30 Sep, 13:15−14:15)
Improving Therapy for Locally Advanced Cervical Cancer

256 INVITED

Image-guided adaptive brachytherapy

P. Petric[1]. [1]*National Center for Cancer Care and Research, Department of Radiotherapy, Doha, Qatar*

Advantages of 4D image guided adaptive brachytherapy (IGABT) over conventional BT include application and dose-planning individualization, dose volume histogram analysis and improved clinical outcome.
Assessment of initial tumor, its regression during treatment and size/topography at IGABT enables individualized refinement of application technique and development of new standard applicators. Image guidance of application can be accomplished pre- or intra-operatively. Common preoperative strategy consists of integration of initial imaging and findings at BT; additional imaging just before the application facilitates insertion. Intraoperative US-guided uterine tandem placement helps preventing uterine perforation and US-guided needle insertion is a feasible method to achieve optimal interstitial implant. Common approach to intraoperative MRI or CT guidance consists of application interruptions to acquire verification images. Open MRI and modified closed-system techniques enable real-time guidance. Optimal BT implant geometry facilitates achievement of planning aims during dose optimization.
IGABT is based on clinical and imaging interpretation of initial tumor spread and residual pathological tissues during treatment. Using optimisation of dwell-times and positions of ^{192}Ir stepping sources, IGABT enables dose escalation to the target volume while respecting OAR tolerance. Small inconsistencies in delineation of these regions may translate to large uncertainties of the optimized dose distribution, challenging the gain of IGABT and complicating interpretation of studies. Adequate training and respecting the recommendations are required to minimize variations. One of the sources of uncertainties is the choice of imaging modality. MRI demonstrates excellent soft tissue contrast and is the modality of choice. However, due to its limited availability, CT- and US-based techniques are gaining increasing attention. Further research is needed to validate their potential in cervix IGABT.
In parallel to monoinstitutional reports, the upcoming results of the EMBRACE (intErnational study on MRI-guided Brachytherapy in locally advanced CErvix cancer) and retro-EMBRACE studies provide evidence for effectiveness of IGABT and improve our understanding of dose-response relationships. For patients with recurrent cervix cancer following radiotherapy, reirradiation is one of the only therapeutic options. IGABT may increase the chance of uncomplicated cure in these patients.
No conflict of interest.

257 INVITED

Optimal management of nodal disease

A. Taylor[1]. [1]*Royal Marsden Hospital, Department of Radiotherapy, London, United Kingdom*

The presence of lymph node metastases is one of the most important prognostic factors for locally advanced cervical cancer. Whereas central pelvic disease can receive a very high dose from brachytherapy, the external beam radiotherapy dose delivered to nodes is limited by normal tissue tolerance. Inadequate treatment to this region can result in pelvic sidewall relapse which is rarely salvaged successfully.
In addition to the prognostic significance, identification of the anatomical location of nodal disease can determine the extent of radiation fields. Standard cross-sectional imaging with CT and MRI using size criteria has low sensitivity and specificity for detecting metastases. CT-PET is the imaging modality of choice for evaluating lymph nodes at diagnosis and for follow up. There remains debate about the role of diagnostic para-aortic lymphadenectomy.
Different approaches have been advocated for improving control of nodal disease although there have been few prospective studies to establish optimal management. Surgical debulking of bulky metastatic nodes is often undertaken prior to radical chemoradiation. Several case series have reported equivalent local control and survival in the resected group compared to a node negative cohort, but at the cost of increased morbidity. Inferior outcomes with poor pelvic control and increased distant relapse are reported for patients with unresectable nodes.
Conventional external beam radiotherapy treatment delivers 45−55 Gy to the pelvis and para-aortic nodes. With advanced radiotherapy techniques it is now feasible to deliver higher doses concomitantly to involved nodal regions. There are limited data on the optimal dose required for control of enlarged nodes and these will be reviewed. Distant failure remains high even with improved pelvic control and more effective systemic therapies are therefore also required.
No conflict of interest.

258 INVITED

Rationale and trials of adjuvant and neoadjuvant therapy with chemoradiation

D. O'Donnell[1]. [1]*St James's Hospital, Haematology Oncology Day Care Centre, Dublin, Ireland*

Chemoradiation remains the standard treatment for locally advanced cervical cancer but a substantial proportion of women relapse after that. Most who relapse die of their cancer or its complications, so there is an urgent need to improve the cure rate after first-line therapy. This talk will describe previous and ongoing trials of therapies added to standard chemoradiation and discuss potential future approaches.
Conflict of interest: *Other substantive relationships: Member of Trial Management Group of INTERLACE trial (academic trial just started of neoadjuvant chemotherapy before chemoradiation for cervical cancer*

Special Session (Mon, 30 Sep, 13:15−14:15)
Survivorship and Follow up

259 INVITED

Meaningfulness of physical activity and exercise in cancer rehabilitation − a meta-synthesis of qualitative research

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Background: Evidence for the health benefits of physical activity and exercise for cancer survivors is accumulating. However, the meaningfulness of physical activity from the perspective of the patient has not yet been established. Meta-synthesis has evolved as a rigorous method for integrating findings from multiple qualitative studies to produce a new interpretation of findings that is more substantive than those resulting from individual investigations. The aim of this meta-synthesis was to aggregate, interpret and synthesize findings from qualitative studies that included cancer survivors' experiences of physical activity and exercise training.
Material and Methods: Four electronic databases were searched systematically for articles published up to May 2013, using keywords and mesh headings. Reference lists of included articles were screened for eligible papers. The meta-synthesis approach was based on the guidelines by Sandelowski and Barroso (Qual Health Res 2003).
Results: 61 papers were critically appraised and 17 papers were identified for inclusion. Most studies included patients with breast cancer and/or patients undergoing treatment or who had recently completed treatment. Three main categories were identified across the studies: (1) Resurrection of continuity (including the subthemes: structure, hope, and goal-setting), (2) Preservation of normality (including the subthemes: social participation and positive distraction), and (3) Reclaiming the body (including the subthemes: enhanced energy and performance, autonomy, and illness resistance). Together, these categories indicate that the meaningfulness of physical activity and exercise for cancer survivors is related to the development of personal strategies including keeping a routine, which may help the individual to feel in control and to sustain or restore confidence in their body and uphold a positive outlook towards the future.

Conclusions: The findings of this meta-synthesis suggest that cancer survivors experience physical activity and exercise as a means to fulfill their mental, social and physical well-being independent of disease status. In addition to the current evidence on the efficacy of exercise training in cancer survivorship, it is incumbent upon clinicians and policy-makers to acknowledge and promote the meaningfulness of physical activity and exercise, and to use this knowledge to provide new solutions to current problems related to recruitment, adherence and implementation.
No conflict of interest.

260 INVITED

Using technology in supportive cancer care

S. Kaasa[1], S.X. Raj[2], A.K. Knudsen[3]. *[1]Norwegian University of Science and Technology and St. Olavs Hospital Trondheim University Hospital Trondheim Norway, European Palliative Research Centre (PRC), Trondheim, Norway; [2]Norwegian University of Science and Technology and Trondheim University Hospital St. Olavs Hospital, European Palliative Research Centre (PRC) and Cancer Clinic Trondheim University Hospital, Trondheim, Norway; [3]Norwegian University of Science and Technology and Trondheim University Hospital St. Olavs Hospital, European Palliative Research Centre (PRC) and The Regional Centre of Excellence, Norway*

Patients in any stage of cancer are suffering from several symptoms. According to studies, subjective symptoms reported by the patients (patients reported outcomes − PRO) are under-reported and under (insufficiently)-recognized during consultations and in patients' records.
Pain, fatigue, dyspnea, constipation, loss of appetite, depression and anxiety are among the most common symptoms. In a meta-analysis on prevalence of cancer pain, 33% reported pain after curative treatment and 64% of the patients with metastatic disease. Even when effective treatment exists for pain and depression as many as 50% of the cancer patients are undertreated for these symptoms.
Inadequate assessment, lack of standardized assessment tools, poor communication and challenges of implementing evidence-based guidelines into clinical practice have been identified as barriers to improving symptom treatment.
There is a need for a tool that combines symptom assessments and classification, evidence- based guidelines and decision making support. These tools should be computerized since this will allow individualized and dynamic symptom assessment, thus improving the efficiency of consultations. Additionally, it may facilitate the long-term follow-up of patients and incorporate the results into patient's electronic medical records. Eir, a computerized decision support system, is under development and testing for implementation in routine clinical practice. This software is primarily based upon PRO's, international evidence-based guidelines and an interactive decision support system. The overall aim by applying the software into clinical practice is to enhance the patient-centered communication and treatment by facilitating an optimal exchange of information between the patients and the health care providers.
No conflict of interest.

261 INVITED

Health-related choices in survivors

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Nowadays the majority of cancer patients receive highly effective treatments that result in long-term, disease-free survivorship. Often, however, in the post-treatment phase cancer patients are left with subtle and sometimes more overt sequelae because of the cancer treatments that can affect their quality of life and their life-related decisions. Although a substantial proportion of cancer survivors spontaneously initiate positive behavioral changes, many do not adhere to follow-up or screening behaviours, and to recommendations in regards to diet, physical activities and smoking behavior therefore. It becomes crucial to promote health-related behaviours, in order to reduce the probability of relapses and comorbidities.
On the other hand, beside life-style changes there is the need to promote the reintegration of cancer survivors at the workplace. Going back to work is important, not only for financial reasons, but also to facilitate the adaptive process to the illness, that, in turn, facilitate an improvement of the survivor's psychological and psycho-social conditions. However, while survivorship following cancer diagnosis is increasing in prevalence, looking for a new job or reentering the job market can be a challenging experience. Several factors may adversely affect employment over the long term. Because of treatment consequences and for a mere psychological reaction to the illness, physical limitations, fatigue, emotional problems, difficulties with concentration and memory, awkward or negative interactions with coworkers, and changing personal priorities make difficult for cancer survivors to maintain or look for a job. Employment discrimination is also an ongoing concern, despite laws or agreements for strategic cooperation to promote and develop values of equality, opportunity and non-discrimination in the workplace toward individuals with a history of cancer.
There is the need, given these premises, to find efficient strategies to foster health promotion and a sensitization campaign for job reintegration among both cancer survivors, organizational management and society, in order to facilitate and improve cancer survivors empowerment and well-being.
No conflict of interest.

Special Session (Mon, 30 Sep, 13:15−14:15)
Controversies in Gallbladder Cancer

262 INVITED

When should we worry about gallbladder polyps?

Abstract not received.

263 INVITED

Management of Stage T1B gallbladder cancer discovered after laparoscopic cholecystectomy

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T 1b lesion is one which invades the muscularis propria but does not involve the perimuscular connective tissue. There is controversy as to the extent of additional surgery needed if a T1b lesion is found at pathologic analysis after laparoscopic cholecystectomy. Published reports have a wide spectrum of recommendations that range from no additional surgery to reports recommending routine additional radical surgery. In fact, the 2009 NCCN guidelines recommend additional hepatic resection and lymphadenectomy for T1b lesion.
In this lecture, we will discuss the published data to date. We will also review the options for preoperative staging, surgical therapy, and long-term follow-up. Overall, we wish to present the spectrum of acceptable care for this stage of disease, as well as present sensible guidelines for treatment of any individual patient.
No conflict of interest.

264 INVITED

Management of Stage 3 gallbladder cancer

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Introduction: Gallbladder cancer represents the most aggressive form of biliary tract cancer (BTC). In most instances it's either diagnosed incidentally during cholecystectomy or at an advanced stage where potential curative approaches are not possible any more. Stage III disease is defined as locally advanced but still amenable for surgical resection; it's either an extension out of the gallbladder wall into adjacent organs and/or spread to regional lymph nodes. The review will summarize current understanding and treatment options for stage III disease.
Methods: Literature search including western and eastern experience will be performed and summarized and accompanied with personal practice.
Results: Surgical resection of stage III gallbladder cancer requires expertise both in hepato-biliary and vascular procedures and deserves therefore best outcomes both short and long-term in high volume centres with a specialized team for such operations. Recommended extend of resection comprises liver resection including a margin of normal liver tissue, the resection of adjacent organs (large bowel, duodenum), eventually the bile duct(s) if involved and the regional lymph nodes (down to the coeliac axis and behind the pancreatic head). Vascular resections and reconstruction is seldom curative as lymphatic spread extends to the para-aortic region. Reported 5 years overall survival figures for stage III disease range from 0−44%, where the benefit of surgical removal is only demonstrated in part of the publications. However the value of adjuvant therapies and its composition on outcome has not sufficiently been studied. Interestingly recent data do suggest that patient's fitness and ability to tolerate systemic therapy enables a similar outcome of gallbladder cancer patients compared to other types of BTC.
Conclusion: Advanced gallbladder cancer requires multidisciplinary approach to overcome dismal prognosis.
No conflict of interest.

Special Session (Mon, 30 Sep, 13:15−14:15)
MRI and Radiation Therapy in Prostate Cancer: Optimisation of Targeting and Delivery

265 INVITED

MRI-guided brachytherapy

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It is possible to evaluate prostate cancer with a combination of MR techniques. These include anatomical T_2-weighted sequences with the addition of diffusion, spectroscopy, intrinsic susceptibility-weighted and/or dynamic contrast-enhanced sequences. This multi-parametric approach improves our ability to locate tumour regions within the gland and to estimate the associated tumour aggressiveness and the risk of progression. These sequences produce a range of quantitative biomarkers that assess a host of physiological and biochemical tumour characteristics. These include clonogen density, oxygenation, blood flow, vascular permeability, interstitial fluid pressure and a range of metabolic parameters. Integration of this information into the radiotherapy planning process offers a range of possibilities.
High dose gradients created during the brachytherapy process result in extremely high degrees of conformity to the planning target. The degree of flexibility in source placement and loading facilitates 'dose-painting' with the opportunity to maximise the dose to the highest risk prostate regions and to moderate or reduce the dose to areas that are unlikely to contain any clinically significant tumour. This in turn may improve the therapeutic ratio for prostate radiotherapy by maintaining or even improving tumour control whilst reducing normal tissue toxicity.
In the salvage setting, following localised relapse after external beam radiotherapy, conventional imaging is rarely capable of locating the region of recurrence. Multi-parametric imaging has a higher detection rate and can guide focal salvage brachytherapy. Furthermore, if primary focal therapy is contemplated then it will be imperative to use the optimum multi-modality imaging series, including multi-parametric MRI, to direct the therapy.
This special session lecture will outline the various MRI techniques and discuss the imaging biomarkers derived from each. The methods of integrating the imaging data into the brachytherapy planning process will be outlined together with a discussion of sources of error. MRI-guided brachytherapy dose-painting in the primary and salvage settings will be shown with clinical examples.
No conflict of interest.

266 INVITED

MRI-guided external beam radiotherapy of prostate cancer

U. Van der Heide[1]. [1]*Netherlands Cancer Institute, Radiation Oncology, Amsterdam, Netherlands*

In radiotherapy, prostate cancer is usually treated by delivering a homogeneous dose to the total gland. Technical inabilities in dose delivery and limited access to imaging prevented a more sophisticated approach: differentiating the dose between the tumor and the rest of the prostate. With improvements in both areas, such treatment options are now being explored.
The use of multi-parametric MRI is highly successful in the localization of prostate cancer. Dynamic Contrast-Enhanced (DCE-) MRI shows the passage of contrast agent in tissue and reflects micro-vessel density and permeability. Diffusion-Weighted Imaging (DWI) is sensitive to the random motion of water in the tissue and reflects tissue cellularity.
A limiting factor in the use of multi-parametric MRI for prostate diagnosis and staging is the interpretation of the images. Here a high level of expertise is required. This is even more so for the delineation in radiotherapy, which is labor intensive and prone to observer variability.
This level of uncertainty may be problematic for treatment modalities such as surgery, cryotherapy, high-intensity focused ultrasound and photodynamic therapy. Here essentially a binary decision is made about what (part of the prostate) to treat and what to spare. Radiotherapy has the capacity to differentiate the dose level locally within a single treatment, based on the varying probability of tumor burden. This differential capacity of radiotherapy avoids therefore a binary decision of what to treat and provides an elegant method to deal with uncertainty in the interpretation of multi-parametric MRI. Using logistical models, areas can be defined with a high positive predictive value for the presence of tumor. This constitutes the gross tumor volume (GTV). Similarly, areas can be defined with a high negative predictive value. This constitutes the low-risk clinical target volume (CTV) where no macroscopic tumor is expected, but presence of microscopic disease is anticipated. The remaining part constitutes the high-risk CTV and reflects the part of the prostate for which the tumor presence is uncertain. With external beam radiotherapy dose differentiation between these target volumes is feasible and this allows for the testing of various dose ranges in randomized clinical trials. For intermediate and high-risk patients, this concept is currently tested in the FLAME trial, a multi-center phase III study of dose escalation to the MRI-visible tumor from 77 to 95 Gy.
No conflict of interest.

Special Session (Mon, 30 Sep, 13:15−14:15)
Medical Treatment of GIST

267 INVITED

How to order the many different medical treatments

Abstract not received.

268 INVITED

Adjuvant treatment: To whom, how much and for how long?

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Adjuvant imatinib administered at the dose of 400 mg/day improved substantially recurrence-free survival of patients with operable GIST in 2 large randomized trials (ACOSOG Z9001 and SSGXVIII/AIO). One of the trials (SSGXVIII/AIO) found that 3 years of adjuvant imatinib improves overall survival as compared with 1 year of imatinib in a population of GIST patients with a high estimated risk for recurrence after surgery, but this observation was based on a limited number of survival events. Based on these data, adjuvant imatinib is recommended for 3 years after surgery to patients who have a substantial risk for GIST recurrence.
Since most patients with local GIST are cured by surgery (approximately 60%), the risk of GIST recurrence should be estimated before starting adjuvant imatinib to identify those patients who are likely cured by surgery alone. Several validated risk stratification schemes are available, including the NIH consensus classification, the modified NIH classification, the AFIP scheme, 2 nomograms and prognostic heat maps. These tools are based on a few standard prognostic factors (tumor size, site, rupture and mitotic count). Prognostic gene expression arrays and comparative genomic hybridization arrays have yielded promising results in small series.
Mutation analysis of *KIT* and *PDGFRA* genes must be carried out from the tumor tissue to further exclude patients who are unlikely to benefit from adjuvant imatinib. Mutations at the *PDGFRA* locus 842 (usually D842V) are relatively common (up to 10% of GISTs) and confer resistance to imatinib. Many patients whose tumor is wild-type with respect of *KIT* and *PDGFRA* are also unlikely to benefit from adjuvant imatinib, including patients with neurofibromatosis 1-associated GIST. Data from advanced GIST suggest that patients with *KIT* exon 9 mutated GIST benefit from higher than the 400 mg daily imatinib dose, but such doses have not been tested in the adjuvant setting.
Longer than 3-year adjuvant regimens have not yet been rigorously evaluated, and the benefits and harms of such regimens remain unknown. Since many GISTs (20−35%) recur during the first 2 years that follow discontinuation of adjuvant imatinib, frequent imaging at 3- to 4-month intervals with CT or MRI during this time period may be beneficial to achieve early detection of recurrence and re-starting of imatinib when the tumor bulk is still small.
Conflict of interest: *Corporate-sponsored research: Novartis*

269 INVITED

How can molecular biology guide future research?

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Gastrointestinal stromal tumors (GISTs), with already registered 3 targeted compounds, represent a molecular targeted therapy model within solid tumors. Most GISTs share a similar genetic profile including *KIT* or *platelet-derived growth factor receptor-alpha* (*PDGFRA*) gain-of-function mutations. Most of GISTs harbour a *KIT* (60−85% of cases) or *PDGFRA* (5%-10%) mutations and approximately 10−15% of GISTs lack of detectable mutations in either receptor, considering these cases such as GIST *wild type* (wt) and indicating that other molecular pathways are also important in the development of GIST.
Molecular biology is leading research in GIST in three different ways:

- Etiopathogenic: Wild type GIST is currently a special interest area of research. Several authors are investigating other pathogenic mechanisms in this context of wt. *IGF1R* is differentially upregulated in wt GIST especially in pediatric population. One well characterized subset

of wt GIST is constituted by epithelioid gastric phenotype, syndromal (Carney triad i.e), with frequent lymph node involvement, multicentric presentation and offering primary resistance to Imatinib with an indolent metastatic evolution. These cases are typically SDH-deficient detected by immunostaining and commonly harbouring SDH mutations.

- Prognostic relevance: Several authors have pointed out the significant poor relapse free survival (RFS) of patients with deletions involving codons 557 and/or 558 when compared with either patient with mutations in exon 11. In addition, investigators have demonstrated that such mutations constitute a time-dependent variable, having their prognostic relevance for RFS within the first 3−4 years after surgery. This fact could contribute to identify a subset of GIST patients with higher and earlier risk of relapse irrespective of clinical prognostic factors. Other studies performing tissue microarrays and microRNA arrays have found some components of Wnt pathway as prognostic relevant for RFS in localized GIST.
- Predictive biomarkers: Meta-analyses compiling two large phase III trials comparing, in metastatic disease, 400 mg vs 800 mg of Imatinib reinforced the previously reported findings that GIST genotype constitutes an independent prognostic factor for time to progression and overall survival. Patients with exon 11 mutations presented better outcome than wt or exon 9 mutations. However for sunitinib the correlation was different: those wt or exon 9 mutated cases had better TTP (19 mounts) than exon 11 mutated (5 months). Unfortunately, the scenario after the emergence of imatinib resistance is highly complex. Polyclonal acquired resistance or genomic amplification could be responsible of secondary resistance. Microenvironment represents an interesting area that translational research should focus on especially after the successful outcome of regorafenib as third line in GIST.

No conflict of interest.

Special Session (Mon, 30 Sep, 13:15−14:15)
The Mouse Hospital in Drug Development

270 INVITED

GEM models to facilitate drug development

Abstract not received.

271 INVITED

Bridging tumor genomics to patient outcomes through a Large Scale Patient Derived Xenograft (PDX) Platform: Non-Small Cell Lung Cancer (NSCLC) Pilot Studies

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Background: Previously described preclinical models have proven suboptimal for directing clinical application of new anti-cancer therapies. Here we detail an integrated research platform engaging core resources at JAX-WEST and the clinical research and genomics facilities at UCDCCC. Pilot studies using this platform are focusing on non-small cell lung cancer (NSCLC) due to molecular targets of interest, such as epidermal growth factor receptor (EGFR), heterogeneity in NSCLC tumor biology and the complexity of related cancer signaling pathways.
Methods: Clinically and demographically annotated cancer patients (pt) seen at UCDCCC and collaborating facilities undergo tumor biopsies of various types which are implanted into JAX Nod Scid Gamma (NSG) mice to develop PDXs. Pt tumors and subsequent PDXs are assessed by histomorphology, clinically applicable molecular biomarkers, gene expression arrays and genome-wide technologies (NGS). NSCLC PDXs are grouped as panels EGFR mutant (MT), KRAS MT ALK+. PDX panels of interest undergo multi-regimen drug testing for differential efficacy, together with pre- and post-therapy NGS and timed tumor pharmacodynamics (PD), to determine mechanisms of primary and acquired resistance in individual PDX models and how to overcome them.
Results: As of June 1, 2013 over 1,000 cancer pt tumors have been xenotransplanted into NSG mice (~160 from NSCLC), including successful PDX formation from small FNA/cell pellets and transportability of specimens by overnight shipping for implantation. NSCLC PDXs show excellent histomorphologic, gene expression and mutational fidelity to host pt tumors, including mutation status for KRAS, EGFR and gene expression levels. Pilot studies in a panel of EGFR MT PDXs with TKI-acquired resistance demonstrate differential drug activity which mimics that of the host pt to the same therapy, and tumor PD at baseline and timed intervals post-therapy provide the basis for subgrouping resistance mechanisms.
Conclusion: This UCDCCC-JAX collaboration has established a large resource applicable to multi-drug testing and tumor PD in a wide range of clinically and genomically characterized tumors, including PDX panels for representative oncogene-driven NSCLCs. An EGFR-directed pilot project supports the feasibility of systematically integrating data derived from these models in order to optimize drug development and treatment strategies to address drug resistance mechanisms. This approach to PDX development and testing will be prospectively integrated into a developing multi-institution clinical trial of the Southwest Oncology Group, designed to advance understanding of differences in inter- and intra-patient tumor biology and hasten the transition to personalized cancer therapy.
Conflict of interest: *Other substantive relationships: Employee, The Jackson Laboratory West*

272 INVITED

Are animal models in early drug development of use?

Abstract not received.

Special Session (Mon, 30 Sep, 13:15−14:15)
Symptom Management via the Internet

273 INVITED

Web-based support to assist cancer patients in reducing symptoms

Abstract not received.

274 INVITED

Symptom management for cancer patients via mobile phones

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Background: In the front line in cancer care is to systematically integrate patient reported outcomes (PRO) in clinical practice. The development of this research program is based on The Participatory Care Model, and builds on how patients can be integrated in their care. The aim is to evaluate the effects of an interactive e-health solution for assessment of symptom burden, generating instant self-care advice and instant access to health care professionals.
Methods: The hypothesis is that the intervention promotes safe and participatory care and thereby improves clinical management and health care costs. The experimental multicenter studies incorporate a mixed-method approach. Ongoing studies include patients with pancreatic and prostate cancer using the mobile phone application in comparison to control groups in standard care.
Outcomes are collected before and after treatment by questionnaires concerning capacity to understand, communicate health needs and promote healthy behaviors (health literacy), symptom burden and management and quality of life and from records and registers about disease progress and health care costs. Interviews concern participatory and meaningful care. Studies are ongoing for patients with prostate and pancreatic cancer and elderly populations living at home or in care homes.
Results: By using technology patients are able to communicate symptoms and receive instant support while cared for on an outpatient basis and at the same time feel reassured that their condition is monitored by health care professionals facilitating safe and participatory care.
No conflict of interest.

Special Session (Mon, 30 Sep, 13:15−14:15)
Improving Hands-on Education for Young Oncologists

275 INVITED

Training surgical oncologists in Europe

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Until recently the surgeon often was considered a person who could take on any case and operate if that was decided. A trend in most european countries is that surgeons have some basic training but then we all split into different sub-specialities. Most of these sub-specialities are organ-based

and in very few countries do we have a sub-speciality named surgical oncology. Still we have an EBSQ examination in surgical oncology and ESSO is living well and healthy running more courses than ever and with a updated core curriculum. The core curriculum reflects the direction of a modern training program to become a surgical oncologist.
New demands on cancer care have changed the working environment for the surgical oncologist and she/he must master certain skills. Among these are diagnostic work-up and communication with the patient and relatives. Earlier this often could be done at the ward during a longer hospital stay. Now most diagnostic procedures are done ambulatory and the communication done at the out-patient ward. A second distinct change is decision-making which earlier was done by the surgeons themselves and now often is made by a multidisciplinary tumour board. In this situation the surgeon must be capable to present the case, assess alternative treatments and lead the board to the best decision. A traditional core activity, the surgical procedure is affected by demands of increased experience and optimal performance by the surgeon and at the same time working regulations and many conflicting tasks give little time for the young surgical oncologist in the operating theatre.
The solution to overcome these demands is to a large extent hands-on training with increased supervised training in patient care, tumour board leadership and basic surgical skills training in simulation and then operating with experienced tutors as assistants.
No conflict of interest.

276 INVITED

Training medical oncologists in Europe

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Medical oncologists need to be trained in both the science and the art of cancer medicine. The science is the easy bit! The greater challenge is to learn how to communicate appropriate explanations of the aetiology, prognosis, and management of a particular cancer to an individual patient. The ever-increasing knowledge base upon which we depend for recommending specific management plans means that there is more and more information that we would like to discuss with individual patients. The more choices there are, the greater the responsibility for giving explanations that are understandable by patients. One of the great challenges for trainees in medical oncology is to learn how to apportion time most appropriately for the giving of information and listening to patients to verify their comprehension. Patient information leaflets and standard protocols are helpful but nothing replaces the personalised consultation to reassure a highly anxious patient at first presentation, a disappointed patient at relapse, or a patient entering the terminal stages of their illness. This presentation will focus on training aspects of communication − appropriate to the different phases of the illness, emphasising how to optimise precious consultation time and to choose the best environment in which to hold these very challenging conversations.
No conflict of interest.

277 INVITED

Training radiation oncologists in Europe

R. Pötter[1], M. Schmid[1]. [1]*Medical University of Vienna, Department of Radiation Oncology, Vienna, Austria*

Training and education of young radiation oncologists in Europe is structured by national radiation oncology societies, national laws and regulations which have led to a great heterogeneity in its practical performance throughout Europe. In order to introduce a minimum joint European standard, in 1991, a "minimum curriculum for the theoretical education in radiation oncology in Europe" was presented by the European Society of Radiotherapy and Oncology (ESTRO), which was endorsed by 22 national radiation oncology societies. This first European curriculum played a major role in harmonizing education and in establishing comparable standards for training in radiation oncology across a considerable number of countries in Europe. In 2004, a second core curriculum edition was published meeting the increasing needs according to the dynamic developments in radiation oncology. Recently, the ESTRO core curricula for clinicians (3rd edition), medical physicist (2nd edition) and RTTs (3rd edition) were updated. The major novelty of the latest editions was the shift from a focus on knowledge and skills (1991, 2004) towards competency based education and training (2012). Beside knowledge and skills, attitude − "to be able to perform a professional act adequately in a given situation" − has become a major goal in education and training now. The following seven competencies were defined in agreement with international preceding developments in this field (CANMED): "medical expertise", "communication", "collaboration", "knowledge/science", "health advocacy/social actions", "management/organisation" and "professionalism".
Furthermore, the integration of radiation oncology has been emphasized as an integral part of the multidisciplinary management of cancer patients including responsibilities of radiation oncologists for diagnosis, treatment decision, performance and evaluation, follow up and supportive care of cancer patients. Recent developments in the field of concomitant radio-chemotherapy and radio-immunotherapy e.g. require specific new knowledge with regard to application and handling of systemic agents, treatment-specific effects and side effects − including their interaction with radiation - and tailored supportive measures. Advances in radiotherapy technology with modern imaging integrated into treatment planning process and performance of complex radiotherapy techniques such as intensity modulated radiotherapy (IMRT), image guided (adaptive) radiotherapy (IGRT) and stereotactic radiotherapy (SBRT) require increasing attention in the training and education process. This includes in particular the ability of (adaptive) tumor and target volume definition, organ at risk selection and delineation, treatment plan evaluation with dose-volume histogram analysis − all within the frame of the overall oncological treatment aims.
The transition to competency based education and training is supported by ongoing developments in the ESTRO School with an increasing number of competency orientated didactic elements within the growing number of "on-site" teaching courses and teaching sessions during congresses focussing on active learning by problem solving, interactive teaching elements, small group tutorials and workshops. In addition, web based and e-learning educational tools and activities were recently introduced into the ESTRO School (e.g. FALCON − web based learning platform for contouring; EAGLE − e-learning teaching courses) in order to further facilitate access to education and training in radiation oncology in Europe and worldwide.
No conflict of interest.

Special Session (Mon, 30 Sep, 13:15−14:15)
EONS−ESO Joint Session − Cancer Surgery and Nursing

278 INVITED

Oncoplastic surgery

M. Cardoso[1]. [1]*Champalimaud Cancer Center, Breast Unit, Lisbon, Portugal*

Breast cancer surgery has evolved in the last 50 years from the radical mastectomy concept to progressive conservation of the gland, which has shown to be an equally effective oncological treatment when combined with radiotherapy.
However, aesthetic results from breast conserving surgery are in 10−30% of cases considered fair or even poor. Increasing sophistication and need for improved global outcomes and patients demand of a better aesthetic outcome has led to the development of oncoplastic surgery. This involves simultaneous excision of the tumour and reconstruction of the defect applying techniques used frequently in cosmetic breast surgery.
Classically the term oncoplastic surgery has been applied to reconstruction in breast conserving surgery but lately mastectomy and immediate breast reconstruction have been progressively included in the designation.
Regarding breast conserving surgery there are two main techniques for oncoplastic surgery: volume displacement and volume replacement. The choice of these depends on the volume of the respected tumour and the total breast size ratio.
The main current indication for oncoplastic surgery is surgeon's preference and capacity to execute the mentioned techniques. There is no doubt that accurate preoperative evaluation of both the tumour and patient characteristics are crucial steps.
If mastectomy is necessary, the whole range of appropriate techniques for breast reconstruction should be offered either immediately if appropriate, or after all adjuvant therapy has been given. Studies have shown that the majority of patients having a mastectomy would like a breast reconstruction if possible. Women choose immediate breast reconstruction because it helps them face the physical and emotional impact of the loss of a breast. With immediate breast reconstruction, a second operation and general anaesthetic can be avoided.
Oncoplastic surgery is becoming progressively available in centers dedicated to breast cancer treatment all over the world. However the monitoring of oncological and aesthetic results has not been walking hand in hand with the dissemination of these new techniques.
A better outcome for patients with oncoplastic surgery is expected but we must support our findings and further progression with the publication of results, ideally, from clinical trials.
No conflict of interest.

279 INVITED

Nurses' role in robotic surgery

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Introduction: Throughout the history of nursing, the discoveries and system of belief of yesterday have served as a platform for the innovations of today. That is especially true for minimally invasive surgery (MIS) approach, exactly indeed perioperative practitioners have been challenged to stay abreast of technology in a field that is a constantly changing landscape of new techniques and improved instruments and equipment.
The "laparoscopic revolution" of the 1980s propelled and encouraged the changes towards a less invasive approaches and new techniques, such as modern robotic-assisted surgery. Science and technology are advancing at an incredible pace and a critical analysis of these new developments become a duty in the perioperative nursing. Nurses, as a member of Robotic Surgical team must represented very good level of professional knowledge, and be an expert in robotic technology, playing a key role in data collection, analyzing trends and outcomes, and identifying safety issues.
The professional nursing staff has an important responsibility to work following best-practice rules, and to analyze periodically roles and habits. This could be an effective instrument in order to improve every-day practice. A team training that involves all members of the robotic surgical team learning together, is the main key to ensuring patient advocacy and safe care. Creation and application of guide lines and specific protocols is giving positive results in daily practice as well.
Conclusions: The role of robotics nurse specialist is both challenging and exciting because the technology is so new and the role is open to interpretation and definition − needs of job description. Daily practice showed us the needs of continues education, especially regarding e nursing skills, creation and revision of guide lines and specific protocols.
No conflict of interest.

280 INVITED

Surgical oncology (several tumor types) in the elderly

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Historically, surgery was the only treatment for cancer however, over the last 50 years a better understanding of the disease has led to a multidisciplinary approach, where every single component of the team interacts in order to optimize treatment outcomes, compliance, quality of life and cost effectiveness.
Despite these important improvements, surgery remains the most widely practiced treatment modality with curative intent in the treatment of solid tumours.
"No surgery − no cure" remains a valid aphorism but "no high quality surgery without nursing" is not less important, particularly when dealing with older cancer patients. Here is why: several clinicians and oncologists claim that there is no need of a dedicated team to deal with older cancer patients; the assumption is that we are all perfectly comfortable in treating senior patients who throng our clinic and take out most of our practice.
The epidemiology is self-explanatory: 2/3 cancers affect older people. Breast, colorectal, lung, liver cancers may all affect young individuals but the probability of this is hugely increased with the patient's age.
Most importantly, as the world population is globally ageing (not only in the most economically advanced countries), we will soon be facing a time bomb, an emergency we should well be prepared to deal with.
The most important point is accepting the diversity of the older individual: as one in two geriatric individuals suffers from cognitive impairment, incontinence, need help for feeding and lack of mobility, with one in four is showing signs of delusion, depression, if not of delirium or aggressiveness, it is crucially important that medical professionals understand these differences and their impact; treatment targets are to be modified, compliance is different, consenting is to be adjusted. Social and familiar support needs to be taken into account when offering active treatment, or simply arranging for imaging or follow-up visits.
The diversity of the elderly individual is thus functional as well as intellectual; these domains will both have to be taken into account when designing a treatment plan. If not, the patient will simply not comply with the prescription, fail to attend, develop serious side effects to confirm how poorly designed the therapeutic strategy was.
To assist on this, numerous scoring systems have been designed to define frailty. Ageing results in decline of several physiological systems, giving rise to vulnerability to changes in health states in response to minor stressors. Frailty is a state of increased vulnerability to poor resolution of homeostasis after a stressor event occurs, increasing the risk of adverse outcomes, including falls, delirium and disability. Frailty is not-uniformly distributed suggesting that a) it is not inevitably associated to ageing and b) frailty can (and should) be identified and actively treated. Regrettably, there has been no consensus of the assessment tool to be used, and this has inappropriately generated some confusion. A significant amount of research has focused on this during the last two decades, when oncologists have joined forces with geriatricians. Comprehensive Geriatric Assessment tools have been tested in the oncological setting and proven useful in predicting complications related to cancer treatment, length of hospital stay and related costs. A full Comprehensive Geriatric Assessment is time-consuming and difficult to use in our busy clinics; most importantly, only a small proportion of patients (18−20%) would benefit of this assessment, as they might not require any intervention. On this background, quick tools have been developed to screen for frailty; such instruments only take a few minutes to administer and they have proven very effective: GFI, VES-13 and fTRST are some of these useful instruments which assist the decision-making process in everyday's clinical practice. However achieved, an indication of the patient's fitness is absolutely mandatory when attempting to predict outcomes, individualizing treatment, consenting patients, designing trials and comparing series and results. However defined, there will be more and more frailty assessment at the GP's practice as well as at admission into hospital.
Modern onco-geriatric literature is loaded with attempts to frame cancer patients with a various tools and associate their outcomes to frailty. The role of onco-geriatric nurses here is particularly relevant: some universities have already set up courses for professionals with an interest in this specific field. Here is a window of opportunity for nurses who might consider a switch toward the end of their training. A degree in Onco-Geriatric, for nurses who have completed their oncology training, is a brilliant career opportunity. Nurses are better set to provide expert and tailored care in two parallel fields.
No conflict of interest.

Special Session (Mon, 30 Sep, 13:15−14:15)
Shared Challenges of Small Group Trials

281 INVITED

Principles of adaptive designs and application

A. Faldum[1], H. Müller[2]. [1]*Westfälische Wilhelms Universitat Münster, Institute of Biostatistics and Clinical Research, Münster, Germany;* [2]*Klinikum Oldenburg gGmbH, Klinik für Allgemeine Kinderheilkunde Hämatologie/Onkologie, Oldenburg, Germany*

In clinical trials a periodical check of safety and efficacy data is often needed. For organizational reasons it is rarely desirable to stop a trial during such an interim analysis. Therefore, new study patients are included in the trial while the interim analysis is ongoing. Disregarding the additional information provided by these interim patients would be unsatisfactory, especially for an office of regulatory affairs. Consequently, the rules for flexible decisions must be adjusted to the recruitment of interim patients.
The KRANIOPHARYNGEOM 2007 trial is the first randomised trial in children and adolescents with craniopharyngeoma. An interim analysis is planned to draw conclusions on efficacy, futility, and safety in time. Primary objective of the trial is the comparison of the quality of life between patients with early and late irradiation after incomplete tumour resection. The quality of life is assessed three years after randomisation. Therefore, patients who are enrolled less than three years cannot be evaluated in the interim analysis. If one of the irradiation time points proves to be superior those interim patients have to be evaluated additionally.
In the context of this prospective randomised adaptive trial, different strategies are discussed to consider the analysis of interim patients. The impact of the proposed modifications on power, sample size, and trial duration is demonstrated. With an adequate consideration of interim patients the maximum sample size can be reduced considerably by 50%. The importance of interim analyses increases with the duration of the trial. The strategy for considering interim patients plays an important role for the credibility of the confirmatory analysis. It is essential to incorporate the decision rules in the analysis plan and adjust the adaptive design to the particular situation in time.
No conflict of interest.

282 INVITED

Multi-arm multi-stage studies for speeding the process of new drug evaluation

M. Parmar[1]. [1]*MRC Clinical Trials Unit, London, United Kingdom*

Background: Despite both the increase in basic biologic knowledge and the fact that many new agents have reached various stages of development during the last 10 years, the number of new treatments that have been shown to improve outcomes for patients has not increased as expected.

Methods: We propose the multi-arm, multi-stage trial design as a way to evaluate many treatments at once making treatment evaluation faster and more efficient than current standard trial designs. The design uses intermediate outcomes to conduct lack of activity analyses, to stop randomisation of further patients to research arms which are unlikely to be effective.
Conclusions: By using intermediate outcomes and testing a number of new agents (and combinations) simultaneously, the new design requires fewer patients, and provides a way of improving outcomes for patients more rapidly. Two trials using this methodology are presented.
No conflict of interest.

283 INVITED

Bayesian designs for early phase clinical trials

P. Thall[1]. [1]*MD Anderson Cancer Center, Department of Biostatistics, Houston, USA*

Scientific evaluation of new drugs, devices, or medical procedures is difficult both technically and ethically. This is especially problematic in early phase trials, where little is known, safety is a paramount issue, and sample sizes are small. Bayesian sequentially adaptive methods are particularly well suited for design and conduct of such trials. In this talk, I first will discuss and illustrate some basic principles of Bayesian statistics and sequentially adaptive "learn as you go" clinical trials. Recently developed Bayesian designs based on elicited joint utilities of multiple outcomes then will be presented, with two illustrative dose-finding trials. The first is an oncology trial that uses utilities of two ordinal outcome variables, toxicity severity and number of efficacy events, to optimize palliative radiotherapy dose in children with brain stem gliomas. The second is a multi-institution trial to optimize pre-intubation sedative dose in pre-term infants with respiratory distress syndrome undergoing the Intubation-Surfactant-Extubation procedure. In this trial, sedative doses are chosen for successive cohorts of infants based on the joint utilities of three clinical outcome variables. Computer simulations that establish numerical design properties will be presented for each trial.
No conflict of interest.

Scientific Symposium (Mon, 30 Sep, 15:00−17:00) **Molecular Classification of CRC: Ready for Prime Time?**

284 INVITED

Pitfalls of and opportunities for molecular characterisation in CRC

P. Quirke[1]. [1]*University of Leeds, Department of Histopathology, Leeds, United Kingdom*

The importance of molecular characterisation of CRC has been robustly demonstrated over the last few years. The finding that Ras mutations predict response to anti epidermal growth factor receptor antibodies has rapidly brought molecular testing into routine practice. Many more will emerge in the future.
Molecular data may contribute to prognosis as well as predicting response to targeted therapy. Before being adopted as a prognosticator a molecular test should be demonstrated to be reproducible, 'effective' i.e to achieve a clinically valuable result, to be properly validated in appropriate series and to be superior to all current methods.
Predictive markers need to ensure they identify appropriate patients who may respond to the drug of interest and not exclude individuals who may respond. They may also be prognostic and therefore this element needs to be evaluated and thus randomised trials are the most appropriate setting for such testing.
Robustly evaluated markers of prognosis are available for loss of the mismatch repair proteins (MMR) and these can be combined with B-Raf testing to help identify HNPCC cases and sporadic deficient MMR cases for prognosis. Other claimed prognostic markers such as mRNA profiling have some way to go before being accepted into routine clinical practice. Braf mutations appear to identify a poor prognosis group of stage IV cancers.
Predictive markers are very valuable but need validation. Unfortunately at present we have a limited number of predictive markers. There are currently no markers for the targeted therapies of Bevacizumab, Regorafenib or Aflibercept. The group who respond to anti-EGFr antibodies is being narrowed as one manufacturer now includes NRas mutations as a contraindication and no doubt as further evidence emerges this will be narrowed again. A number of new markers are under investigation but they need validation in clinical trial material from more than one trial. Thought also needs to be given to the identification of molecular lesions that may be relatively uncommon in colorectal cancer but to which there are effective targeted agents that have been proven to work in other cancers. Her-2 amplification occurs in 2.6% of our stage IV cancers but this small group might benefit from anti-Her2 antibody therapy. International trials covering these rare targets need to be developed.
The molecular characterization of CRC's is worthwhile and will contribute to improving outcomes in colorectal cancer.
Conflict of interest: *Ownership: None. Advisory board: None. Board of directors: None. Corporate-sponsored research: Genomic health Oncotype Dx research funded. Amgen Piccolo trial support for research testing. Affymetrix testing of oncoscan chips.*

285 INVITED

Precision medicine for colorectal cancers

A. Bardelli[1]. [1]*University of Torino − IRCC, Department of Oncology, Torino, Italy*

The EGFR-targeted monoclonal antibodies cetuximab and panitumumab paved the way to the individualized treatment of metastatic colorectal cancer (mCRC). In the last 5 years it has become evident that mCRCs respond differently to EGFR-targeted agents and that the tumor-specific response has a genetic basis. After the initial response, secondary resistance invariably ensues, thereby limiting the clinical benefit of anti-EGFR therapies. Understanding the molecular bases of secondary resistance to cetuximab and panitumumab is required to design additional therapeutic options. We found that molecular alterations in KRAS and MET are causally associated with the onset of acquired resistance to anti-EGFR blockade in colorectal cancers. We optimized a diagnostic platform to identify resistance-associated genetic alterations in the blood of patients (liquid biopsy) months before radiographic documentation of disease progression. Preclinical models of relapse including cell lines and patient-derived xenografts (*xenopatients*) allowed us to assess new lines of therapy. Overall our results provide the rationale for delaying or reversing resistance to anti EGFR therapies in mCRCs and support the initiation of innovative − molecularly driven- clinical trials.
No conflict of interest.

286 INVITED

Finding genetic dependencies in BRAF and KRAS mutant tumors

R. Bernards[1]. [1]*The Netherlands Cancer Institute, Division of Molecular CarcinogenesisCenter for Biomedical Genetic and Cancer Genomics Center, Amsterdam, Netherlands*

Cancer remains difficult to treat, even with the new generation of targeted cancer drugs. By far the most formidable obstacle is the rapid emergence of therapy resistance. Indeed, many of the new cancer drugs elicit powerful initial responses, leading to dramatic effects on "progression free survival", but far less long-term benefit is seen in terms of overall survival.
Combination therapies can help fight therapy resistance, but with an arsenal of over 1000 cancer drugs in clinical development, the number of possible combinations seems nearly endless. In my laboratory we employ functional genetic screens to find powerful combinations of cancer drugs by exploiting the concept of "synthetic lethality". Using RNA interference-based genetic screens with collections of shRNAs that target drugable gene families, we search for genes whose inactivation is particularly synergistic with clinically-relevant cancer drugs. Such screens can identify drug combinations that are far more powerful than the sum of the two single agents. We aim to understand the molecular rationale for the observed synergy between two cancer drugs. Once we have insight into the molecular mechanism, we aim to bring such rationally-designed combinations to the cancer clinic as soon as possible through our clinical collaborations in our comprehensive cancer center.
As a second approach, we use genome wide loss-of-function genetic screens in cancer cells that are sensitive to the drug-of-interest to search for genes whose down-regulation confers resistance to the drug-of-interest. Such genetic screens can identify novel mechanisms of drug resistance. This in turn may suggest strategies that help prevent drug resistance.
Examples of genetic screens that help optimize the treatment of KRAS and BRAF mutant cancers will be presented.
No conflict of interest.

287 INVITED

Relevance of non K-RAS mutations for new drug selection

Abstract not received.

Society Session (Mon, 30 Sep, 14:45−16:45)
European Society for Medical Oncology (ESMO)

288 INVITED

The development of targeted therapies in the genomic era: What is the expected impact on breast cancer?

F. Andre[1]. [1]*Institut Gustave Roussy, Department of Medical Oncology, Paris, France*

Molecular characterisation of breast cancer has shown that this disease includes a very large numbers of sub-entities. This concept of disease fragmentation according to the presence of oncogenic drivers is challenging the conventional way of developing drugs in the breast cancer field.
First, the disease fragmentation makes mandatory to re-organize the organisation of cooperative groups into large consortium. Indeed, a single cooperative group is no longer able to develop a drug when a genomic segment accounts for less than 10% of breast cancer.
Second, since most of the breast cancer patients are treated outside the comprehensive cancer centers, there is a need to perform molecular screening in peripheral centers, and then attract patients with a genomic alteration to the centers of drug development.
These two changes could allow making feasible drug development in rare genomic segments. Nevertheless, these rare genomic segments defined by single genomic alteration will then be sub-fragmented into further segmentation. This further level of complexity will make extremely difficult the development of targeted therapy in a biomarker-defined stratum of patients. From this point, we will have to change the way clinical research is being done. One possible solution to overcome the problem of paucity in rare genomic segments is the development of clinical trials that will test whether the use of a genomic algorithm improves outcome in breast cancer patients. In this model, several drugs are being tested in the same experimental arm, each of them matched to specific genomic alteration. This new model of clinical trials could allow including all breast cancer patients in the same trial.
Finally, these genomic algorithms should integrate genomics of other pathways than oncogen-de addiction including DNA repair system, immunology system and metabolism, in order to propose a personalized medicine based not only on kinase inhibition.
No conflict of interest.

289 INVITED

Molecular screening and patient selection for phase I/II trials

P. Bedard[1]. [1]*Princess Margaret Hospital, Division of Medical Oncology and Hematology, Toronto, Canada*

The traditional model of drug development in oncology involves phase I testing to establish the maximum tolerated dose and phase II testing to evaluate activity in tumour-type specific cohorts. With an increasing repertoire of available targeted cancer drugs and potential therapeutic combinations, drug development has evolved to include molecular enrichment of early phase clinical trials. This involves early proof-of-concept testing of new cancer drugs in patients whose tumours harbour sensitizing genomic alterations. Many large academic centres and co-operative clinical research groups have recently launched molecular screening programs to identify patients with “druggable” mutations who can be matched to genotype-directed early phase clinical trials. There are a variety of molecular screening approaches that have been used, including single gene testing; genotyping panels that cover recurrent oncogenic hotspot mutations; genome-wide testing for copy number alterations; and targeted next generation DNA sequencing of cancer relevant genes. The key considerations for molecular screening, such as use of archival tumour tissue or fresh biopsy of a metastatic lesion; testing in a clinical or research laboratory; turnaround time for the reporting of results; the interpretation of clinical actionability; the identification of incidental findings in heritable cancer susceptibility genes with germline testing; and access to a investigational targeted therapies will be discussed.
Conflict of interest: *Advisory board: Sanofi, Novartis, Roche. Corporate-sponsored research: GlaxoSmithKline, Sanofi, Novartis, BristolMyersSquibb, Roche, Genentech, Servier*

290 INVITED

Increased fragmentation of solid tumors: Implications for patient care

J. De Grève[1]. [1]*Oncologisch Centrum UZ Brussel, Medical Oncology, Brussels, Belgium*

Fragmentation of solid tumors is the gateway to personalized medicine. Fragmentation relies on clinical, pathological criteria and molecular criteria. Clinical/pathological criteria mostly provide prognostic information and are more subjective. The molecular criteria are more objective and predictive. The earliest model is HER2 in breast cancer and the most sophisticated lung adenocarcinoma.
Today, the clinical oncologist deals with individual driver mutations and single agent targeted therapies (with or without chemo); the cancer researcher has an integrative approach: pan-genomic interrogation at gene and RNA level, proteomics and functional pathway analysis. That analysis will lead to an even more sophisticated fragmentation of cancers and ever-smaller patient cohorts with shared characteristics. Not all of the possible combination therapies will be testable in the clinic. Therefore interest has emerged in panels of xenografts with representative genomic profiles (avatar mice) in which to test drug combinations before bringing them to the clinic.
Currently genomic testing uses validated companion diagnostics. Limitations are the incomplete sensitivity and expense of commercial diagnostic kits and amount of biopsy material available. In lung cancer, ten percent of biopsies are insufficient for a definitive exclusion of an EGFR mutation and most biopsies will allow only a couple of assays (e.g. EGFR and Alk). On the other hand there will be a couple dozen of genes and resistance mutations to be examined to select the appropriate treatment.
For all of these reasons we need comprehensive methods for mutation screening: defined cancer gene panels that correspond to drugs that are in development or registered.
For each patient a molecular diagnostic report is to be tied to the initial pathological report and accompany the patient as a “molecular passport”. If the ensuing fragmentation does not immediately benefit the treatment of a particular patient, it might allow so in the near future without having to resort to last minute diagnostic efforts in a progressive disease context.
Oncologists need molecular based guidelines that link molecular profiles with therapeutic options.
The limitations of tissue quantities and quality as well as the future need to monitor for resistance mutations and the reluctance of patients for undergoing re-biopsies or the technical impossibility asks for additional approaches such as circulating tumor cells (CTC’s).
Currently the interval between initial demonstration of high efficacy and marketing of new drugs can is too long. The development of drugs that fit into the fragmentation model should accelerate for early access to patients in medical need and simplified for reducing development cost. Additional measures need to be taken in order to keep this affordable.
For rare mutations we need mutation-driven studies in which patients with a particular mutation (whichever cancer type) can access a corresponding drug. Significant efficacy (RR) in a small cohort of patients should then suffice for registration and broad access.
The advantage of the fragmentation of cancers is that treatments have become more efficient and less toxic. This fragmentation is only beginning to govern patient care and no doubt will amplify and lead to steady progress in outcome for all cancer types.
No conflict of interest.

Scientific Symposium (Mon, 30 Sep, 14:45−16:45)
Do Resistance Mechanisms Require Combination Treatment in Immunomodulated and Targeted Therapies?

291 INVITED

New strategies for immunotherapies

S. Quezada[1]. [1]*University College London, UCL Cancer Institute Department of Haematology, London, United Kingdom*

Mobilising and reprograming the immune response with immune modulatory antibodies has emerged as a promising anti-cancer strategy, capable of producing significant and durable responses as demonstrated in recent high-profile immunotherapy trials targeting the immune-modulatory receptors PD-1 and CTLA-4.
Nonetheless, despite the success of therapies aiming to redirect or enhance T cell responses against tumours (*e.g.* vaccination, adoptive T cell transfer and immunomodulatory antibodies), complete responses remain limited to a fraction of treated patients, and there is an urgent need to explore the mechanisms underlying response and resistance in order to improve the efficacy of these novel therapeutics.
By focusing in the study of effector and regulatory tumour-reactive $CD4^+$ T cells my group is interested in the mechanism underpinning the activity of different immune-modulatory antibodies, and the potential positive and negative impact that the tumour microenvironment may have in the recruitment, survival and function of different T cell subsets. We will discuss data on the critical role played by tumour-reactive $CD4^+$ T cells in tumour progression and elimination as well as new therapies

capable of neutralising the immune-suppressive nature of the tumour microenvironment, and promoting potent rejection of fully established cancers.
No conflict of interest.

292 INVITED
Resistance mechanisms to BRAF targeted agents

K. Flaherty[1]. [1]*Massachusetts General Hospital Cancer Center, Boston, USA*

For half of the advanced melanoma population, selective BRAF inhibitor therapy has transformed the natural history of disease and provided a platform for developing molecularly targeted therapy combinations. The clinical utility of vemurafenib, FDA approved BRAF inhibitor, has been validated by another potent and selective agent, dabrafenib. However, two clinical limitations of BRAF inhibitor therapy frame the problem for the melanoma field: *de novo* and acquired resistance. Insights into the mechanisms underlying both of these phenomena have set the stage for clinical investigation of several novel BRAF inhibitor based combination therapies. Foremost among them is the combination of a MEK inhibitor with BRAF inhibitor. Preliminary clinical evidence suggests that this combination may supplant single agent BRAF inhibitor therapy near future as the standard approach for metastatic patients. Yet resistance remains a challenge and strategies to target non-MAP kinase pathway dependent mechanisms are needed.
Optimal schedule of administration has not yet been explored clinically and represents an opportunity to maximize the impact of already available agents. Opportunities to further exploit the profound dependence that BRAF mutant tumors have on the MAP kinase pathway are evident with emerging preclinical data with HSP90 and ERK inhibitors. Intercepting pathways that are activated as a consequence of BRAF inhibitor therapy, such as up regulation of BCL2A1 and ERBB3, represent tractable strategies for improving on the early impact of therapy. And, blocking compensatory pathways not impacted by BRAF inhibitor therapy such as the PI3K pathway (in some cases) and growth factor receptor activation derived from the tumor microenvironment provide further opportunities for improving on a backbone of optimal MAP kinase pathway inhibition. As this broad array of novel therapeutic strategies are investigated clinically, an immediate need arises for the development of predictive biomarkers that allow for the novel combinations to be deployed in as personalized a fashion as BRAF inhibitor therapy was itself.
Conflict of interest: *Advisory board: Roche/Genentech, GlaxoSmithKline, Novartis*

293 INVITED
Resistance mechanisms to immunotherapy

A. Ribas[1]. [1]*University of California Los Angeles, Medicine, Los Angeles, USA*

As immunotherapy approaches for cancer become more widely used and have higher response rates, it is important to understand how some tumors may escape its control. There are two main types of immunotherapy for cancer with significant activity, therapies that stimulate T cells in vivo, and adoptive cell transfer (ACT) transfer therapy where T cells are expanded ex vivo and reinfused to patients.
A hallmark of tumor immunotherapy has been the extremely long duration of the tumor responses noted with a variety of agents, including vaccines, cytokines and immune modulating antibodies. As such, the issue of resistance to these immunotherapies is mainly innate resistance, where many patients do not respond to therapy and the ones who respond unfrequently develop acquired resistance. Multiple immune self-regulating mechanisms limit such immune responses to cancer antigens. It has become clear that an important one is adaptive resistance by expressing PD-L1 when tumor cells are infiltrated by T cells producing interferons. Blocking PD-1/PD-L1 interactions with specific antibodies results in unprecedented high response rates for this mode of immunotherapy, with most of the responses being durable.
ACT with tumor-infiltrating lymphocytes (TIL) or T cell receptor (TCR) engineered lymphocytes results in a higher frequency of initial tumor responses. Resistance can be innate, when tumor cells do not respond to the infusion of a large pool of tumor-specific activated lymphocytes, but it can also be acquired resistance with progression after an initial tumor response. In the ACT setting, acquired resistance is common. This can be due to a decreased functionality of T cells after ACT, where T cells initially have high antitumor activity but they then lose it over time, or because the cancer adapted to the therapy. Acquired resistance due to tumor adaptation was thought to be due to the outgrowth of subclones that do not express a certain tumour antigen and therefore survive ACT using engineered T cells specific for that antigen, or as a result of some or all cells in a tumour lacking key proteins in the cellular pathway by which antigens are 'presented' to T cells. However, such processes are uncommon in the tumor biopsies studied by many groups. Recently, Tuetling and colleagues proposed a mechanism of acquired resistance to ACT immunotherapy where the antitumor T cells produce cytokines (i.e. TNF-alpha) that are used by the cancer cells to de-differentiate and lead to escape from immune recognition. Demonstration that this process happens in humans may lead to improved ACT-based therapies for cancer.
Conflict of interest: *Ownership: Kite Pharma. Advisory board: amgen, GSK, Merck, Roche. Board of directors: Kite Pharma*

294 INVITED
Resistance to combination therapies

F. Hodi[1]. [1]*Dana-Farber Cancer Institute, Boston MA, USA*

Success with targeted and immune therapies for the treatment of melanoma has provided a new basis to approach clinical development. The potential for combinatorial approaches to improve patient outcomes has never been so promising. CTLA-4 blockade with ipilimumab as a single agent or in combination with dacarbazine chemotherapy can improve survival in patients with metastatic melanoma. Vemurafenib has demonstrated a survival advantage in patients whose tumors harbor a BRAF V600E mutation. Potential resistant mechanisms to immune checkpoint blockade as well as known resistant mechanisms to selective BRAF inhibition will be discussed. In addition, PD-1 blockade as well as BRAFi/MEKi combinations have already showed additional promise for progress against resistant mechanisms. Challenges will be discussed how to provide synergistic benefits to patients without significant increases in side effects. Potential combinatorial approaches include targeted therapies with immune checkpoint blockade, anti-angiogenic therapies, and combined immune therapy reagents. Based on preclinical and early clinical experiences, the possible combinations of checkpoint blockade with cytokine, targeted therapy, and anti-angiogenic agents will be discussed. Understanding mechanisms of resistance to these novel therapeutic approaches and potential means to counteract these will shed insight into future best approaches to patient care.
Conflict of interest: *Advisory board: Bristol-Myers Squibb, Genentech, Merck, Novartis*

Scientific Symposium (Mon, 30 Sep, 14:45−16:45)
The Elderly Cancer Patient

295 INVITED
Adherence in elderly patients: The importance of adequate and continuous dosing

L. Noens[1]. [1]*University Hospital Ghent, Department of Haematology, Ghent, Belgium*

The number of oral anti-cancer drugs is rising constantly. However the issue of poor adherence to these medications still is not acknowledged. Its importance in failed treatments or underestimated effectiveness makes it mandatory to create awareness and to develop pragmatic strategies to enhance medication adherence. The striking example of the impact of suboptimal adherence to the Bcr-Abl inhibitors in CML illustrates the need for understanding the best approaches to adherence-enhancing interventions. The observations can be extrapolated to any longterm oral treatment for chronic conditions.Therefore adherence should be assessed routinely, and specifically in oral cancer therapies. The development of methodologies improving adherence has gained attention in recent years. The literature reveals a variety of non-adherence determinants. Focusing on predictors of non-adherence, listed from most frequent: adverse events, side effects, disease and treatment duration, the patient-physician relationship and disease related education. Patient characteristics are age, gender, disease severity, comorbidities and health believes and expectations. Treatment related factors are dosing schedule and co-medication. The findings on the relationship between adherence and age are contradictory across studies. Given the rate of comorbidities and therefore the extented list of medications, older patients carry a higher risk of becoming a poor adherer with dire consequences. In the prospective CML trial, age and living alone were among the risk factors, indicating the importance of social support and daily assistance. Regimen complexity is also a barrier to adherence, with additionally other constrains such as food or storing conditions. Another very important issue is "drug forgiveness" i.e. the non-adherence margin that should be defined for all oral cancer therapies. From a follow-on analysis of the CML-trial, we demonstrated the need for optimal adherence: no margin for non-adherence in CML! The poor adherence risk also depends on the hospital

discharge management of patients with an extended list of medications. Certainly for older people, special attention has to be focused on their proper medication management, ideally prior to discharge and with the aid of relatives, but also by implementing helpful devices and last but not least home-care provision. Unfortunately, for measuring adherence there is no gold standard method available. Every method has its drawbacks. Although an improved awareness on barriers to adherence is slowly emerging, most of the strategies for improvement are still under development. Methods that may be effective for long-term adherence are centered around more frequent interaction with the patient. The advantages of oral treatment for many conditions, including cancer, mandate that all members of the care team use effective strategies and tools to encourage proper adherence, specifically in older patients.
Conflict of interest: *Advisory board: BMS/Novartis*

296 INVITED

Polypharmacy in the elderly patient

F. Van den Berkmortel[1]. [1]*Atrium Medical Center, Heerlen, Netherlands*

The connection between aging and cancer is significant, with more than 60% of all cancers occurring among those over 65 years of age. Persons over the age of 65 represent approximately 15% of the population, but account for more than a third of all prescription drugs taken and an even higher percentage of nonprescription drugs. Except for concomitant use of 5 or more drugs, polypharmacy also includes the use of unnecessary/potentially inappropriate medication, underuse and non-prescribed medication (herbal/complementary agents). An average use of 5−9 drugs was reported in old cancer patients. In elderly cancer patients use of preventative and complementary medication was reported in 30−80%. Approximately 5−10% of hospital admissions of elderly patients are related to adverse drug reactions. An exponential increase in the incidence of adverse drug reactions is observed with the addition of each drug to an existing regimen. In ambulatory cancer patients about 30% was exposed to potentially interacting pairs of drug. Complementary medication such as St. John's wort, ginseng and garlic imposes a higher risk for drug interaction in patients using chemotherapy. Drug compliance decreases in proportion to the number of drugs prescribed, meaning that anti-cancer and symptom control medication may not be taken because of the burden of other medication, leading to poor disease control, increased healthcare costs, and increased mortality. Several tools either using specific lists such as Beers criteria, Screening Tool of Older Persons' Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) or using general guidelines such as the Medication Appropriateness Index (MAI) have been developed to guide optimal treatment. In intervention studies a reduction in the number of medications and/or use of potentially inappropriate medications was reported although reduction in mortality or hospital admission is less clear. A multidisciplinary approach is needed to address the issue of polypharmacy in the older cancer patient. In the presentation the challenges of polypharmacy in elderly cancer patients will be discussed.
No conflict of interest.

297 INVITED

The geriatric navigator/assessment

B.A. Esbensen[1]. [1]*Copenhagen University Hospital Glostrup, Department of Nursing and Health Science, Glostrup, Denmark*

Background: During the last decades, several studies have described substantial variation in changes in functional ability. Quality of Life (QoL) among elderly people is highly affected by dependency in Activities in Daily Living (ADL) following reduced functional ability. The aim of this presentation is to focus on overall results from a mixed method study aiming to explore dependency in elderly persons newly diagnosed with cancer and to focus on Comprehensive Geriatric Assessment (CGA) as a tool in clinical practice.
Method: In total, 101 elderly (aged 65+) newly diagnosed with cancer were included in the quantitative part of the study (median age 74.74 (IQR 8.75); N = 74 Women); whereas 16 elderly participated in the qualitative part (median age 73.90 (IQR 5.19); N = 12 women). Issues about quality of life and dependency were covered in a questionnaire. Open-ended interviews were the tool to getting closer to the experience of being dependent in old age.
Results: In total, 72.3% were independent in all Instrumental-ADL functions, and 17.8% were independent in regard to Personal-ADL. Factors significantly associated with low quality of life were e.g. 'need more help in daily living', 'dependency in ADL' and 'getting help from adult children'. '*Dependence on health care*' was an essential consequence of getting cancer in old age, and implied a change in social identity − from being an ordinary person to becoming a patient. *'Everyday life controlled by bodily limitations'* meant that bodily complaints limited everyday life. Fatigue restricted daily living, led to dependency and was a reminder of both growing old and of illness.
Conclusion and further perspective: Combining different approaches was seen as complementary, and by integrating different methods a more complete picture was achieved about elderly persons with cancer. The results highlight that dependency affects the elderly negatively and that appropriate intervention strategies aiming to identify a person's resources is recommended.
Attention to ADL capacity in the elderly seems vital to identifying those who experience limitations. When considering cancer in the elderly, other problems are also prevalent, and a narrow perspective on the cancer may be detrimental to the older person.
CGA is suitable to identify vulnerable individuals in order to optimize adjusted care. CGA has proved to be a sound procedure to recognize the heterogeneity of the elderly population and focus their care plans accordingly. Such assessment leads to a deeper understanding of how dependence influences to a more accurate intervention. Combining different approaches was seen as complementary, and by integrating different methods a more complete picture was achieved about elderly persons with cancer.
No conflict of interest.

Scientific Symposium (Mon, 30 Sep, 14:45−16:45) **Interrogating Minimal Residual Disease: What is New?**

298 INVITED

Circulating tumour cells as a liquid biopsy in breast cancer: Are we there yet?

M. Ignatiadis[1]. [1]*Institut Jules Bordet, Medical Oncology, Brussels, Belgium*

Recent next generation sequencing (NGS) studies have shown that breast cancer (BC) is characterized by a considerable inter- and intra-tumoral heterogeneity and that this heterogeneity is one of the drivers of tumor evolution. The detection and characterization of Circulating Tumor Cells (CTCs) in the peripheral blood of patients with BC is expected to provide an opportunity for real-time evaluation of tumor evolution, monitoring treatment response and understanding treatment resistance. There have been several challenges associated with the study of CTCs as a "liquid biopsy". First, around two thirds of metastatic BC patients and a considerably lower proportion of early BC patients have detectable CTCs with widely used technologies. Secondly, even in patients with detectable CTCs, these cells are often rare events in peripheral blood and therefore downstream applications depend on the use of limited material. As a consequence, for comprehensive genomic analysis of these cells, DNA amplification is required and this may introduce several biases that need to be carefully corrected. Recent advances hold the promise to address these challenges. The most widely used technologies for CTC detection depend on the use of antibodies against Epithelial Cell Adhesion Molecule (EpCAM), a protein expressed by epithelial tumor cells but not blood cells. Several lines of evidence suggest that technologies relying on EpCAM do not adequately capture CTCs with an Epithelial–mesenchymal transition (EMT) phenotype, a biologically aggressive and potentially relevant subpopulation. The optimization of existing technologies including microfluidics together with enrichment approaches that rely on multiple markers or on the physical properties of CTCs (e.g. filter technologies) can address this problem. All these technologies need to undergo appropriate analytical and clinical validation. Ultimately, clinical utility needs to be demonstrated. Currently, there is only one technology for CTC detection (CellSearch, Veridex) that has been cleared by the Food and Drug Administration (FDA) as an aid in monitoring metastatic breast, colorectal and prostate cancer patients. Several ongoing trials are evaluating the role of CTC detection using CellSearch in treatment decision making. However beyond enumeration, there are already examples of CTC phenotypic and molecular characterization (e.g. androgen signaling in prostate cancer, epidermal growth factor mutations in lung cancer and the ratio of mesenchymal to epithelial CTCs in BC) to monitor treatment response/resistance in clinical studies. In early BC, a pioneering phase 2 study including 75 patient with HER2-negative early BC showed that trastuzumab can eliminate Cytokeratin-19 mRNA-positive CTCs and reduce clinical relapses. The molecular analysis of CTCs could complement analysis of primary/metastatic tumor and together with circulating DNA might ultimately lead closer to precision cancer medicine.
Conflict of interest: *Advisory board: CellSearch, Veridex*

299 INVITED

Circulating tumour DNA sequencing: From targeted mutations to whole genome resolution

Y. Lo[1]. [1]*Chinese University of Hong Kong, Hong Kong SAR, China*

Background: Tumour DNA has been found in the plasma of cancer patients. We have explored the use of techniques capable of detecting targets at single DNA molecule resolution for analysing plasma DNA in cancer patients.
Material and Methods: Patients with lung cancer and hepatocellular carcinoma (HCC) were recruited from the Prince of Wales Hospital in Hong Kong. Digital PCR was used to detect epidermal growth factor receptor (EGFR) mutations in lung cancer patients. Shotgun massively parallel sequencing (MPS) was used to analyse plasma DNA from the HCC patients' plasma.
Results: Digital PCR allowed the sensitive, specific and quantitative detection of EGFR mutations in the plasma of lung cancer patients. Such detection demonstrated a good correlation with the clinical course. MPS analysis of plasma DNA from HCC patients allowed genomewide copy number aberrations and single nucleotide variations of the tumour genomes to be detected from the patients' plasma. MPS also allowed the fractional circulating tumoral DNA concentration for each patient to be measured.
Conclusion: Digital PCR and MPS are powerful methods for the detection of tumour-derived DNA in the plasma of cancer patients.
Conflict of interest: *Ownership: Sequenom. Other substantive relationships: Patent filing*

300 INVITED

Noninvasive monitoring of cancer dynamics using circulating tumour DNA

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Improved methods for detection of residual disease, quantification of tumour burden, and molecular characterization, will help management of cancer care. Presence of circulating tumour DNA fragments in patient plasma has long been recognised, however only recently have technologies matured that allow these entities to be effectively studied and exploited as diagnostic tools. Different analysis methods can work together, allowing noninvasive assessment of both levels and genetic characteristics of circulating tumour DNA (ctDNA). Analysis of mutation patterns in ctDNA can help select suitable therapies, and can help identify novel resistance mechanisms in patient cohorts or the emergence of resistance in individual patients. Accumulating evidence suggests that levels of ctDNA are an informative prognostic factor in advanced epithelial cancers, and that changes in the levels of ctDNA correlate with disease progression and response to treatment. Because this analysis relies on readily accessible blood samples, those can be collected serially over clinical follow-up, providing a window into tumour dynamics. Our studies in cohorts of patients with advanced metastatic cancers show that in many patients, serial analysis of ctDNA provides the earliest indication of disease progression or response. For earlier cancers, only limited quantitative data on ctDNA levels is at present available. Potential applications of ctDNA as a diagnostic aid span a wide range of clinical scenarios, but further studies are needed to establish the clinical utility, limitations, and performance characteristics. As methods become more accessible, these are likely to emerge in the coming years.
No conflict of interest.

Scientific Symposium (Mon, 30 Sep, 14:45−16:45)
Evidence-based Radiation Oncology: The Large Database Perspective

301 INVITED

Biomedical knowledge integration: The oncology platform

Abstract not received.

302 INVITED

Radiomics: Promoting evidence through image features from radiographic images

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Individualized medicine requires techniques that enable visualization, quantification and time series of disease processes in a non-invasive way in individual patients. Medical imaging is intuitively very suitable for this purpose. Over the past decades, medical imaging has progressed in four distinct ways allowing quantitative imaging: innovations in medical devices (hardware), innovations in imaging agents, standardization in imaging protocols, and innovations in imaging analysis. By these we have witnessed medical imaging in clinical oncology evolving from a primarily diagnostic tool to a theragnostic tool by a multitude of techniques involved in the treatment and characterization of tumors and normal organs and tissues. "Radiomics", the extraction and analysis of large amounts of advanced features from medical images, addresses this subject. The central hypothesis of radiomics is that these radiomic features are related with the underlying tumor phenotypes and gene-expression profiles, thereby potentially providing valuable diagnostic, prognostic or predictive information. However, there are distinct processes involved in radiomics, each with its own challenges. The first step involves the acquisition of high quality and standardized imaging, for diagnostic or planning purposes. From this image, the macroscopic tumor is defined, either with an automated segmentation method or alternatively by an experienced radiologist or radiation oncologist. Quantitative imaging features are subsequently extracted from the previously defined tumor region. These features involve descriptors of intensity distribution, spatial relationships between the various intensity levels, texture heterogeneity patterns, descriptors of shape and of the relations of the tumor with the surrounding tissues (i.e. attachment to the pleural wall in lung, differentiation). The extracted image traits are then subjected to a bioinformatics analysis using machine learning techniques for feature selection and model building. The most informative features are identified based on their independence from other traits, reproducibility and prominence in the data. The most promising features are assessed with outcome, for example survival time or gene-expression. In this presentation I will give a detailed description of the radiomics workflow and show recent results from our groups and collaborators.
No conflict of interest.

303 INVITED

Promoting evidence through correlation of radiology information to genomic data: The Radiogenomic Consortium

C. West[1]. [1]*University of Manchester, School of Medicine, Manchester, United Kingdom*

Radiotherapy patients show individual variation in toxicity, which can impair quality-of-life and is dose-limiting. Modern radiotherapy techniques improve outcomes but future gains require biological optimisation − information on patient radiosensitivity being particularly useful. Radiosensitivity is a complex, polygenic, heritable trait. Rare homozygote mutations in some genes (e.g. *ATM*) have large effects but most of the variation in radiosensitivity is attributed to large numbers of common genetic variants (mostly single nucleotide polymorphisms − SNPs) each conferring small, but together clinically exploitable, effects. As effect sizes for common variants are small, large databases are required to identify the genetic variants involved. A Radiogenomics Consortium was established in 2009 to facilitate large cooperative studies. The consortium has >150 members and from ~80 institutions in ~18 countries. Two published cooperative studies involved meta-analysis of SNP data for *TGFB1* and *TNF* in >2,000 patients and highlight the ability to pool radiotherapy databases across centres and countries to link genotype with toxicity. Common variants are identified in genome wide association studies (GWAS) with no prior assumption of the genes involved. The area of work is challenging because of the amount of data that must be collected: prospective assessment of toxicity (including pre-treatment); information on dose and other treatments; data on modifiers and confounders of the relationship between genotype and toxicity such as age, smoking history, co-morbidities. The Radiogenomics Consortium is carrying out a meta-analysis of four GWAS from prostate cancer cohorts recruited in the UK, Spain, Canada and USA ($n \approx 1{,}600$). Unpublished data show validation of several loci at genome-wide-appropriate levels of significance and that there are many more loci, which will achieve statistical significance given larger sample sizes. The meta-analysis shows the feasibility and potential of large-scale national and international cooperation to correlate radiotherapy and genomic data.
No conflict of interest.

304 INVITED

Promoting evidence by methods from large clinical databases: The EURECCA Consortium

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European Cancer Audit (EURECCA) is a multidisciplinary platform to improve the quality of cancer care through auditing, feedback and standardizing cancer care management in Europe. EURECCA mission

is achieving and assuring high quality of cancer management in Europe, accessible to all patients.
EURECCA supports and services include data collection and analysis to detect 'best practices', to promote patterns of care, refining achievable key indicators for each country, preferably with maximal effect at minimal (time/money -consuming) costs, for starting the European Cancer Audit.
First experiences in sharing large databases from National Registry and single Institutions will be reported, focusing on methods, constrains and evidences in colonrectal cancer.
No conflict of interest.

Scientific Symposium (Mon, 30 Sep, 14:45−16:45) **Innovative Treatment Modalities in Sarcoma**

305 INVITED

Proton or carbon ion therapy for chondrosarcomas and chordomas?

Abstract not received.

306 INVITED

MDM2 and CDK4 as a therapeutic target in sarcomas

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MDM2 amplification occurs across many tumor types but is particularly common in sarcomas. It is observed in a subset of liposarcoma (LPS), intimal sarcoma, surface osteosarcoma. LPS is the most frequent histological type of soft tissue sarcoma and well-differentiated (WD) and dedifferentiated (DD) LPSs are the most frequent subtypes (incidence ~1/100000/year). WD/DD LPS has a simple genomic profile characterized by a molecular and diagnostic hallmark: the amplification of the 12q14−15 segment, including MDM2 and most often (80%) CDK4. Molecular diagnosis can be obtained by FISH, and overexpression detected by IHC is an important part of the diagnostic tools. In advanced/unresectable disease, cytotoxic agents provide limited response rates (~10%) and resulting in short median progression free survival (PFS) (2 to 6 months). For these tumors innovative approaches introduced early in advanced phase might be proposed. The administration of Nutlin 3a, RG7112, in WD/DD LPS has been reported to enable the reactivation of p53 in vivo in cancer patients, with the induction of apoptosis, cell cycle arrest, increase of circulating MIC-1 as a potent biomarker. Antitumor activity was observed in some of these patients. Very interestingly, antitumor activity was observed in one patient with an associated p53 mutation. Other agents affecting MDM2/p53 protein interaction are currently being investigated. CDK4 inhibitor PD0332991 has also recently been explored in patients with advanced *CDK4*-amplified well-differentiated or dedifferentiated liposarcoma, with detectable antitumor activity. The development of these agents as single agent, combinations, in sarcomas with or without MDM2 amplification and p53 alteration will be discussed.
Conflict of interest: *Advisory board: Roche, Novartis, Pharmamar, Bayer, Amgen, GSK. Corporate-sponsored research: GSK, Novartis, Roche, Pharmamar*

307 INVITED

Targeted treatment of Ewing sarcomas: Current status

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Ewing sarcoma, although rare, is an excellent paradigm of high grade malignancy in the diagnostic, prognostic and clinical setting. The presentation of disease varies, with bone sites predominating over soft tissue, and younger patients (peak incidence age 15) commoner than older patients. Following core biopsy, it requires both specialist histopathology diagnosis of round blue cell tumour with associated immunocytochemistry antibody markers, and confirmation of the t(11:22) translocation, usually with fluorescent in situ hybridisation. Once diagnosed and staged, treatment currently comprises systemic multi-agent dose intense chemotherapy that includes etoposide, followed by local disease control with surgical resection, reconstruction and radiation therapy. Variations to the conventional treatment are currently minimised because of treatment protocols such as the EuroEwing 99/2008/2012 trials.
Despite standardisation of the molecular basis, clinical diagnosis and management, there are a wide range of clinical outcomes and complications of treatement. A few patients are refractory to standard treatment, some relapse locally, and of those, many also relapse systemically with decreased overall survival. There are a number of poorly understood questions that underpin any prospect of effective targeted and personalised therapy for Ewing sarcoma. These include: the identification of the molecular abnormalities at diagnosis beyond the diagnostic translocation, what is the clonal variation and heterogeniety of response to chemotherapy at the genomic level, i.e. are there common variants that account for recurrent disease, whether there are new aquired mutations or chromosomal abnormalities depending on the treatment and whether comprehensive genomic abnormalities can be identified and are actionable with clinical impact.
Some of these key mechanistic issues will be discussed and the resulting options with respect to targeted therapy options also presented. The overwhelming data points to the poorly appreciated heterogeneity of Ewing sarcoma, in terms of somatic genetics and treatment responses when targeted therapies have been attempted. This will require a more personalised approach to genomic and next generation sequencing technology and so a more informed basis to treatment decisions and combinations. This data will ultimately require us to move away from toxic systemic chemotherapy studies currently underway to more challenging molecular stratified small sample number trials, but with marked improvements in outcome. Identifying at risk patient subgroups with both molecular and clincial criteria, but that are enriched for benefit to selective targeted agents, are the required next steps.
Conflict of interest: *Other substantive relationships: Performing early phase EuroSarc clinical trials with Astellas and Takeda-Millenium drugs.*

308 INVITED

Denosumab in giant cell tumours: When and for how long?

Abstract not received.

Scientific Symposium (Mon, 30 Sep, 14:45−16:45) **Cancer Pharmaceutics**

309 INVITED

Development of biosimilars

H. Schellekens[1]. [1]*Utrecht University, Departments of Pharmaceutical and Innovation Sciences, Utrecht, Netherlands*

Legislation allowing the approval of competitor versions of biopharmaceuticals, so-called biosimilars, has been in place in the European Union (EU) since 2004. For the marketing authorization of a biosimilar the European Medicine Agency (EMA) expects a full quality dossier and in addition, comparative analytical, pre-clinical and clinical studies demonstrating comparable quality, safety and efficacy to a product authorized in the EU. At present 13 biosimilar products have been authorized in the EU, epoetins, filgrastims and human growth hormones. These products are comparatively simple molecules, homologues of human proteins with a physiological function and are used clinically mainly as supportive or supplemental therapy.
As the patents of some of the top selling and expensive monoclonal antibodies (MABs) used in cancer therapy are about to expire, there is a lot of interest in developing biosimilar versions of these products. Compared to currently approved biosimilars, MABs are much larger and complicated products. A European guideline for biosimilar MABs was relatively recently released. However, the development of biosimilar monoclonal antibodies will not be as simple as the first generation of biosimilars. Unlike the existing biosimilars, monoclonal antibodies have multiple biological functions, are used for functions that are normally not performed by antibodies and also are very specifically directed to intervene locally in the disease process that are complicated and not very well known.
The concepts that have been used to show clinical similarity and extrapolation of indication will very difficult and even in many cases impossible to apply in the development of biosimilar monoclonal antibodies. The regulatory approach to this new class of biosimilars should be reconsidered, before affordable alternatives for the expensive anticancer monoclonal antibodies can be developed.
Conflict of interest: *Corporate-sponsored research: Research concerning quality of biologic products in the third world sponsored by Sandoz*

310 INVITED

Chemotherapy drug shortages in Europe: A call to action

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The increasing worldwide demand for essential oncology drugs coincides unluckily with short supply of raw materials, production problems (as contamination of materials, aging production plants, deficiencies in good manufacturing practice), reduced productive capacity because of limited profit margins for generic drugs and administrative over-regulation, resulting in gray markets, stockpiling, price gouging and drug shortages. In the long run, this could promote an increasing use of costly, not sufficiently established innovative treatments instead of well-tried generic drugs.
Identifying drug shortages: To prevent drug shortages in Europe, action has to be taken according to the early notification program of the US Food and Drug Administration (FDA). This includes establishing a register of essential cytotoxic drugs, predictive analytical methods to detect potential drug shortages and identifying the patients most likely to be adversely affected by them.
Preventing drug shortages: This includes:
- Identifying clinically working criteria for being "medically necessary" (a drug that is used to treat or prevent cancer for which there is no alternative drug available).
- Establishing a program to support manufacturers and pharmacies to produce essential generic cytotoxic drugs.
- Alerting manufacturers of predicted or observed increases in demand for critical drugs.
- Identifying alternative manufacturers for critical drugs when more than one manufacturer exists.
- Installing a website that is updated daily with information on current shortages, including all sources of each drug and how long the shortage is expected to continue (according to the websites maintained by the American Society of Health System Pharmacists [ASHP] and the FDA).

Actions that have been proposed by the European Society for Oncology Pharmacy (ESOP) and by the Drug Commission of the German Medical Association will be addressed in this talk.
No conflict of interest.

311 INVITED

Stability of biological anticancer drugs in practical situations

A. Astier[1]. [1]*CHU Henri-Mondor − APHP, Department of Pharmacy and UMR CNRS 7054, Créteil cedex, France*

Background: It is of paramount importance for hospital pharmacists to have well-documented data about the real stability of an opened drug formulation, after reconstitution of a lyophilised product or after dilution in various vehicles. Indeed, it is critical for pharmacists to be sure that their handling techniques and current practices of transportation or storage are not deleterious for the final administered drug (FAD), i.e. a drug diluted in a specific vehicle at its final concentration in the administering device (bag or syringe). Clearly, these real-life practices must be validated by studies independent of the manufacturer to insure the safety of the FAD to the patient. Unfortunately, only limited industry-independent studies on the stability of mAbs in practical situations were available.
Materials and Methods: We have studied the stability of several monoclonal antibodies (cetuximab, trastuzumab, rituximab and bevacizumab) and an enzyme (L-asparaginase), submitted to thermal and/or mechanical which can occur in practical situations. To assess a complete stability profile (chemical, physical and biological), we used several complementary (orthogonal) methods following the recommendations of the ESOP European consensus.
Results: We demonstrated that diluted rituximab and trastuzumab can be kept at 4ºC for 6 months and also at room temperature for months without any degradation, especially in terms of aggregation which is the main marker of instability. This excellent thermal stability was also demonstrated for bevacizumab and cetuximab. It is interesting to note that the corresponding manufacturers indicate only a stability of 24 hrs. L-asparaginase is stable until seven days after reconstitution (8 hrs for the manufacturer). However, their stability under mechanical stresses is more complex, depending mostly on the presence of air/liquid interfaces. Indeed, we demonstrated that the role of hydrophobic air interfaces is critical during the use of pneumatic-network transportation. If bags were emptied of air, the use of pneumatic- network transportation is not deleterious.
Conclusion: The tested biologicals in their FAD are remarkably more stable than indicated by the manufacturers. For mechanical stresses that can appear during handling and transportation, the presence of air/liquid interfaces should be avoided. Stability studies in real-life situation permit to extend the stability limits of very costly biologicals and would be extremely helpful both for practical and financial reasons.
No conflict of interest.

312 INVITED

Ensuring prescription and delivery accuracy for cytotoxics

K. Meier[1]. [1]*Heidekreis Klinikum GmbH, Department Hospital and Clinical Pharmacy, Soltau, Germany*

Introduction: Antineoplastic chemotherapy describes a group of hazardous drugs commonly used in the treatment of cancer. Potential risks are not only recognised for patients, but extend to pharmacists and other healthcare workers. Guidelines for safe handling are well established in the traditional settings of hospitals and ambulatory clinics for the IV chemotherapy. In tumour therapy, documentation, quality management and standardisation of interdisciplinary processes are increasingly gaining importance in form of therapy protocols and guidelines for clinical treatment.
Method: Non-adherence, application errors and interactions due to insufficient education of the patient can compromise therapeutic success. An adequate, quality assured, multi-professional care is therefore urgently required for oncology patients receiving oral chemotherapy. A programme is set up in Germany to teach 20,000 community and hospital pharmacist in the next year in supporting patients the best in taking oral cytotoxic drugs. This initiative aims to reach the following goals for oncology patients:
1. On-site optimisation of oral chemotherapy and improvement of pharmaceutical care for oncology patients.
2. Cost-effective and reliable care for cancer patients due to professional collaboration of local physicians, pharmacists and other healthcare professionals at the right time.
3. Recognising and solving drug-related problems related to oral chemotherapy.
4. Enhancing the quality of life of oncology patients through a coordinated management of side effects and interactions during and after therapy.
5. Providing new insight as a contribution to health services research and to encourage drug safety.

Results: Not only the way to win the societies of doctors and community pharmacists but also to engage the industry to jump over their own marketing shadow. Finally the support of the agency for data privacy protection is giving all other interested parties the chance to become part of it.
Conclusion: The increasing role of oral cytotoxic drugs and the growing demand of its good use can finally only insured by well trained pharmacists. The campaign which is starting in Germany by 250 teaching meetings is followed in Austria, Estonia and Slovenia in order to demonstrate the good outcome in a few years.
No conflict of interest.

313 INVITED

Is there a dose-effect relationship for biological anticancer drugs?

Abstract not received.

Scientific Symposium (Mon, 30 Sep, 14:45−16:45) **Integrating Genetic Information Into Daily Clinical Practice**

314 INVITED

Integrating germline cancer gene testing into routine cancer care

N. Rahman[1]. [1]*Institute of Cancer Research, Section of Cancer Genetics, Sutton, United Kingdom*

Genetic testing of cancer predisposition genes is one of the major activities of Clinical Genetics. Currently, nearly 100 genes associated with predisposition to cancer are known, but in most countries testing is very restricted with respect to the number of genes and the number of people tested. The value of genetic testing in individuals with cancer is underappreciated; it provides important information with respect to the cause and optimal treatment of the current cancer, and the risk and optimal management of future cancer. Moreover, testing cancer patients followed by cascade testing of mutation carriers is an effective and efficient way of identifying unaffected mutation carriers in whom screening and risk-reducing strategies can be deployed. The Mainstreaming Cancer Genetics (MCG) Programme is a UK national cross-disciplinary initiative to develop the NGS assays, analytical and interpretive pipelines, clinical infrastructure, training, ethical and evaluation processes required.

In collaboration with Illumina we have developed a NGS panel targeting 97 cancer predisposition genes with >1500 probes (called the TruSight cancer panel) and have completed detailed evaluation of performance, sensitivity and specificity under different levels of multiplexing, coverage and throughput. We are using bespoke analytical pipelines developed for high-throughput clinical diagnostic data analysis (called GAMA) and clinical interpretation (called CIGMA). We are implementing a new mixed-model of cancer gene testing whereby consent for medical testing (i.e. in cancer patients) is undertaken by oncologists, with only the mutation carriers seen by geneticists. Predictive testing (i.e. in unaffected individuals) will continue to be undertaken in genetics. We have developed protocols and e-learning modules to deliver the required training for oncologists. We hope this model will allow throughput of testing to greatly increase, whilst retaining input and support from Genetics, where it is required. We are piloting the new model in ovarian and breast cancer patients. A key first aspiration of the MCG programme is to make genetic testing available to all ovarian cancer patients, 15% of whom have a germline cancer predisposition gene mutation. www.mcgprogramme.com

Conflict of interest: *Other substantive relationships: Collaboration with and provision of reagents from Illumina*

315 INVITED

Expression profiling in breast cancer: Ready for clinical use?

M. Maetens[1], C. Sotiriou[1]. [1]*Institut Jules Bordet, Breast Cancer Translational Research Laboratory, Brussels, Belgium*

For more than a decade now, microarrays have been the methodology of reference for the study of gene expression profiling (GP). In the breast cancer (BC) field, this technology has been implemented in the attempt to dissect the biological complexity of the disease and define its clinical course.

Several studies have demonstrated that BC consists of different diseases with specific molecular profiles and clinical behaviors that can help selecting patients for enrollment in clinical trials and orienting therapeutic approaches. Microarrays have also been used to identify gene expression signatures (GS) with a prognostic and/or predictive value. After a wave of “first generation signatures” mostly based on the ability of proliferation to discriminate which patients can be spared aggressive treatments, signatures of “second generation” have explored the prognostic value of gene related to immune response and stromal compartment. Multigene classifiers have also been developed to predict response to either generic or specific endocrino- or chemotherapies. Despite the reliability of microarray technology has been demonstrated, the clinical implementation of GS is still limited mostly in relation to the uncertainty of their added value compared to standard clinical-pathological factors. While the results of three large randomized trials will help establishing the clinical role of some of the GS tested, the advent of next generation sequencing (NGS) technologies, in particular RNA sequencing (RNA-seq), appears to enrich the discovery spectrum compared to other GP technologies. These discoveries will surely have an impact on the management of BC in the future. To date however, their integration in the clinical setting is still premature.

While subtyping of BC and treatment decisions still largely rely on classical clinical and pathological parameters, efforts should be invested in overcoming the hurdles that prevent the integration of high throughput technologies into daily clinical practice.

Conflict of interest: *Advisory board: Novartis, Nanostring, Roche, Merck. Other substantive relationships: C Sotiriou discloses co-ownership of several patents involving gene expression signatures*

316 INVITED

Genetic analysis in advanced cancer patients: What test for which patient? Matching patient, biomarker and drug

J. Rodon[1], R. Dienstmann[2], J. Tabernero[1]. [1]*Vall D’Hebrón University Hospital, Medical Oncology, Barcelona, Spain;* [2]*Massachusetts General Hospital Cancer Center, Molecular Pathology, Boston, USA*

Uncovering the genetic changes of cancer through genomic profiling in the clinical setting could provide insights into the management of a patient. Different platforms have been used in different clinical settings or moments of the disease for diverse clinical decisions. Nowadays, genomic technologies such as next generation sequencing platforms are able to analyze point mutations, copy number alterations, translocation mapping, and exon/allele specific transcriptome profiling in a reasonable timeframe. In Early Drug Development, some of these technologies are quickly being implemented for selecting patients that may benefit from an experimental drug. Therefore, phase I trials are being transformed in an arena where biomarkers, technology and experimental drugs are being tested.

The implementation and future routine use of technologies such as large-scale genome sequencing, will not only unravel the biology of each tumor but transform the way we test novel agents.

No conflict of interest.

317 INVITED

Impact of genetic analyses on patients − what to tell our patients?

M. Abramowicz[1]. [1]*Université Libre De Bruxelles, Brussels, Belgium*

Technical advances in massively parallel sequencing (MPS) of DNA will soon change clinical practice. The biological interpretation of genetic findings however limits clinical applications.

MPS of *tumor DNA* allows for better molecular pathology, and drug sensitivity of cancer cells. MPS of *patient DNA* (germline mutations) allows for individual profiling of specific cancer risks. Currently, this approach is clinically validated only for high penetrance mutations, i.e. mutations causing a Mendelian or near-Mendelian, hereditary cancer syndrome, e.g. hereditary breast and ovarian cancer, and Lynch syndrome, which represent about 5% of breast cancer and of colon cancer respectively. The decision to test for an inherited mutation is not straightforward and depends on the personal and family history. Among the many variants identified in cohorts of patients with a inherited cancer syndrome, a sizeable proportion are currently of unknown clinical significance (VUCS). Patients must be informed before testing of the limitations of the test, of potential impact in relatives, and on medical options in genetic risk carriers. For example, while evidence shows that risk-reducing oophoro-annexectomy is superior to surveillance of ovaries in *BRCA1* mutation carrying women, evidence is much scanter for prophyllactic mastectomy, at least in terms of mutation-associated mortality.

Testing for low penetrance mutations currently has little clinical utility as compared to the clinical history-based evaluation of the risk and empirical follow-up. This is however likely to change in the future, adding significant complexity to risk assessment and strategic decision making.

Incidental findings are those discovered by coincidence while investigating other symptoms. An example is the serendipitous discovery, in a fetus investigated for malformations, of a chromosomal microdeletion encompassing the *MLH1* gene causing Lynch syndrome, with expected consequences for the future adult, and for some of his relatives. Likewise, finding a germ-line change while investigating tumor DNA may have further consequences for the patient, and family relatives.

Implementing MPS in clinical practice will require thorough information of the patients, which in turns calls for education of both patients and medical teams.

No conflict of interest.

Scientific Symposium (Mon, 30 Sep, 14:45−16:45)
Lifestyle, Exercise and Vitamins

318 INVITED

Fit or fat? Energy balance in cancer risk and prognosis

C. Ulrich[1], K. Steindorf[1], J. Wiskemann[2]. [1]*German Cancer Research Center, Preventive Oncology, Heidelberg, Germany;* [2]*German Cancer Research Center, Medical and Preventive Oncology, Heidelberg, Germany*

Energy balance and its underpinnings, physical activity, dietary intake, and obesity, are known to play a role in the primary prevention of cancer. Low levels of physical activity and overweight or obesity have been associated with multiple cancer types, particularly of the colorectum and postmenopausal breast (for physical activity) or the colorectum, postmenopausal breast, liver and esophagus (for obesity). A number of biologic mechanisms have been discerned, including effects on systemic inflammation, immune function, insulin-like growth factors, insulin resistance, steroid hormones, vitamin D levels, and antioxidant defenses and DNA repair. Finally, weight-loss results directly in gene-expression changes in the adipose tissue.

In addition, energy balance can also affect the the well-being and prognosis of cancer patients. Among cancer patients, initial clinical studies illustrate benefits of exercise training on quality of life or fatigue as well as fitness levels, strength and cachexia. Epidemiologic studies also suggest a positive influence of physical activity on prognosis, particularly for colorectal cancer patients. However, many questions remain regarding causality of the associations, interrelationships between exercise and body weight, and the most appropriate type and timing of exercise training of cancer patients.

No conflict of interest.

319 INVITED

Interplay between the cancer genome and epigenome: opportunities in elucidating mechanisms of carcinogenesis and cancer prevention

Z. Herceg[1]. [1]*IARC, Mechanisms of Carcinogenesis Section Epigenetics Group, Lyon, France*

The evolution of common human cancers involves the gradual accumulation of genetic and epigenetic cancer-promoting changes with different mechanisms assuming primary roles during different stages of cancer development. Recent international sequencing efforts have revealed comprehensive genomic landscapes of common human cancers and the Human Epigenome Project will not only yield an unparalleled view of the "normal" epigenome in different tissues but also identify epigenome variations against which environmental exposure can be assessed. The remarkable advances in our knowledge of carcinogenesis and the cancer genome can now guide the development of new strategies for therapy. These advances are also expected to accelerate the revival of cancer prevention research. I will discuss opportunities and challenges in identifying functionally important "*driver*" events and environmental factors associated with these changes as well as how comprehensive portraits of the cancer genome and epigenome and mechanistic advances in identifying "driver" genes and pathways may provide an evidence base for the next generation of cancer prevention efforts.
No conflict of interest.

320 INVITED

Diet and cancer

Abstract not received.

321 INVITED

Are there any vitamins we can recommend?

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Introduction: The World Health Organization and U.S. guidelines neither recommend nor warn against taking a daily vitamin supplement. However, 49% of Americans report using a dietary supplement. We evaluated the evidence in support or against vitamin supplements for cancer prevention.
Material and Methods: We reviewed nutritional surveys comparing actual versus recommended levels for various vitamins, and observational studies, randomized trials, and meta-analyses for vitamin supplements in relation to cancer.
Results: Surveys indicate that many individuals have vitamin intake or blood levels below the recommended standard, particularly for vitamin D. Confounding factors and reverse causation (high risk or more health conscious individuals may take more supplements) make observational studies difficult to interpret. For cancer prevention, only long-term trials are useful. So, although a recent meta-analysis of 21 randomized trials reported no significant effect of multivitamins, only 4 trials extended beyond 7 years. Any potential effect (beneficial or harmful) depends critically on the underlying nutritional status. Thus, the marked reduction in gastric cancer in the Linxian General Population Nutrition Intervention Trial may not be generalizable to populations with better nutrition. Perhaps the most compelling evidence derives from the trial among 14,641 (presumably well-nourished) U.S. male physicians, which found a significant 8% reduction in total cancer incidence (and a non-significant 12% reduction in cancer mortality) over a median follow-up of 11.2 years.
Substantial basic science and observational evidence suggests that adequate vitamin D status may be important for cancer prevention. One randomized trial of 1100 IU vitamin D_3 in 1179 women showed a strong protective effect against total cancer incidence with 4 years of intervention. Two other trials tested too low (400 IU) or unphysiologic (100,000 IU/3 months) dosages. A major trial is now assessing the efficacy of 2000 IU/day.
Conclusions: Given the safety, low cost, and magnitude of potential benefit, it seems reasonable for most individuals to take a multivitamin supplement and perhaps extra vitamin D. However, the evidence appears insufficient for a major public health policy intervention, and supplements rank low in importance to health compared with other modifiable activities such as smoking cessation, physical activity, and maintaining a healthy diet and weight.
No conflict of interest.

Scientific Symposium (Mon, 30 Sep, 14:45–16:45)
Chip Technologies

322 INVITED

The impact of chip technology on cancer medicine

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The molecular pathology of cancer is governed by step-wise accumulation of somatic mutations in genes or regulatory DNA sequences with important tasks in the life of a normal cell. Pathways involved are those directing programmed cell death, proliferation, cellular differentiation, and perhaps autophagy.
Techniques such as cytogenetics or later FISH are suitable to light up those alterations which imply structural aberrations of chromosomes or chromosomal material. In their early days molecular genetic tests often looked into a single locus per test, e.g. a PCR assay. It has long become clear that these techniques, valuable as they are, overlook the complex orchestrated "ensemble" of molecular alterations that are present in a given cancer case.
The chip technology, and new generation DNA sequencing have overcome these limitations and have brought new light as well as new problems into the field. Initially microchips or -arrays were used to discover comprehensive gene expression profiles (GEP) in a cancer. Next these patterns were compared to normal counterpart tissues oft he given cancer or other cancer cases. Depending on the reference material used, distinct cancer profiles or signatures come up which encompass important pathways, as well as many irrelevant or minor alterations. Nowadays complete sequence information of particular cancers has become available with astounding myriads of sequence alterations detectable, particularly in solid tumours. For example, in a lung cancer case one gene mutation or acquired sequence variation was found per 3 cigarettes that the patient had smoked until diagnosis. Not all findings are relevant, however. To separate genetic wheat from molecular chaff is in no way trivial, as molecular alterations in cancer are hierarchically organised, with few driver mutations at the top and many molecular epiphenomena at lower ranks. Efforts to identify driver mutations are important as these may offer the best chance to discover new targets for therapy. Treatment of ELM-ALK positive lung adenocarcinoma with crizotinib is a good example.
In breast cancer, established targets, such as the hormone receptors or HER2 were discovered prior to the aera of modern molecular genetics. Gene expression profiling has helped to define several types (or perhaps entities) of breast cancer, i.e. luminal A or B type breast cancers, or triple-negative cancers. Often these subtype diagnoses are now made in routine pathology reports, merely based on immunohistochemistry patterns. Whilst some of these combined markers may indeed come close to identifying cancers harbouring one or the other GEP, the correlation between immunohistochemistry findings and GEP data is not strict. Furthermore, and perhaps more importantly, it remains to be seen which specific therapies will work particularly well in one breast cancer subtype (i.e. luminal A), and perhaps less in another one. Trials to pinpoint such predictive markers and the effect of specific treatments are underway, but most of them are not mature at present. Increasingly, commercial assays testing gene signatures in cancer biopsies are offered to predict benefit or perhaps harm from one chemotherapy or another. There seems to be a lot of enthusiasm in the oncological community to use these tests (e.g. oncotype dx) in practice. However, they must be viewed with caution at present, as the trial data necessary to assess test value (i.e. prospective randomised trials suitable to prove the predictive power of a given marker) are not yet mature. Also new driver mutations are eagerly awaited in breast cancer, similar to non-small cell lung cancer which has become a paradigm disease for the rapid discovery of new molecular therapies.
Conflict of interest: *Advisory board: Nestle, Switzerland*

323 INVITED

Direct profiling of cancer biomarkers using novel chip technology

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Robust, practical platforms that detect low levels of biomolecules (<1000 copies) are urgently needed to advance medical care by diagnosing and predicting the progression of cancer and other disease states. Electrochemical methods providing low cost and direct biomarker read-out have attracted a great deal of attention for this application, but have, to date, failed to provide clinically-relevant sensitivity. We exploit controlled nanostructuring of electrode surfaces to promote surface accessibility and enhance capture rate and efficiency to solve this long-standing problem, and showed that the nanoscale morphologies of electrode surfaces control their sensitivities (*Nature Nanotechnol.,* 2009). In addition, we have worked towards integrating nanomaterials-based electrodes into a chip-based

platform to facilitate multiplexed analysis in a robust, practical format. Recently, we have developed an assay that is able to detect nucleic acids, proteins and small molecules, with universally high sensitivity levels (*Nature Chemistry*, 2012). Our efforts to use these components to detect biomarkers in tumors and circulating tumor cells will be featured in this lecture.
No conflict of interest.

324 INVITED
Lab-on-chip tracing circulating tumour cells

L. Lagae[1], C.X. Liu[1], D. Latta[2], O. Henry[3], C. O'Sullivan[3], T. Roeser[4], J. Lundeberg[5], L. Kvastad[5], I. Riley[6], E. Borgen[7]. *[1]Imec vzw, Life Science Technologies, Leuven, Belgium; [2]IMM, Mainz, Germany; [3]URV, Chemical Engineering, Tarragona, Spain; [4]Thinxxs, Zweibrücken, Germany; [5]KTH, Science for Life Laboratory, Stockholm, Sweden; [6]Labman Automation, North Yorkshire, United Kingdom; [7]Oslo University Hospital, Pathology, Oslo, Norway*

Circulating tumor cells (CTC) are currently believed to be the primary pathway for cancer metastasis. The isolation and cellular/genetic analysis of CTCs is important not only for clinical prognosis but also for personalized therapy. The extremely low CTC amount (<1 CTC/mL blood) demands identification and isolation of individual viable CTCs, as well as multi-gene analysis for single CTCs. The vision of the EU funded MIRACLE project is to develop the first automated system that can isolate viable circulating tumor cells (CTC's) from blood with high purity and perform multigene-analysis for individual CTCs. We employed a two-step CTC isolation process: immunomagnetic CTC isolation followed by single cell electrical impedance spectroscopy (EIS). The integrated circuit based EIS, in particular, identifies CTCs based on their lower electrical impedance in comparison to normal cells. After CTC isolation, we perform multi-gene amplification & detection on single cell level, based on multiplex ligation dependent probe amplification (MLPA). Integrating both the cell isolation and the gene amplification-detection modules in a single system, we aim at an automated miniaturized system for CTC detection and analysis. The high specificity, sensitivity & flexibility of CTC analysis will allow accurate early prognosis for metastasis and will foster fundamental studies on metastasis at single cell level. This talk will summarize the progress and main results obtained in the currently ongoing MIRACLE project.
No conflict of interest.

325 INVITED
Biosensor chip in detection of cancer

Abstract not received.

Scientific Symposium (Mon, 30 Sep, 14:45−16:45) **Targeted Drugs and Personalised Medicine in Paediatric Oncology**

326 INVITED
B-RAF as a druggable target in paediatric malignancies

Abstract not received.

327 INVITED
Targeting the sonic hedgehog pathway in paediatric malignancies

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Aberrant Hedgehog (Hh) signaling is involved in tumorigenesis through promotion of cell proliferation, survival, and differentiation in numerous human cancers, including medulloblastomas (MB), basal cell carcinoma (BCC), and rhabdomyosarcoma. Hh signaling in cancer may occur through a cancer cell-autonomous role, paracrine signaling involving tumor and stromal interactions, or autocrine signaling via cancer stem cells. Pathway activation through mutations in *PTCH1* or *SuFu* (loss of function), or *Smo* (gain of function) leads to ligand independent, constitutive signaling through Gli and its transcription factors. Such mutations have been identified in approximately 20% to 30% of sporadic MBs. A direct example of the linkage between constitutive activation of the pathway and tumorigenesis is Gorlin syndrome, an autosomal dominant disease, caused by mutation in PTCH (chromosome 9q22.3). Gorlin patients have an increased tendency to develop BCC, MB, rhabdomyosarcoma, and ovarian neoplasia. Other pediatric malignancies such as neuroblastoma, rhabdomyosarcoma, hepatoblastoma, and glioma are found with increased expression of HH pathway proteins (Shh, PTCH1 and Gli1) suggesting that Hh signaling may play a role in the pathogenesis of these tumors too.
Inhibition of the HH pathway was first found for the steroidal jeveratrum alkaloid cyclopamine isolated from the corn lily that causes fatal birth, holoprosencephaly and cyclopia. Cyclopamine, Smoothened (Smo) knockdown with Smo small hairpin ribonucleic acid, or recently developed Smo small molecule inhibitors promoted G1 cell cycle arrest and prevented growth of glioma and osteosarcoma *in vitro* and *in vivo*. Oral administration of Smo inhibitors caused more than 90% tumor regression in genetically defined *in vivo* MB xenograft models characterized by heterozygous deletion of *PTCH*. Pharmacodynamic studies showed nearly complete and sustained inhibition *Gli1* mRNA expression in tumor samples. The proof-of-concept for the clinical utility of this class of agents has been established in patients with metastatic or locally advanced BCC. A clinical phase 1 trial of the SMO inhibitor LDE225 showed promising efficacy in children with HH-activated MB and a phase 3 pivotal trial is currently underway. However in view of the role of the Hh signaling in the normal growth and development of tissues, the use of SMO inhibitors in children needs to be carefully assessed in order to manage the potential adverse effects, in particular, on bone growth plates, developing teeth, and the immature reproductive system.
The inhibition of HH pathway is one of the encouraging examples for how detailed knowledge of molecular and genetic abnormalities may pave the way to more efficiently target specific pathways leading to a personalized treatment with beneficial on patient outcome.
Conflict of interest: *Advisory board: Novartis*

328 INVITED
Targeting the mTOR/AKT/PI3K pathway in paediatric malignancies

A. Pearson[1]. *[1]Institute of Cancer Research/Royal Marsden Hospital, Sutton, United Kingdom*

mTOR / PI3K/AKT pathway in paediatric malignancy: The mammalian target of rapamycin (mTOR)/phosphoinositide-3-kinase (PI3K)/AKT signalling pathway is deregulated in many poor prognosis childhood malignancies, through:

1. Increased levels of MYCN oncoprotein − Amplification of the *MYCN* oncogene and increased MYCN protein levels occurs in poor prognosis paediatric tumours, neuroblastoma, medulloblastoma and rhabdomyosarcoma. Intracellular MYCN protein levels are maintained by proteasomal degradation mediated by E3 ubiquitin ligases whose interaction with MYCN is controlled by phosphorylation of serine and threonine residues, which is in turn is regulated by the mTOR / PI3K/AKT pathway. Therefore, pathway inhibitors can destablise MYCN protein.
2. Aberrant activation of the PI3K pathway as demonstrated by high levels of AKT phosphorylation. This has been shown in poor prognosis neuroblastoma, medulloblastoma, high grade glioma and rhabdomyosarcoma. In this situation combined inhibition of the PI3K and RAS/RAF pathway may be valuable.
3. Aberrant activation of TORC1 and/or TORC2 with high levels of S6 and 4EBP1 phosphorylation.
4. Intrinsic PI3K pathway activating mutations (PI3KCA [medulloblastoma, high grade glioma] AKT) or deletions (PTEN [high grade glioma]) − although these generally occur less frequently in paediatric than in adult cancers.

Inhibitors − Different classes of agents inhibit the pathway:

- mTOR inhibitors: rapalogues: everolimus, temsirolimus, deforolimus and ridaforolimus;
- TORC 1 and 2 inhibitors (one of their major benefits is the lack of feedback): AZ2014 and OSI027;
- PI3K inhibitors: GDC0941, BKM, BYL;
- Combined PI3K and mTOR inhibitors: BEZ 235, GDC980;
- AKT inhibitors: MK-2206, perifosine

Consensus in neuroblastoma: At a recent Innovative Therapies for Children with Cancer European Consortium (ITCC), European Network for Cancer Research in Children and Adolescents (ENCCA), International Society Paediatric Oncology Europe Neuroblastoma Group (SIOPEN) symposium to prioritise targets for neuroblastoma (the Neuroblastoma Drug Development Strategy meeting, NDDS) the target TORC1/2 was given top priority for clinical development for neuroblastoma. mTOR inhibitors were ranked high, however AKT and PI3K inhibitors were given low priority.
Clinical studies: Despite the strong rationale for targeting this pathway clinical studies to date have been completed only with rapamycin derivatives − phase I (oral and intravenous ridaforolimus, temsirolimus, everolimus) and II studies (temsirolimus). Paediatric combination trials of rapalogues with IGF-1R monoclonal antibodies and other therapies are ongoing as are studies of AKT inhibitors (MK-2206 and perifosine).
Conclusion: Paediatric early clinical trials of TORC 1 and 2 and PI3K/mTOR inhibitors are eagerly awaited as are combinations with MEK inhibitors.
No conflict of interest.

329 INVITED

Disialoganglioside GD2 directed immunotherapy of neuroblastoma

H. Lode[1], N. Siebert[1]. [1]*Klinik und Poliklinik fuer Kinder, Greifswald, Germany*

Background: Targeting of GD_2 emerges as an important option for the treatment of neuroblastoma.
Here, we report preclinical and clinical advances in passive and subsequent active immunotherapeutic approaches to this challenging problem.
Material and Methods: Clinical passive immunotherapy results using ch14.18/CHO in combination with IL2 relate to an ongoing Phase I/II clinical trial in relapsed and refractory disease. Active immunizations against GD_2 were studied in a GD_2 expressing syngeneic animal model and in a few patients in the compassionate use setting.
Results: Passive immunotherapy with ch14.18/CHO in combination with IL2 shows activity related to effective immunomodulation indicated by an increase in NK-cells, effective antibody levels and neuroblastoma specific ADCC and CDC. An improved pain toxicity profile was observed using a long term infusion schedule folowed by objective clinical responses in treated patients.
Active immunotherapy was studied using mimotopes of ganglioside GD_2, since GD_2 itself is a weak and T-cell independent antigen. Peptide and protein vaccines were effective against neuroblastoma in a preclinical neuroblastoma mouse model. Patients immunized with a GD_2 mimotope developed a long lasting GD_2 specific humoral immune response.
Conclusions: Passive immunotherapy with anti-GD_2 antibody ch14.18/CHO shows activity in relapsed/refractory disease and active immunization with GD_2 mimotopes may be a future concept to further consolidate such responses achieved with ch14.18/CHO.
No conflict of interest.

Special Session (Mon, 30 Sep, 17:00–18:00)
Risks and Benefits of Organ Preservation in Treating Rectal Cancer

330 INVITED

Selecting patients suitable for organ preservation through imaging

Abstract not received.

331 INVITED

Tailoring neoadjuvant radio-chemo-therapy treatment for organ preservation

Abstract not received.

332 INVITED

The oncological and functional risks of the organ preservation experimental treatment approach

C. Coco Martins[1]. [1]*Centro Hospitalar Torres Vedras, Lisbon, Portugal*

We increasingly face conservative surgery for rectal cancer and even the so called 'wait and see' approach, as far as 10–20% patients can reach a complete pathological response at the time of surgery. But what can we say to our patients about risks? Standard surgery with mesorectal excision gives a <2% local recurrence with a post operative death rate of 2–8% (may reach 30% at 6 months in those over 85), but low AR has some deterioration in bowel function and in low cancer a permanent stoma may be required. Also a long-term impact on urinary and sexual function is possible. Distant metastasis rate seem to be identical in the standard and conservative approach. It is difficult to evaluate conservative approach because a not clear standardization of surgery for low rectal cancer. Rullier et al tried to clarify, and they found identical results for recurrence (5–9%), disease free survival (70%) at 5 y for coloanal anastomosis and intersphinteric resection. Other series have found local recurrence higher than with standard approach and functional results may be worse and, in some situations, salvage therapy is compromised or has more complications. In this context, functional outcomes are very important but most studies are incomplete in measuring bowel function in the context of conservative approach. In 2005 Temple et al made a survey of 122/184 patient after sphinter preserving surgery and found a 96.9% of incomplete evacuation, 94.4% clustering, 93.2% food affecting frequency, 91.8% gas incontinence and proposed a systematic evaluation with a specific questionnaire. In which concerns 'Wait and see' approach for complete clinical responders, it was first advocated by Habr Gama for tumors up to 7 cm, with a low locoregional failure of 4.6%, 5 y overall survival 96%, 72% for disease free survival; one fifth of patients failed in the first year; a Dutch trial had identical results but others had worse recurrence rates; in other series 25% of patients could not be salvaged even with APR; 30% have subsequent metastatic disease what seems equal for 'wait and see' and operated patients. In a recent review Glynne Jones considers that all the evaluated 'wait and see' studies are heterogeneous in staging, inclusion criteria, design and follow up after chemoradiation and that there is the suggestion that patients who progress while under observation fare worse than those resected. He proposes long-term observational studies with more uniform inclusion criteria. We are now facing a moment where we may be more aggressive in early cancer and neoadjuvant treatment to be more conservative in the subsequent treatment but we need a better stratification of patients, better evaluation of results and more clear prognostic markers.
No conflict of interest.

Special Session (Mon, 30 Sep, 17:00–18:00)
New Treatment for Complex Basal Cell Carcinoma

333 INVITED

New treatment opportunity for non-resectable BCC

N. Basset-Seguin[1]. [1]*Hôpital Saint Louis, Department for Dermatology, Paris, France*

Background: The discovery of the implication of the patch sonic hedgehog pathway in the pathogenesis of basal cell carcinoma (BCC) has brought new therapeutical strategies for the treatment of non resectable (La BCC)or metastatic BCC (mBCC). While most BCC are curable by surgery, some tumors are very aggressive, relapse frequently and are no longer accessible to radiotherapy or conventional surgery due to either high morbidity of the surgical procedure (eye exenteration, amputation of the nose or the ear), or the extension of the surgery, or the recurrence of basal-cell carcinoma after two or more surgical procedures and an expectation that curative resection would be unlikely. Additionally some rare cases of BCC can metastasize (mBCC) and have a very poor prognosis. Molecular and genetic studies have shown that almost all basal-cell carcinomas contain genetic alterations in the hedgehog signaling pathway (driver mutations), resulting in aberrant pathway activation and uncontrolled proliferation of basal cells. Most commonly, these alterations cause loss of function of patched homologue 1 (PTCH1), which normally acts to inhibit the signaling activity of smoothened homologue (SMO), a seven-transmembrane protein. Vismodegib is the first of the class of smo inhibitors that has been shown to have anti tumoral efficacy for advanced BCC.
Material and Methods: A review of phase I and II studies using Vismodegib in advanced BCC is presented.
Results: A phase 1 study of vismodegib involving 33 patients with advanced basal-cell carcinoma showed a 58% confirmed response rate and a median duration of response of 12.8 months. A phase 2 Erivance study enrolling 33 mBCC and 63 La BCC has shown an initial evaluation of overall response rate (ORR) by independent review of 30% for mBCC and 43%for La BCC. This efficacy is maintained over time. Major and most frequent side effects are muscle spasms, alopecia, dysgyueusia, weight decrease, fatigue and nausea. The ongoing phase II multicentric study Stevie aims at recruiting above 800 patients. The primary endpoint of the study is safety and the initial report (150 patients with > months follow up)has shown that among the 138 patients with LaBCC and the 12 patients with mBCC 75% were still on the drug while about 25% in each group had stopped the drug. Reasons for arrest were mostly sides effects or patients desire or death (N = 7, but none of them were thought related to the drug). The efficacy observed in the Stevie study is comparable to that observed in the Erivance study. Tumor relapse after stopping the drug seems to be variable according to investigator experiences.
Conclusion: Vismodegib is a very exciting new treatment option for aggressive BCC. Long term use is limited by some side effects but new therapeutical regimens might improve the tolerability.
Conflict of interest: *Advisory board: with Roche*

334 INVITED

Optimisation of hedgehog inhibitor use

Abstract not received.

Special Lecture (Mon, 30 Sep, 17:00–17:45)
Can Drug Approval Keep Pace With Translational Research in Cancer?

335 INVITED

Can drug approval keep pace with translational research in cancer?

B. Chabner[1]. [1]*Massachusetts General Hospital, Department of Medicine, Boston MA, USA*

The past decade has witnessed a remarkable acceleration in cancer drug discovery, beginning with the landmark studies of bcr-abl inhibitors, and their subsequent approval for chronic myeloid leukemia, and herceptin for Her2 amplified breast cancer. The first of these targeted agents, imatinib, showed that a nearly 100% response could be achieved with a targeted small molecule in a disease uniformly characterized by a molecular lesion. Studies of the second agent, herceptin, illustrated the value of patient selection (those with Her 2 amplified tumors) in enriching a relatively modest response rate. Re-inforcment of the principle of patient selection to enrich response rates and guide drug use came from studies of gastro-intestinal stromal tumors and EGFR mutations in non-small cell lung cancer. This work has set the stage for a radical shift in cancer drug approval. With a strong targeted agent and appropriate patient selection, it is now possible to define a highly responsive patient subset in otherwise chemotherapy-resistant patients, leading to early and convincing evidence for drug benefit in expanded cohorts in Phase I trials. No longer does it make sense to require the painful process of randomized Phase III trials to gain drug approval. What has evolved is the notion that with a properly targeted agent and with an available assay for the presence of the mutated or amplified target, it is possible to demonstrate the unique benefit of a new drug in Phase I. Ongoing studies of second generation EML-4/ALK inhibitors in non-small cell lung cancer, such as the Novartis LDK 378 compound, may provide the first example of a drug approvable based on a Phase I trial. Strategies to expedite future studies, including collaborative networks among major cancer centers in Phase I, expanded gene sequencing facilities, and oncology training programs that emphasize the interplay of tumor genomics and drug development, will be discussed. The need for a national plan for tumor genotyping, as part of this effort, will also be emphasized.

No conflict of interest.

Special Session (Mon, 30 Sep, 17:00–18:00)
Molecular Imaging

336 INVITED

MOBILE (Mapping of Oxygen By Imaging Lipids relaxation Enhancement) – New approach to imaging hypoxia by MR

F. Colliez[1], B.F. Jordan[1], J. Magat[1], T. Duprez[2], B. Gallez[1]. [1]*Université Catholique de Louvain, Biomedical Magnetic Resonance Research Group, Brussels, Belgium;* [2]*Université Catholique de Louvain, Radiology Department, Brussels, Belgium*

Quantitative follow-up of changes in tumor oxygenation can find relevant applications in radiation therapy planning as well as with regard to anti-angiogenic and anti-vascular treatments optimization. Because of its paramagnetic properties, oxygen may act as an endogenous MRI contrast agent by changing proton relaxation rates. Variations in T_1 and T_2* are potentially valuable MRI tools to monitor changes in tumor oxygenation: T2* is sensitive to the relative Hb/HbO2 ratio in vessels, while T_1 change is sensitive to dissolved oxygen in tissues. Changes in tumor oxygen concentrations have been shown to produce changes in relaxation time T_1 of water, but this technique still lacks a good sensitivity. To increase the sensitivity, we developed an innovative MRI technique that exploits the higher solubility property of oxygen in lipids than in water. This MRI pulse sequence, called *MOBILE* for Mapping of Oxygen By Imaging Lipids relaxation Enhancement, sensitively monitor tissue oxygen levels by selectively measuring the T_1 of lipid protons.

To assess the sensitivity and the quantitative properties of *MOBILE*, measurements of Lipid R_1 (=1/T1) were compared to absolute values of pO_2 obtained by Electron Paramagnetic Resonance (EPR) oximetry. This was achieved in two mammary tumor models (MDA-MB-231 and NT2), in response to a hyperoxic breathing challenge (carbogen breathing) and to a hypoxic challenge (administration of the vascular disrupting agent combretastatin CA4). We found a direct correlation between Lipid R_1 and pO_2 values, with Lipid R_1 being about 3 to 4 times more sensitive than R_1 measured in water.

We are also currently working on the clinical translation of the method. The *MOBILE* sequence was implemented on a 3 Tesla clinical scanner and was successfully applied in the brain of healthy human volunteers exposed to an oxygen breathing challenge (n = 11), in stroke patients (n = 9), in brain tumors (n = 6), and in head and neck tumors (n = 7).

In conclusion, *MOBILE* arises as a promising non-invasive and sensitive tool for diagnosis and therapeutic guidance in cancer treatments involving hypoxia.

No conflict of interest.

337 INVITED

Preclinical and clinical optical imaging

G. Van Dam[1]. [1]*Groningen University Hospital, Department of Surgery, Groningen, Netherlands*

In recent years, significant progress has been made in both optical imaging systems and fluorescent contrast agents for clinical applications. NIRF imaging with a free-floating imaging device mounted on the ceiling of the operating theatre or on a microscope articulating arm during surgery for cancer will enable visualization of tumor delineation, locoregional metastases, remnant disease as well as e.g. tumor-containing lymph nodes. Hereby, the surgeon can both detect (diagnostic) and excise (therapeutic) malignant tissue and possible residual disease at the same time. The use of NIRF optical imaging has a range of advantages. Most prominent among these is the fact that it is very safe technology, simple to operate, fast, high resolution (as low as 10 μm), relatively inexpensive and makes use of non-ionizing radiation. Based on the above, it is clear that intra-operative imaging is on the verge of entering standard clinical practice for surgery. Not only the imaging system but also the availability of clinical grade tumor-targeted probes is of the utmost importance for a succesful introduction into clinical practice. This talk will give an overview of the current concepts and future perspectives of intraoperative fluorescence image-guided surgery using non-targeted and targeted optical contrast agents for the first-time ever used in patients with ovarian cancer and the anticipated developments within the next 5 years. It will become clear that Europe will play a major role in bringing this technology into the clinic and the necessity of standardization of methodology when applied in multicenter studies.

No conflict of interest.

338 INVITED

PET/MR imaging

A.J. Beer[1], M. Eiber[2], M. Schwaiger[1]. [1]*Technische Universität München, Department of Nuclear Medicine, Munich, Germany;* [2]*Technische Universität München, Department of Radiology, Munich, Germany*

The introduction of whole-body PET/MR scanners combining magnetic resonance (MR) imaging and positron emission tomography (PET) in one system 3 years ago raises great expectations especially in the field of oncological imaging. In this talk a short overview of the different systems and general technical background for PET/MR is given. The focus will be on the current and future use of whole-body PET/MR in oncology for clinical indications as well as for more research oriented applications.

For routine clinical applications in oncology, basically all indications lend themselves for PET/MR where on the one hand we know that MR is superior to CT and where on the other hand we know that PET might give additional information. In these cases there is the logistical advantage of a one-stop-shop examination and also the advantage of very exact image fusion which might provide synergistic effects. Examples are head-and-neck-cancer imaging and imaging of pathologies in the pelvis like ovarian- and cervical cancer or prostate cancer imaging. Concerning research oriented applications, there is great promise in using all the functional, physiological and biological information that both PET and MRI can provide to get more insight in tumour biology and tumour heterogeneity than was possible before with only one modality. This concept of multimodality multiparametric imaging of tumour biology might be beneficial e. g. for biopsy planning, prognostic stratification of patients during primary staging and for early response evaluation during therapy.

Finally one potential benefit of PET/MR is that it not only brings technology together but that it also has the chance to bring people together. That means that to exploit all the potential advantages of PET/MR, physicists, physicians, technicians, clinicians and basic scientists have to come together and join their expertise to make optimal use of these exciting new technique for the maximum benefit for our patients.

Conflict of interest: *Other substantive relationships: speaker for Siemens Medical*

Special Session (Mon, 30 Sep, 17:00−18:00)
Current and Future Approaches for Recurrent Glioblastoma

339 INVITED

Does surgery at relapse impact survival?

J. Tonn[1]. [1]*Klinikum der Universität München-Großhadern, Dept. of Neurosurgery, München, Germany*

Up to now, no treatment standard exists for recurrent glioblastoma. There is even no consensus reached about the value of re-operation. However, patients in whom another operation might be of additional benefit can be identified by means of clinical and imaging parameters.
First, early post-op imaging after the initial surgery according to the RANO criteria helps to visualize tumor remnants and thus, in future, to separate tumor progression from real recurrency.
Second, pseudo-progression or any unspecific contrast enhancement should be excluded by either short-term repetition of MRI or additional PET using aminoacid tracer like 18-FET or 11-C-Met.
Third, a simple scoring system rating size of the lesion, clinical status of the patient and location of the tumor in less or more than 2 eloquent regions helps to assess the potential benefit of a re-operation.
Frequent follow up including clinical assessment and MRI imaging helps to detect recurrent tumor early when the tumor mass is still small and asymptomatic − good preconditions for re-operation.
As the molecular markers like mutation of the IDH-1 gene, LOH 1p/19q and the methylation of the *MGMT* promoter do not change in recurrent glioma, there is no need for re-operation just to determine the molecular status of the recurrent tumor tissue. However, if any doubt exists about either the dignity of the lesion or its histology, tissue sampling is mandatory. This can also be done as a stereotactic serial biopsy whenever the patient is not likely to benefit from extensive cytoreductive re-operation.
Conflict of interest: *Advisory board: Roche, MerckSerono*

340 INVITED

Recurrent glioblastoma: Role of focal therapy in an infiltrative disease

B.G. Baumert[1]. [1]*MediClin Robert-Janker Clinic & University of Bonn Med Ctr Cooperation Unit Neurooncology, Bonn, Germany;* [2]*Radiation Oncology (MAASTRO) GROW Maastricht University Medical, Netherlands*

Patients with a glioblastoma have an increasing survival after initial standard treatment with combined radiochemotherapy with temozolomide and have a good performance status which makes most of them eligible for retreatment. However, to date re-irradiation has not been investigated in randomized controlled trials.
Results from retrospective and cohort studies report survival rates for high grade glioma of 5−14 months with a median of 9−11 months. This broad range depends primarily on the tumour grade: low grade glioma recur less and usually later than high grade glioma. These differences in overall survival emphasize the need to take into account prognostic factors such as primary histology, age, performance status, re-resection and corticosteroid use. Also the time interval since first radiation is a prognostic factor based on initial histology: previous histology of low grade glioma results in a longer interval to develop a recurrence as well as longer survival. Different prognostic scores are being developed to identify patients for re-irradiation or retreatment like the recursive pattern analysis for recurrent glioblastoma. Preliminary single institution data based on a matched pair analysis found a difference in overall survival between patients with a primary GBM with or without re-irradiation (own data). Whether a retreatment with combined chemoradiotherapy and temozolomide transfers a survival advantage is unclear. According to results reported in the literature a clinical response with improvement or stabilization of symptoms can be reached in about 60−70% of the patients after re-irradiation.
The majority (ca 80%) of glioma recur locally within 4 cm from the original site, thus often within the previous radiation field or at the margin of the primary radiation border. Re-irradiation is therefore usually given in the same area as primary radiotherapy and cerebral radiation necrosis is a potential risk for toxicity. This risk depends on the total radiation dose of both radiotherapy treatments and the time interval between first and second treatment as well as the tumour volume. Radiation-induced cerebral necrosis was found to occur at cumulative doses from both treatments above 100 Gy. Studies using a conventional fractionation scheme and/or a restricted radiation volume report a low toxicity rate of 10%. If the total cumulative dose is beyond 100 Gy and a defined time interval between both treatments is taken into account, occurrence of cerebral necrosis is low. A higher cumulative dose can be considered when the treatment volume is kept small (e.g. stereotactic radiotherapy). In the Maastricht group of re-irradiated patients the rate of radiation necrosis was 6% (based on MR imaging). However, during further follow-up tumour progression on MRI was observed at the same location where radiation necrosis was suspected earlier.
First research of recurrence pattern after reirradiation found that the cumulative recurrence pattern is predominantly distant especially if patients are surviving longer, whereas first recurrences are observed predominantly local.
In conclusion, it can be said that for a subgroup of patients selected by prognostic factors, taking into account radiotherapy dose prescription and timing, re-irradiation is effective, has impact on survival and can improve clinical symptoms with low toxicity.
No conflict of interest.

341 INVITED

What is the best option for recurrent glioblastoma in 2013 and 2023?

A. Brandes[1]. [1]*Bellaria Maggiore Hospital, Medical Oncology, Bologna, Italy*

Despite efforts and novel options in the treatment of recurrent glioblastoma, this disease remains almost incurable, with a limited survival expectancy. The upcoming strategy of inhibiting tumor angiogenesis has generated different treatment modalities, which have been transferred into clinical practice in recent years, and found in the inhibition of VEGF with bevacizumab (Avastin) the best clinical results. Our understanding of angiogenesis inhibition in glioma therapy is continually evolving. After the first two key noncomparative phase II studies, the BRAIN study and the NCI 06-C-0064E study, that found a significant improvement in efficacy with bevacizumab compared with historical data, other randomized trials have been performed showing a role of this drug in combination with chemotherapy, survival rates at 9 months of about 60%.
Moreover, the continuation of bevacizumab beyond progression in patients who received this monoclonal antibody in combination with radiotherapy and temozolomide, is under investigations, since this approach has been showed to increase survival in colorectal carcinoma, thus showing that the future backbone of some cancer types will be based on the block of angiogenic pathways during the entire natural history of these diseases.
A novel study, M028347, is a randomised, placebo-controlled, phase III trial, which aims to evaluate whether bevacizumab plus standard-of-care therapy improves overall survival in patients with glioblastoma who have progressed after first-line bevacizumab plus standard radiotherapy and temozolomide. However, despite these efforts, disease recurs and further options are limited.
Thus, as in other cancer types, basic research is moving to find driver mutations able to impact the fate of glioblastoma cells. Several putative alterations have been found, such as FGF mutation/amplification, or PI3KCA mutations, as well as MET alterations.
In conclusion, improvements in cancer survival observed over recent years appear to be the sum of incremental gains achieved with the introduction of novel treatments alongside other advances in patient care. In the next 10 years we expect to continue this incremental improvement in survival, as well as identification of specific treatments for subgroups of glioblastoma patients characterized by specific genetic signatures.
No conflict of interest.

Tuesday 1 October 2013

Scientific Symposium (Tue, 1 Oct, 09:00−11:00)
Breast and Prostate Cancers: What we can Learn From Each Other?

342 INVITED

Role of micro-environment in resistance to endocrine therapies

Abstract not received.

343 INVITED

Androgen-receptor: A two-edge sword?

W.D. Tilley[1], T.E. Hickey[1]. [1]*The University of Adelaide, Dame Roma Mitchell Cancer Research Laboratories, Adelaide, Australia*

The androgen receptor (AR) is a key oncogenic driver and therapeutic target in prostate cancer, with recent studies of advanced disease revealing diverse adaptive mechanisms to sustain AR signalling under therapeutic conditions that aim to silence the receptor. On the horizon are new targeting

strategies aimed to outsmart known adaptive mechanisms, particularly in terms of targeting regions of the receptor that lie outside of the ligand binding domain. While these new strategies hold great promise for more effective AR inhibition, historical experience of employing androgen deprivation therapy raises a key question: will more effective AR silencing lead to more durable disease regression and significantly extend life for men with metastatic prostate cancer or will it reveal yet unknown treatment-induced adaptations that allow the disease to persist? These advances in knowledge of AR signalling and its targeting are now also being actively employed in the field of breast cancer with clinical trials already begun or commencing to examine the efficacy of AR target therapies for the treatment of metastatic disease. As a large majority of primary and secondary breast cancers display immunoreactivity for the AR, it represents a prevalent therapeutic target. However, unlike normal and malignant prostate tissues, AR signalling is not essential for breast development and appears to have dichotomous roles in breast cancer, with ascribed tumour suppressive or oncogenic capacities. On the one hand, AR signalling exerts an anti-estrogenic, growth inhibitory influence in normal breast tissue and in estrogen receptor (ERa) positive luminal breast cancers. On the other hand, evidence has been accumulating to support the concept that AR exerts an oncogenic influence in ERa negative breast cancers with a molecular apocrine phenotype and may play a role in the development of treatment resistance to anti-estrogen therapies currently in clinical use for ERa positive disease. Due to the inherent heterogeneity of breast cancer and the potential for AR signalling to exert tumour suppressive or oncogenic effects on different cell types within breast tissues, understanding the molecular mechanisms whereby AR signalling can elicit distinct gene expression programs and opposing proliferative responses in different breast cancer contexts is critical to the effective deployment of AR targeting therapies for treatment of women with breast cancer.
No conflict of interest.

344 INVITED

Micro-environment and bone metastases

R. Coleman[1]. [1]*Weston Park Hospital, Department of Clinical OncologyCancer Research CentreAcademic Unit of Clinical Oncology, Sheffield, United Kingdom*

Bone metastases result from the complex interactions between cancer cells in the bone marrow microenvironment, haematopoietic stem cells (HSC) and normal bone cells. Disseminated tumour cells (DTC) home to the HSC niches adjacent to Nestin+ cells in the perivascular space of small bone marrow arterioles at the bone surface and/or the lining osteoblasts. There, they can remain quiescent and in a dormant state for years prior to subsequent activation, the development of micro-metastatic foci and either stimulation of osteoclast function resulting in the development of a bone metastasis or onward dissemination to other metastatic sites. Thus, while the phenotype of the primary tumour and the ability of tumour cells to undergo epithelial mesenchymal transition (EMT) may influence the capacity of DTC to home to bone in the first place, it is the adaption of DTC to the bone microenvironment and the interactions with the many cell types within the bone marrow that probably determine whether a DTC is able to progress to a life-threatening metastasis, not only in bone but also at other sites. Bone-targeted treatments such as bisphosphonates (BPs) and denosumab (Dmab) have profound effects on the cellular interactions within the bone marrow micro-environment. Extensive preclinical research led to the hypothesis that BPs and Dmab might influence the course of the disease and led to the design of adjuvant studies in breast cancer and castrate resistant prostate cancer (CRPC).
Prostate cancer has the propensity to metastasize almost exclusively to bone and provides an ideal clinical setting for the evaluation of bone-targeted treatments. In a study in CRPC with unfavourable PSA kinetics, denosumab significantly increased bone metastasis-free survival by a median of 4.2 months over placebo (HR = 0.85; 95% CI 0.73–0.98, P = 0.028), and delayed time to symptomatic first bone metastases.
In women with early breast cancer, improvements in both disease free (DFS) and overall survival have been demonstrated in several large randomised adjuvant trials. The evidence for this is particularly strong with zoledronic acid but appears to be confined to patients with low levels of reproductive hormones including premenopausal women receiving ovarian suppression therapy and those who have passed through menopause at the time of diagnosis. In this group of patients, study level meta-analysis has shown an 18% improvement in DFS (hazard ratio [HR]=0.82; 95% CI 0.74–0.92, 2P=<0.001) with reductions in relapse rates not only in bone but also at extra-skeletal and loco-regional sites. Conversely, in premenopausal women, an increase in visceral and loco-regional relapse was seen that outweighs any reductions in bone metastases with marked heterogeneity of treatment effect according to menopausal status. The EBCTCG is currently performing a formal meta-analysis of the world-wide evidence and, if confirmed, these findings are likely to change clinical practice for postmenopausal women with breast cancer.
Conflict of interest: *Other substantive relationships: Expert testimony − Novartis. Speaker bureau − Novartis, Amgen.*

345 INVITED

A critical role for snail-regulated EMT in PI3K and MAPK pathway co-activation-induced prostate cancer progression and metastasis

H. Wu[1], M. Ruscetti[1], N. Kobayashi[1]. [1]*UCLA, Molecular Biology Institute, Los Angeles, USA*

The PI3K and RAS/MAPK pathways are co-activated in a high number of metastatic human prostate lesions, but the mechanisms of their collaboration are poorly understood. We show here that PI3K and RAS/MAPK pathway co-activation sensitizes the prostatic epithelium to TGF-b stimulation and leads to the upregulation of *Snail,* a key epithelial to mesenchymal transition (EMT) transcription factor. Downregulation of *Snail*, either by genetic deletion or co-inhibition of the PI3K and RAS/MAPK pathways in a metastatic prostate cancer model delays EMT-associated cancer progression and prevents distant macrometastasis. Mechanistically, cancer cells with EMT features are hypersensitive to SNAIL loss-induced and p53-dependent apoptosis. Our findings identify the critical role of SNAIL in the PI3K and RAS/MAPK co-activation-induced EMT program and prostate cancer metastasis *in vivo.*
No conflict of interest.

Society Session (Tue, 1 Oct, 09:00−11:00)
European Association of Urology (EAU)

346 INVITED

Post-chemotherapy RPLND for testis cancer

S. Horenblas[1]. [1]*The Netherlands Cancer Institute, Urologische Oncologie, Amsterdam, Netherlands*

While surgical resection of residual masses after induction chemotherapy of non seminomatous germ cell tumors (NSGCT) is considered standard approach, questions and controversies remain. There is hardly any controversy in the management of the patient typically presented to the urologist with negative markers after chemotherapy with a large mass in the retroperitoneum. Results of surgery have been excellent with a low risk of recurrence. Template surgery has evolved based on mapping studies of the lymphatic landing zones. These studies were mostly done in low stage tumors and extrapolated to postchemotherapy surgery. However there is no consensus on the extent of surgery. While some advocate a full formal retroperitoneal lymph node dissection, removing all lymphatic tissue in the retroperitoneum, we and others advocate the removal of the lesion only. A limited removal has been helpful in decreasing the morbidity. Since the unraveling of the anatomy of autonomic nerves, nerve sparing surgery is considered standard procedure in low stage NSGCT. In certain patients this can also be achieved in a complete postchemotherapy RPLND. However, restricting the extent of the surgery has been beneficial especially to the maintenance of antegrade ejaculation without jeopardizing oncological results.
Most experts in the field agree there is no indication for surgery in patients with masses <1 cm, despite evidence in the literature that up to 30% of masses with a diameter<1 cm can contain viable tumor or mature teratoma. We and others continue to observe these patients as long term follow up has shown extremely low recurrence figures, far below the figures found in the past.
Recent figures have shown a shift in pathology of the resected specimen. Traditionally fibrosis/necrosis was found in 40%, mature teratoma in another 40% and viable germ cell tumor in 20%. Probably due to more effective chemotherapy and stage migration, figures have shifted to fibrosis in 50% and viable tumor in only 10%.
All agree there is no true benefit in removing dead tissue. Despite all efforts to use risk factors in order to better stratify patients for surgery and omitting surgery in patients with a high probability of necrosis/fibrosis in the mass, the best prediction models have a 20% false negative rate. So far these prediction models have had a limited place at best in the selection of patients.
Future imaging modalities could change daily practice as it has been the case with PET-CT scan in seminoma patients. As mature teratoma cannot be distinguished from necrosis/fibrosis, PET-CT scan has been not very helpful in NSGCT.
The biology of mature teratoma is unpredictable with growth (“growing teratoma syndrome”) and malignant transformation, resulting in chemotherapy resistant adenocarcinoma and sarcoma. Surgery is the only effective

treatment of mature teratoma and should therefore strive for complete removal.
Completeness of resection is an independent and consistent factor of clinical outcome.
While surgery has been advocated in NSGCT for small residual masses, this had not been the case in seminoma. Shrinkage of the mass has been observed in a majority of patients, restricting surgery to masses >3 cm.
PET-CT scan has been helpful in identifying patients with viable tumor.
Postchemotherapy RPLND is a technically demanding surgery. It is reasonable to restrict this type of surgery to dedicated centers where the procedure is performed by experienced surgeons.
No conflict of interest.

347 INVITED

New medical treatment options in prostate cancer

M. Wirth[1]. [1]*Universitätsklinikum Carl Gustav Carus, Department of Urology, Dresden, Germany*

A survival benefit for patients treated with Abiraterone and Cabazitaxel after failure of first line docetaxel treatment in CRPC has been proven in phase III studies. The final analysis of the Cougar 301 study confirmed again this survival benefit for patients treated with abiraterone.
Therapy with abiraterone before docetaxel chemotherapy was investigated in a further phase III study (COU-AA-302). This study included asymptomatic or mildly symptomatic patients with CRPC and showed a benefit in the primary endpoint progression free survival in favour of patients treated with abiraterone compared to placebo. Also a clear trend towards improvement of overall survival, although not significant, was seen in patients treated with this substance. This study led to the approval of abiraterone for asymptomatic and mildly symptomatic patients with CRPC not pretreated with docetaxel by the FDA and the EMA.
In a phase III trial the effect of Enzalutamide in patients with progressive disease after chemotherapy with docetaxel was investigated. In this study enzalutamide increased overall survival compared to placebo from 13.6 months to 18.4 months (HR 0.63, $p < 0.001$). For other secondary endpoints (PSA-response, response in soft tissue metastases, time to first skeletal event) also a benefit was achieved with enzalutamide. Therefore Enzalutamide was approved for the treatment of progressive CRPC after docetaxel therapy by the FDA and approval of the EMA is expected soon.
An alpha-emitting radionuclide (radium-223 dichloride-"Alpharadin") was tested in CRPC-patients with bone metastases. Patients included in the trial were progressive after docetaxel or unfit for docetaxel. Alpharadine led to a survival benefit of 14 months in comparison to 11.2 months (Placebo and best supportive care). Alpharadin has recently been approved by the FDA and approval in Europe is also expected soon.
In conclusion there are several new medical treatment options for patients with advanced and metastatic prostate cancer.
No conflict of interest.

348 INVITED

Sequencing surgery and drugs in renal cell cancer

P. Mulders[1]. [1]*Radboud University Medical Centre Nijmegen, Department of Urology, Nijmegen, Netherlands*

Kidney cancer treatment has changed substantially during the last decade. The targetted therapies have been implemented in the algoritms of treatment of metastatic renal cell carcinoma. This has led to an improvement in survival over the immunotherapy era a decade ago. Several agents can be used in first and second line for the treatment of this disease, approved for mainly progression free survival benefit. Moreover different toxicity profiles, although class specific, are apparent and should be implemented in treatment decisions. Mode of action is important for the best sequence decision, although cross reactivity may exist and will have its impact.
The discussion on the best sequence also includes the timing of surgery in combination with targetted agents. Pro and cons of nephrectomy will be discussed.
The role of targetted agents in the neoadjuvant and adjuvant is still unclear. Trials are ongoing to select out the best treatment sequence.It is clear that manh treatment options are available and results of pivotal trials should be implemented to improve the survival of renal cell carcinoma and decrease toxicities.
Conflict of interest: *Advisory board: astellas, bayer, pfizer, novartis, dendreon, gsk. Corporate-sponsored research: astellas, bayer*

349 INVITED

Update on the management of muscle invasive bladder cancer

H. Van Poppel[1]. [1]*University Hospitals KU Leuven, Urology, Leuven, Belgium*

Background: Radical cystectomy is considered the gold standard for treating muscle invasive bladder cancer. Despite progress in diagnosis and treatment a considerable number of patients die from metastatic disease.
Materials and Methods: A number of items were looked after in recent publications.
Results: *Timely indication for cystectomy*: Timely indication of cystectomy and performance of surgery for BCG resistant T1GIII and for muscle invasive bladder cancer is clearly an important prognostic factor. Delaying the surgery is associated with a significant decrease in survival probability.
Adequate extent of surgery: Radical cystectomy in males refers to cystoprostatectomy with or without urethrectomy. In female patients it involves an anterior exenteration with resection of the internal genitalia, resection of the anterior vaginal wall and cystourethrectomy unless the urethra is used for bladder replacement. In both sexes, an extended lymphadenectomy needs to be performed since a number of patients with limited nodal disease can be cured. While the exact template is not yet clearly defined most experts include external and internal iliac vessels, obturator fossa and common iliac vessels up to the ureteral crossing.
Combination with systemic chemotherapy: The EAU Guidelines 2010 state that neoadjuvant cisplatin containing combination chemotherapy should be considered in muscle invasive bladder cancer, irrespective of the definitive treatment. In contrast, it remains clear that neoadjuvant chemotherapy is not recommended in older patients with poor performance status or in patients with impaired renal function.
Cystectomy in experienced centers: Mortality and morbidity following cystectomy is strongly related to the number of cystectomies performed by the center per year. This is clearly a factor that patients (and insurance companies) should consider. Urological surgeons must be aware of their own figures and critically analyze whether a sufficient number of procedures is performed to maintain surgical skill.
What type of urinary diversion? While bladder substitution procedures will be proposed in younger patients in which the urethra can be preserved, it is obvious that the majority of patients in most centers still undergo a cutaneous Bricker diversion. Comparative studies by the Cochrane collaboration has not come to a specific recommendation for the diversion type. Cutaneous continent diversions are more difficult and more complicated.
Conclusion: Radical cystectomy, once indicated, should not be postponed. An extended lymph node dissection is an integral part of the procedure. Neoadjuvant chemotherapy should be discussed with healthy younger patients with large T2 or T3 bladder cancer. Urinary diversion should be chosen following the patients preference and the surgeons expertise.
No conflict of interest.

Scientific Symposium (Tue, 1 Oct, 09:00−11:00)
Metabolism and Cancer

350 INVITED

Targeting treatment-related hypermetabolism in cancer

C. Schmitt[1]. [1]*Charité Campus Virchow, Department of Haematology and Oncology, Berlin, Germany*

Cellular senescence, a DNA damage-initiated terminal cell-cycle block, is an important component of chemotherapeutic drug action. The Eμ-*myc* transgenic mouse was previously established as an excellent model to explore the role of candidate genes and candidate programs (such as apoptosis) in aggressive B-cell lymphomas in response to chemotherapy. We previously demonstrated the essential role of the histone H3 lysine 9 methyltransferase Suv39 h1 in oncogene-induced senescence; here we characterize biological features and clinical impact of Suv39 h1-dependent TIS in Eμ-*myc* transgenic mice.
Tumor-bearing mice entered TIS in their lymphomas and achieved a much better long-term treatment outcome when compared to mice harboring TIS-incapable Suv39 h1-deficient lymphomas. While TIS lymphomas presented with a sharp decline in ^{18}F-fluoro-deoxythymidine positron emission tomography (PET) activity (scanning DNA synthesis as a functionality of dividing cells), they − unexpectedly − exhibited even enhanced ^{18}F-fluoro-deoxyglucose PET signal intensities (scanning glucose metabolism). *In vitro*, TIS lymphomas showed increased glucose uptake, a higher glycolytic rate and higher ATP levels. Mechanistically, due to the overwhelming production of senescence-associated secretory proteins, senescent cells displayed massive proteotoxic stress (endoplasmic reticulum stress and

the unfolded protein response), which they buffered by strongly enhanced and energy-consuming autophagy to clear the toxic proteins. In turn, TIS lymphomas − as well as a large variety of senescent human cancer cell lines and primary tumor samples − underwent cell death when exposed to autophagy or glycolysis inhibitors. Importantly, this sequential treatment also produced lymphoma regression and improved long-term outcome *in vivo*. Hence, metabolic targeting can be employed to effectively eliminate senescent cells, which are potentially harmful because they secrete proinflammatory cytokines and may eventually resume proliferation, thereby giving rise to a relapse. These findings represent a proof-of-principle how to utilize a cancer-specific condition (not a single molecular lesion) in a conceptually novel anticancer strategy that produces little harm to normal tissues.
No conflict of interest.

351 INVITED
HIFs, hypoxia, and tumor progression

C. Simon[1]. [1]*University of Pennsylvania, Philadelphia, USA*

Solid tumors exhibit heterogeneous microenvironments, often characterized by limiting concentrations of oxygen (O_2), glucose, and other nutrients. How oncogenic mutations alter stress response pathways, metabolism, and cell survival in the face of these challenges is incompletely understood. Here, we report that constitutive mTORC1 activity renders hypoxic cells dependent on exogenous desaturated lipids, as levels of de novo synthesized unsaturated fatty acids are reduced under low O_2. Specifically, we demonstrate that hypoxic $Tsc2^{-/-}$ cells deprived of serum lipids exhibit a magnified UPR response, but fail to appropriately expand their ER, leading to IRE1-dependent cell death that can be reversed by the addition of unsaturated lipids. UPR activation and apoptosis were also detected in Tsc2-deficient kidney tumors. Importantly, we observe this phenotype in multiple human cancer lines and suggest that cells committed to unregulated growth within ischemic tumor microenvironments are unable to balance lipid and protein synthesis due to a critical limitation in desaturated lipids.
No conflict of interest.

352 INVITED
Targeting the PI3K pathway in cancer

P. Workman[1]. [1]*The Institute of Cancer Research, UK Centre for Cancer Therapeutics, Sutton, United Kingdom*

The PI3 kinase pathway is frequently hijacked in cancer, for example by mutation of *RAS* and the *PIK3CA* gene encoding PI3 kinase p110a, loss of PTEN and increased activity of receptor tyrosine kinases. Numerous PI3 kinase inhibitors are now progressing through clinical trials (Shuttleworth SJ, Silva FA, Cecil AR, Tomassi CD, Hill TJ, Raynaud FI, Clarke PA, Workman P. Curr Med Chem. 2011;18:2686–714). I will provide an update on the mechanism of action of PI3 kinase inhibitors, including GDC-0941 which we discovered in collaboration with Piramed and Genentech. Key issues include isoform selectivity, the selection of pharmacodynamic and predictive biomarkers and the elucidation of potential resistance mechanisms (Clarke PA, Workman P. J Clin Oncol. 2012;30:331−3). I will place PI3 kinase inhibitors in the overall context of the selection of new drug targets in the genomic era and the development of drug combinations to overcome tumour heterogeneity, clonal selection and drug resistance. I will describe a new mechanism of action for protein kinase inhibitors involving chaperone deprivation (Polier S, Samant RS, Clarke PA, Workman P, Prodromou C, Pearl LH. Nat Chem Biol. 2013; 9:307−12).
Conflict of interest: *Ownership: Piramed, Chroma Therapeutics. Advisory board: Piramed, Wilex, Nextech Ventures, Chroma Therapeutics. Board of directors: Chroma Therapeutics. Corporate-sponsored research: Piramed, Chroma Therapeutics, Astellas*

353 INVITED
Metabolism in cellular senescence and therapy

D.S. Peeper[1]. [1]*Netherlands Cancer Institute, Division of Molecular Oncology, Amsterdam, Netherlands*

In response to various stress signals, such as the unscheduled activation of oncogenes, cells can activate tumor suppressor networks to avert the hazard of malignant transformation. A large body of evidence indicates that oncogene-induced senescence (OIS) acts as such a break, withdrawing cells from the proliferative pool virtually irreversibly, thus acting as a vital pathophysiologic mechanism protecting against cancer. In spite of the established role of OIS in preventing tumorigenic expansion both in animal models and humans, we have only begun to define the underlying mechanism and identify the key players. For example, while deregulation of metabolism is intimately linked to the proliferative capacity of cells, and despite of the wide belief that senescent cells remain metabolically active, little has been investigated in detail about the role of cellular metabolism in OIS.
By metabolic flux profiling and functional perturbations we find that the mitochondrial gatekeeper Pyruvate Dehydrogenase (PDH) is a crucial mediator of senescence induced by $BRAF^{V600E}$, which is encoded by a common oncogene in melanoma and other cancers. OIS is accompanied by suppression of the PDH-inhibitory enzyme pyruvate dehydrogenase kinase 1 (PDK1) and induction of the PDH-activating enzyme pyruvate dehydrogenase phosphatase 2 (PDP2). The resulting concerted activation of PDH enhances metabolic flux of pyruvate into the tricarboxylic acid (TCA) cycle, causing increased respiration. Restored PDK1 expression abrogates OIS, thereby licensing $BRAF^{V600E}$-driven melanoma development. Conversely, PDK1 depletion causes regression of established melanomas and eradicates subpopulations resistant to targeted BRAF inhibition. These results reveal a mechanistic relationship between OIS and a key metabolic signaling axis, which may be exploited therapeutically.
No conflict of interest.

Scientific Symposium (Tue, 1 Oct, 09:00−11:00) **Innovative Molecular Imaging Strategies for Radiotherapy Individualisation**

354 INVITED
What reliable knowledge can molecular imaging offer nowadays to radiation oncologists?

W. Oyen[1]. [1]*Radboud University Medical Centre, Department of Nuclear Medicine, Nijmegen, Netherlands*

In the past decade molecular imaging with positron emission tomography (PET) has become increasingly important in clinical oncology. A wide variety of radiopharmaceuticals for PET is available to delineate and characterize tumors. The most extensively used radiopharmaceutical used is the glucose analogue F-18-fluorodeoxyglucose (FDG), depecting the metabolic activity of tumors. The introduction of integrated PET/CT was a major step forward, especially for the adequate evaluation of anatomically complex areas. Nowadays, FDG-PET is almost exclusively performed on integrated PET/CT scanners.
Besides the obvious contribution of FDG-PET/CT to more adequate staging of patients with a wide variety of cancer types, there are a number of indications that specifically aid radiation oncologists to improve patient management, treatment and follow-up. In this presentation the potential and pitfalls of FDG-PET/CT for tumor characterization and delineation, early therapy response assessment and prediction, treatment adaptation and detection of recurrent disease are discussed.
No conflict of interest.

355 INVITED
Cetuximab Zirconium, a new generation of functional imaging

F. Hoebers[1], H. Aerts[1], J. Van Loon[1], G. Van Dongen[2], P. Lambin[1]. [1]*MAASTRO-clinic, Radiotherapy Department, Maastricht, Netherlands;* [2]*VU University Medical Centre, Department of Nuclear Medicine and PET Research, Amsterdam, Netherlands*

Personalized medicine which aims at offering a patient the treatment that best suits the characteristics of the tumor of the individual patient, has been applied using genomic-based approaches by molecular tumor profiling and characterization. These analyses are often based only on biopsy specimens, thereby neglecting intra-tumor heterogeneity. In addition to genomic studies, efforts have been made to characterize tumors based on protein expression (receptor) profiles. However, regarding the Epidermal Growth Factor Receptor (EGFR), no association has been reported between receptor status and response to its blocking antibody cetuximab (Bonner, 2010). We hypothesized that the effect of cetuximab is also exhibited by other factors than receptor status alone, including e.g. vascular perfusion and interstitial pressure.
Non-invasive imaging offers the potential to study a tumor and to address its full spatial and temporal heterogeneity. This lecture will focus on the development and application of ^{89}Zr-cetuximab for the in vivo imaging of cetuximab uptake.
As the biologic half-life of cetuximab in the blood is 65−95 hours, a positron emitter with a long half-life is needed to visualize its uptake. For this purpose, cetuximab has been successfully labeled with ^{89}Zr (half-life 78 hours) in preclinical animal models and PET with ^{89}Zr-labeled cetuximab

was performed on tumor-bearing nude mice, using cell lines with varying EGFR expression levels (Aerts, 2009). Uptake of labeled cetuximab was demonstrated only in the EGFR-positive tumors. However, the level of EGFR expression did not correlate with ^{89}Zr-cetuximab uptake, confirming our hypothesis.
The first in human phase 1 study using ^{89}Zr-cetuximab has now recently been completed and showed a heterogeneous uptake pattern of cetuximab with no additional toxicity beyond the expected skin rash associated with cetuximab therapy. Currently, the multicenter international randomized phase II ARTFORCE trial (NCT01504815) is open for accrual, in which patients with locally advanced Head and Neck Cancer will undergo ^{89}Zr-cetuximab PET-scanning before chemoradiation. One of the primary endpoints is the correlation of the ^{89}Zr-cetuximab uptake and treatment-specific outcome.
No conflict of interest.

356 INVITED
Hypoxia-PET and its predictive value in HNSCC

Abstract not received.

357 INVITED
Amino acid PET

A. Grosu[1]. [1]*University of Freiburg, Department of Radiation Oncology, Freiburg, Germany*

The higher sensitivity and specificity of amino acids (AA)-PET in the diagnosis of gliomas in comparison to CT and MRI was demonstrated in many clinical trials. Summarizing the data of the literature we found between 1983 and 2008 45 trials including 1721 patients, which investigated the role of MET-PET in diagnosis of gliomas. Eleven studies including 706 patients were based on PET/MRI/CT stereotactical biopsies. Between 2000 and 2008 12 trials including 361 patients evaluated the role of FET-PET in the diagnosis of brain gliomas. In 3 studies evaluating 126 patients the results were based on PET/MRI/CT stereotactic biopsies. All these studies have shown that the sensitivity and specificity of MET-PET and FET-PET for malignant gliomas is significantly higher (85−95%) in comparison to MRI, which has a high sensitivity but a lower specificity.
Following topics will be discussed:
1. Amino-acids PET (AA-PET) for tumor detection and differentiation between tumor and treatment-related-changes in brain gliomas. The sensitivity and specificity of L-(Methyl-^{11}C) methionine (MET-PET) and ^{18}F- O-(2) fluoroethyl-L-tyrosine (FET-PET) for tumor tissue will be discussed.
2. Comparison between different AA tracers in diagnosis of brain gliomas and metastases.
3. Integration of AA-PET in treatment planning of brain tumors: radiation therapy, surgery, chemotherapy.
4. AA-PET and Bevacizumab.
5. Other tumor entities in which the integration of PET could give additional information about tumor extension and biology: meningiomas, glomus tumors, brain metastases

No conflict of interest.

Scientific Symposium (Tue, 1 Oct, 09:00−11:00)
How to Put Evidence into Daily Nursing Practice

358 INVITED
Introduction: The Euro-PEP Project

A. Margulies[1]. [1]*Zurich, Switzerland*

Identifying a clinical care problem poses little difficulty to staff nurses, but the process of defining and identifying the clinical problem, and implementing those ideas through a change in practice can be more difficult. If guidelines do not exist for particular symptoms or supportive care issues, much time and effort has to be invested to find the evidence. Do nurses have the time in their daily practice or are they given the time from their supervisors or management?
The original inspiration for the Euro-PEP project came from the Oncology Nursing Society, U.S.A. The Euro PEP project has been developed in partnership with them and funded by EONS and the European Commission as part of the European Action Against Cancer.
The documentation provides a concise summary of the evidence, a synthesis of patient assessments, a summary of evidence based interventions, and expert opinions to help guide you in the interpretation of European standards along with the references and source material.
Evidence based practice is propagated in many oncology settings. One finds guidelines from various societies, institutions and countries, however one size does not fit all. Often the guideline has to be adapted to the individual work setting, and the Euro PEPs gives the guidance to do this. The material has been reviewed through a rigorous process by some of the leading experts and practitioners in the field.
In this session, five Euro-PEPs will be presented, each demonstrating how they can be implemented as well as showing the necessity to filter inappropriate care measures while initiating practice change. Using such information can only result in improvement of cancer care and patient safety.
No conflict of interest.

359 INVITED
Lymphoedema − prevention and treatment in daily practice

M. Sneddon[1]. [1]*University of Glasgow, Glasgow, United Kingdom*

Lymphedema is the accumulation of lymph fluid causing persistent swelling of the affected body part due to obstruction of the flow of fluid in the lymphatic system. In the oncology setting, the most common causes of lymphedema are radiation therapy and lymph node dissection. Lymphedema can occur in one or more extremities and can involve the corresponding quadrant of the trunk. Lymphedema arises in 15−28% of women treated for breast cancer. Lower extremity lymphedema occurs in up to 80% of those who had lymph node dissection in the groin or those who have compression of pelvic or inguinal lymph nodes. It can also affect the head and neck, breast, genitalia and lower limbs, depending upon surgeries and radiation therapy performed. Understanding which patients are most at risk facilitates early recognition and intervention which will improve outcomes of treatment, facilitate self management and improve quality of life.
Research based evidence for various lymphoedema prevention and treatment interventions is variable in quantity and quality but increasing research activity suggests that some emergent therapies may have much to offer. The content of the Euro PEP will be presented and key aspects of the current evidence base highlighted with discussion of how it can be used to guide clinical practice in relation to reducing risk of lymphedema, reducing complications and severity of lymphedema, supporting self management and ensuring patients have access to appropriate treatment interventions.
No conflict of interest.

360 INVITED
Peripheral neuropathy: Dealing with a difficult side effect

A. Margulies[1]. [1]*Zurich, Switzerland*

Patients report tingling, numbness, numbness, difficulty in walking. Approximately one third of patients who receive neurotoxic agents such as taxanes, platinums, vinca alkaloids, or bortezomib can develop painful neuropathy that significantly interferes with their daily activities and consequently quality of life.
Oncology nurses can play an important role in not only in the assessment of this side effect, but also with the management. The medical treatment is limited, but with initial assessment and follow-up, managing pain, maintaining safety, and maximizing physical function goals can be achieved.
The Euro-PEP “Peripheral Neuropathy” includes evidence based information to guide nurses and the healthcare team to make better management decisions. This session will discuss clinically feasible management approaches that might relieve or lessen the symptoms of a chemotherapy induced peripheral neuropathy.
No conflict of interest.

361 INVITED
Dyspnoea − an oncological challenge

A. Daibes[1]. [1]*Institut Jules Bordet, Medical Department, Brussels, Belgium*

Dyspnea is a subjective experience of breathing discomfort and one of the most frequent, refractory and distressing symptoms for patients with cancer especially in advanced stages.
It often coexists with fatigue, depression and anxiety.
It is estimated to occur in 15−55% of cancer patients at diagnosis and up to 18−79% during the last week of life, depending on the site of tumour.
It is not always possible to identify the cause(s) of dyspnea. Even if identified, it is difficult to treat these causes, mainly in patients with advanced cancer.
Currently, there is no internationally agreed upon roadmap to guide treatment for dyspnea. Changing the Caregivers’ mentalities seems to be one obstacle towards achieving this.

No single tool measures all the dimensions of dyspnea. Asking patients how short of breath they feel, by using a numeric rating scale, is the most accurate measure of dyspnea severity.
The EONS Putting Evidence into Practice (PEP) project, which resulted in the Euro PEPs, has provided a summary of evidence for cancer related symptoms. This study will present and discuss the measures included in the Euro PEPs concerning dyspnea.
Immediate-release oral and parenteral opioids are recommended for practice in relieving shortness of breath in cancer patients. This is the only evidence-based practice recommendation to alleviate dyspnea.
No conflict of interest.

362 INVITED
Pain management

Abstract not received.

363 INVITED
Radiation skin reactions

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The majority of patients undergoing radiotherapy (RT) experience acute radiation skin reactions, to some degree. Most patients have mild reactions (erythema) but 30−40 % also experience more severe reactions, such as dry and/or moist desquamations. The severe reactions often result in pain, itching, discomfort and sleeping problems. The management of radiation skin reactions vary a great deal between departments and local remedies with non-evaluated skin care products are not unusual. There is an increasing number of published studies on prevention and management of radiation skin reactions. The Euro-PEP's present an overview of the current evidence base and have been adapted to European conditions.
In this presentation, the content of the Euro PEP for radiation skin reactions will be presented and discussed with focus on how to improve clinical practice. What products could be used safely and which should be avoided? Strategies for skin care, the importance of systematic assessments and assessment tools will also be discussed as well as risk factors and information/education to patients.
No conflict of interest.

Scientific Symposium (Tue, 1 Oct, 09:00−11:00) **Geriatric Assessment and Their Clinical Applications**

364 INVITED
Definition of aging and functional decline

S.R. Kristjansson[1]. [1]*Diakonhjemmet Hospital, Department of Medicine, Oslo, Norway*

Background: The aim of this presentation is to define aging and describe the importance of assessing functional decline in older cancer patients.
Material and Methods: Literature search in databases and textbooks to identify review articles and chapters discussing aging, frailty and functional decline in older cancer patients.
Results: Aging is a gradual biological event, and there is no universally accepted age cut-off for defining older cancer patients. However, most studies define older patients arbitrary as aged 65 and above or 70 years and above. In general, all age-related changes in humans lead to reduced function. However, with increasing chronological age, the heterogeneity between individuals becomes larger. Thus, cancer patients' vulnerability towards side effects of treatment and remaining life expectancy is better explained by frailty or biological age than by chronological age alone. As reduced organ function associated with aging often leads to functional decline, one of the main treatment goals in older cancer patients is to optimize functional status. Curiously, few studies on older cancer patients include information about pre-treatment functional status, and functional decline following treatment is not a common endpoint. This is especially evident in studies of cancer surgery. As well as being an important treatment goal, functional status is a powerful predictor of negative outcomes as well as survival. Functional status is also a hallmark of the concept of frailty. It seems that the most important predictive information of functional status is obtained by objective measurements of physical performance such as gait speed or timed up-and-go. Such measurements should be included in a pre-treatment assessment of older cancer patients, and functional trajectories should be assessed during the treatment course.
Conclusion: Aging is associated with loss of function, but the heterogeneity between individuals is high, and chronological age alone is insufficient for treatment decisions. Functional status needs to be assessed before treatment, preferably by physical performance measures, in order to manage and prevent functional decline during and after treatment. Furthermore, functional status predicts negative treatment outcomes and survival.
No conflict of interest.

365 INVITED
Comorbidities

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Incidence and prevalence of co-morbidities are increasing with advanced age. Whereas co-morbidities are of major importance in clinical decision making they are hardly included in clinical trials. Co-morbidity is defined as one or more additional disease in the presence of an index disease. In this case the index disease in cancer. Multi-morbidity is defined as the sum of all morbidities/diseases. A number of validated tools are available to a structured assessment of co-morbidities. The presence of co-morbidity is associated with increased vulnerability to cancer treatment of poorer prognosis regarding survival. The most widely used scores are the Charlson-Comorbidity-Score and the Cumulative Illness Rating Score. Functional decline and presence of co-morbidity are associated however not strongly. It is therefore important to assess both functional status and co-morbidity. Future research should focus on the different impact of various co-morbidities on the vulnerability/toxicity of cancer treatment and on the prognostic importance. The longer the prognosis of a cancer diagnosis, the more effective the treatment, the more co-morbidities determine the major cause of death.
No conflict of interest.

366 INVITED
Importance of nutrition in geriatric oncology

P. Soubeyran[1]. [1]*Institut Bergonié, Bordeaux, France*

With the increasing of life expectancy, the number of elderly with cancer is rising quite rapidly. Older patients with cancer will experience more toxicity from treatment because of multiple comorbidities, concomitant medications and multiple geriatric problems including malnutrition. To avoid complications, better evaluation of patients is needed. It may lead to treatment dose reduction or even geriatric intervention on the altered dimension.
It is already demonstrated that nutritional status is a major prognostic factor in cancer patients. This is true also in the elderly with cancer but many questions remain to be answered.
The first topic is the evaluation of nutrition which can be performed through monitoring of albumin level or weight follow-up but also by the more specific MNA (MiniNutritional Assessment) tool. This questionnaire has already demonstrated its value to predict early death and chemotherapy-related toxicity. However, mainly because it is time-consuming, few older patients benefit from it. This is why screening procedures have been developed among which the G8 questionnaire, a tool derived from MNA.
Another major question to solve is the value of nutritional intervention. While it is well known and performed in cancer patients, its value to improve outcome in the elderly with cancer is not demonstrated. One randomized phase III trial, focused on patients at risk of malnutrition, has been completed recently. Results are pending.
Overall, nutrition is certainly a major topic to work on in the elderly with cancer and answers to these questions may help oncologists find clues to improve outcome.
No conflict of interest.

367 INVITED
Is frailty assessment effective?

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Frailty is often conceptualized as a state of late life decline and vulnerability characterized by weakness and decreased physiologic reserve. Frailty is associated with reduced resistance to stressors, and increased vulnerability/ risk for future poor clinical outcomes, such as falls, disability, adverse drug reactions, institutionalization, or death. Cross sectional studies suggest that about 4% of persons older than 65 years are frail, increasing up to 26% after age 85. Frailty is a dynamic process and is often associated with multimorbidity and disability. But frailty is certainly not identical to multimorbidity and disability which can precede or follow the occurrence of frailty. Frailty is a unifying notion in the care of elderly patients that directs attention away from organ-specific diagnoses towards a more holistic viewpoint of the patient.

Dysregulation in multiple physiologic systems, especially stress response systems including the immune and endocrine system, is a key feature of frailty and contributes to sarcopenia (age-related loss of skeletal muscle strength), a key physiologic component of frailty. Efforts are being done to develop 'biomarkers' of frailty (e.g. pro-inflammatory cytokines) that can be reproducibly measured in different settings, and that can predict outcome in addition to clinical evaluation.
Despite general agreement on the necessity and usefulness of the concept of frailty, there is still a lack of consensus definition and standardized assessment tool. Operational definitions like the frailty definition of Fried mainly rely on the musculoskeletal component of the frailty syndrome (sarcopenia). The most commonly used measurements for frailty screening are physical function, gait speed, and muscle strength. Besides the well validated but difficult to implement Cardiovascular Health Study index from Fried, other tools have been proposed such as the study of osteoporotic fractures index (SOF) which is much easier to measure in clinical practice, the Short Physical Performance battery (SPPB), or short single item functional tests like the timed-up-and go test of hand grip strength test.
Importantly, interventions have been proposed that are not (yet) focused on frailty per se, but rather on components of frailty, and can be reasonably applied to patients with frailty, such as exercise and nutrition interventions. The development of comprehensive geriatric assessment (CGA) in oncology is a major step forward in the care of older cancer patients. Recent studies confirm that CGA is sensitive to the reliable detection of degrees of frailty, and could be the gold standard to detect frailty. Nevertheless, functional tests measuring muscle strength have received (too) little attention in geriatric oncology settings so far. International efforts are required to establish uniform definitions and measurement tools for frailty and muscle strength in older cancer patients, which can be integrated in clinical care and research.
No conflict of interest.

Scientific Symposium (Tue, 1 Oct, 09:00−11:00) **Diagnosis and Treatment of Oncological Emergencies**

368 INVITED

Malignant bowel obstruction: The surgeons' perspective

W. Bemelman[1]. [1]*Academic Medical Center, Department of Surgery, Amsterdam, Netherlands*

Patients presenting with emergent left sided colonic obstruction vary with respect to stage of the colonic cancer (metastasized or not) and operative risk. Several strategies can be adopted.
With curative intention:
– Immediate resection of the obstructing tumor: The disadvantage of acute resection is that the frail patient might die of this invasive approach, the stoma rate is high and the oncologic quality might not be optimal in the emergency setting. The advantage is that the obstruction and the tumor is treated right away.
– Delayed resection after initial decompression either via colonic stent placement or a decompressive stoma: This bridge to definite surgery is used to optimize the patient, to stage the patient properly and to operate the patient by the most appropiate surgical team in the elective setting.

Stent placement before elective surgery, also known as a bridge to surgery, had been shown to decrease mortality, morbidity, and number of colostomies in uncontrolled studies. Prospective studies show less favorable results. Transverse colostomy via a threphine method is minimally invasive and associated with low morbidity and mortality rates. It is the surgical bridge to elective resection. The literature on diverting colostomy for obstructing left-sided colon cancer is scarce. This minimal invasive surgical intervention probably guarantees a more optimal decompression than stenting and avoids oncological risk of (micro) perforation.
With palliative intention: Conservative management avoiding resection is indicated in the patients in the metastasized setting or in the very frail who have a too high operative risk. The obstruction is treated by palliative stenting or a decompressive stoma done via a minilaparotomy.
There is a large controversy with respect to the use of the colorectal stent as bridge to surgery. In France and the Netherlands, the stent is underused due to the disappointing results of national trials conducted in these countries. In other countries, there is a great enthusiasm with respect to stenting.
Apart from conflicting short term results of colorectal stenting, data are accumulating with respect to the oncologic risk of stenting as bridge to surgery. Increased local recurrence and a shorter disease free survival are reported particularly in the patients having had an overt or silent stent perforation.
There is no evidence what is the most optimal strategy in patients with left sided colonic obstruction. Fit patients who can be treated with curative intent, are probably best managed with immediate surgical resection avoiding the risk of stent perforation which compromises long term oncologic outcome.
No conflict of interest information specified.

369 INVITED

Conservative treatment of malignant bowel obstruction

D. Currow[1]. [1]*Flinders University, Palliative and Supportive Services, Adelaide, Australia*

Malignant bowel obstruction is a frequently encountered cause of morbidity and mortality in people with cancer. High rates of this are seen with ovarian and primary peritoneal cancers. Causes include intra-luminal and intra-peritoneal lesions.
Two key elements in evaluating bowel obstruction are:
a. whether there is clinical evidence of a single level bowel obstruction or of multiple levels; and
b. the person's overall well being.

The person with established cachexia (not simply weight loss secondary to anorexia or starvation) is unlikely to tolerate even minimally invasive procedures and arguably, the catabolic insult may hasten his/her death.
Single level obstruction, whether as the initial presentation of cancer, at recurrence or related to surgical complications such as adhesions, is almost always best palliated by surgery, expect very late in the disease trajectory. At that time, the use of self-expanding metal stents, argon plasma coagulators or laser are options for single-level colonic lesions.
From recent epidemiological data from the SEER data base, multi-level obstruction secondary to cancer should be considered a pre-terminal event and is rarely amenable to meaningful palliation with surgery. The aim of therapy is reduce the symptoms of vomiting, nausea and pain, each of which can be effectively palliated.
Potential medical therapies include the use of dexamethasone, H_2 antagonists and somatostatin analogues such as octreotide. The latter two are primarily designed to reduce the volume of gastric secretions. A recent phase III study failed to demonstrate any benefit of octreotide over placebo, with octreotide apparently causing much more colicky abdominal pain.
The role of nasogastric tubes beyond initial decompression is limited, and any parenteral hydration should be approached with care. Palliative procedures may include a venting gastrostomy in a highly selected sub-group of patients.
No conflict of interest.

370 INVITED

Management of hemoptysis

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Hemoptysis is defined as coughing up blood from the respiratory tract. About 30 % of all the cases are due to malignancy, while hemoptysis occurs in 10−30 % of the patients with lung cancer. Hemoptysis is usually mild (<200 ml/24 h) rather than a real emergency, but massive hemoptysis capable of causing respiratory distress may occur in about 5 % of the cases. Although in most cases the blood is originated from the tumor growth, other etiologies do occur also with cancer patients (e.g. respiratory infection, pulmonary embolism, bronchiectasis, and side effects of oncologic therapy). Optimal therapy depends on the etiology and severity of hemoptysis as well as performance status and prognosis of the patient.
General management includes correction of coagulopathies, antibiotics for respiratory infection, cough suppressants and a trial with tranexamic acid (500–1000 mg thrice a day). In the case of massive hemoptysis the primary goal is to prevent asphyxia by oxygen, positioning the patient on the bleeding side down, and, if definitive therapy is available, endotracheal or unilateral intubation.
Radiotherapy is the treatment of choice for non-massive cancer related hemoptysis with response rates ranging from 70 to 90%. The alleviation of hemoptysis is equal with short course and low dose radiotherapy (e.g. 8−10 Gy in 1 fraction or 16−17 Gy in 2 fractions) when compared to higher doses. Higher doses and multiple fractions are, however, associated to a slightly better survival in patients with good performance status (about 5 % in 1 year), but with a cost of more acute toxicity. Endobronchial brachytherapy is also highly effective and may be used in selected cases, but it has no proven efficacy over external beam radiation therapy (EBMT). Therefore, EBMT is recommended as first line modality for hemoptysis.
Bronchoscopy is used as a diagnostic procedure and to remove blood from tracheobronchial tree. In addition, several techniques are available to control the bleeding (argon plasma coagulation, electrocautery, laser and

tamponade with balloon), but no studies exist on the superiority of these procedures.
Bronchial artery embolization is very effective in the management of severe hemoptysis, but only few studies have included patients with malignancy. Nevertheless, response rates up to 89% have been reported also in cancer patients.
Surgery is definitive therapy for bleeding local tumor, but it is not generally an option for patients with hemoptysis and advanced cancer due to high mortality and morbidity especially in emergency setting.
In the last weeks of life hemoptysis is reported in 9 % of lung cancer patients. Conservative management including radiotherapy is offered to patients in palliative care, while invasive procedures are usually futile. Massive hemoptysis at the end of life is a rare but possible phenomenon, which usually requires rapid sedation of the patient together with support for the caregivers and family.
No conflict of interest.

371 INVITED
Spinal cord compression

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MSCC occurs in 5−10% of cancer patients during the course of their disease. Radiotherapy (RT) alone is the most common treatment. For patients with a poor survival prognosis, short-course RT (8−20 Gy in $\leqslant$1 week) is preferable to longer-course RT (30−40 Gy in 2−4 weeks) to reduce the burden of treatment for these often debilitated patients. Short-course RT results in similar functional outcome as longer-course programs. However, longer-course RT leads to better re-calcification and local control of MSCC. Since relevant re-calcification can only be expected several months following RT and since the probability to develop a local recurrence of MSCC increases with survival time, patients with a favourable survival prognosis appear better treated with longer-course RT. The survival of patients with MSCC can be estimated with the help of prognostic scores.
Highly selected patients with an extraordinarily favourable survival prognosis may be also considered for high-precision RT such as radiosurgery (RS) and stereotactic body radiotherapy (SBRT) in order to better spare the surrounding normal tissues. Another group of patients who may benefit from SBRT are those with MSCC from a less radiosensitive tumour. However, the tolerance doses of both spinal cord and vertebral bone must be considered when using RS and SBRT. The maximum dose to the spinal cord should not exceed 13 Gy in 1 fraction or 21 Gy in 3 fractions, and the maximum dose to the vertebral body should not exceed 15.5 Gy in 1 fraction or 25.5 Gy in 3 fractions. However, sufficient long-term data are currently lacking.
Upfront decompressive surgery with direct stabilization in addition to RT is recommended for selected patients with a good performance status, a favourable survival prognosis, involvement of only one spinal segment, and MSCC from a solid tumour. Also patients with a less radiosensitive tumour appear to benefit from additional surgery.
If an in-field recurrence of MSCC occurs, re-RT appears safe if the cumulative biologically effective dose (BED) is $\leqslant$120 Gy_2. If longer-course RT has been initially given, the cumulative BED may exceed 120 Gy_2. These patients should be treated with decompressive surgery if possible and indicated. Otherwise, high-precision RT should be considered.
Currently, the recommendations for the treatment of MSCC are based mostly on non-randomized studies. More randomized trials are required to better define the best (individual) treatment for this oncologic emergency.
Conflict of interest: *Advisory board: Amgen, AstraZeneca. Corporate-sponsored research: MerckSerono, Novartis Oncology. Other substantive relationships: MerckSerono, Novartis Oncology*

Scientific Symposium (Tue, 1 Oct, 09:00−11:00) **Molecular Profiling in Neuro-Oncology**

372 INVITED
Glioblastomas

W. Wick[1]. [1]*University of Heidelberg, Abteilung NeuroonkologieNeurologische Klinikund Nationales Tumorzentrum, Heidelberg, Germany*

The World Health Organization (WHO) Classification of Tumors of the Nervous System classifies and grades tumors by histological criteria. This classification associates the presumed histogenetic origin and WHO grades I to IV to the expected clinical course. It has fundamental clinical relevance since its diagnostic classification determines whether the individual patient will be managed after surgery by watchful waiting or decide for further treatment, commonly radiotherapy, chemotherapy or both. Since the analysis of outcomes with nitrosoureas in the late nineties, there is knowledge about *O6-Methyl-Guanine-Methyl-Transferase* being decisive for benefit from alkylating chemotherapy. This was formally addressed and operationalized by the EORTC 26981/NCIC CE.3 trial, in which patients with a tumor haboring a methylated (inactive) *MGMT* promoter did considerably better than those without this methylation, most of all in the temozolomide-containing treatment arm.
Recent practice-changing academic clinical trials have defined a role for routine assessment of *MGMT* promoter methylation in glioblastoma of the elderly. Moreover, high-throughput analyses have led to the identification of new mutational targets in gliomas, notably isocitrate dehydrogenase (IDH) and histone H3, and allowed to subclassify gliomas into distinct molecular subgroups defined by age, localization, and outcome, although not yet benefit from therapeutic interventions. Large scale genome-wide epigenetic screens revealed distinct subgroups of patients, basically on grounds of IDH, two distinct histone H3 mutations, the mesenchymal signature and expression of receptor-tyrosine kinase-related genes. In clinical trials or daily practice, so far only *MGMT* has a role as an eligibility criterion and a decisive biomarker for elderly patients' treatment. Apart from further prognostic marker/signatures, it was only the RTOG-0825 trial comparing standard of care $\pm$ bevacizumab that now suggests a predictive role for a nine-gene classifier for bevacizumab treatment.
In the future, validation of existing markers needs to be done, new targeted treatment developments should inherit a biomarker program, as a unsupervised approach to deduct targets from large-scale approaches would be desirable.
Conflict of interest: *Advisory board: Roche, MSD. Corporate-sponsored research: Boehringer Ingelheim, MSD, Apogenix, Eli Lilly*

373 INVITED
Anaplastic gliomas

M. Van den Bent[1]. [1]*Erasmus University Medical Center, Neuro-Oncology, Rotterdam, Netherlands*

In anaplastic glioma, three clinically relevant molecular markers have now been identified: combined 1p/19q loss, IDH1/2 mutations and MGMT promoter methylation. To complicate this, these markers are correlated: 1p/19q co-deleted tumors as a rule have IDH mutations, and IDH mutations are related to CpG Island hyperMethylation (CIMP) of which MGMT promoter methylation is a part. IDH mutations aear to be an early eventin gliomagenesis, and the current understanding is that most tumors with an astrocytic phenotype will have TP53 mutations, and tumors with an oligodendroglial phenotype have the 1p/19q co-deletion. Glioblastoma with IDH mutations tend to have a more favorable outcome than gradeIII gliomas without IDH mutations. Several studies have shown the more favorable outcome of 1p/19q co-deleted tumors; but also, grade III tumors with an IDH mutation have a better prognosis than IDHwt tumors. Recent trials have shown that 1p/19q loss is a predictive marker for benefit to adjuvant PCV chemotherapy, but the current evidence suggest that other markers may allow a better identification of patients benefitting to adjuvant chemotherapy.
MGMT promoter methylation is in glioblastoma related to more benefit to concurrent temozolomide. Surprisingly, in studies in grade III glioma MGMT promoter methylation was found to be of prognostic siginficance, even in radiotherapy treated patients. This may be related to the simultaneous presence of IDH mutations and CIMP, but more recent studies suggest that examination of MGMT promoter methylation using a genome wide array may in fact be predictive for benefit to adjuvant chemotherapy. Thus, some of the differences found between studies on the clinical impact of MGMT promoter methylation studies may actually be related to differences in the used techniques, which assess different regions of the CpG islands in the MGMT promoter region.
Recently, several new mutations have been identified (CIC and FUBP in 1p/19q co-deleted tumors, mutations in the ATRX gene in other IDH mutated tumors). It has been suggested these may further guide the molecular classification of glioma, but this requires validation. From a clinical perspective, the most attractive markers are those that predict benefit to a specific treatment.
To conclude, 1p/19q has diagnostic, prognostic and therapeutic implications. IDH identifies a subgroup of grade II/III diffuse glioma, with CIMP and MGMT promoter methylation. The role these latter markers have in therapeutic decisions is still unclear, but may eventually come down to MGMT promoter methylation. And the presence of that marker is not limited to 1p/19 co-deleted, IDH mutated or CIMP positive tumors, but may occur as a single event. Further research in independent (randomized) clinical studies is required to increase our understanding of the role these markers can play in clinical decision making.
Conflict of interest: *Advisory board: MSD*

374 INVITED

Brain metastases

R. Soffietti[1]. [1]*University of Torino, Neuroscience, Torino, Italy*

The huge amount of information on new molecular compounds and the advances in understanding the molecular pathways that mediate brain colonization have led to an increase of interest in preclinical and clinical investigations in the field of brain metastases. Targeted therapies can be employed either on established brain metastases or in a prevention setting. Targeting angiogenesis is an attractive approach. Up to date, large clinical trial datasets have shown that antiangiogenic agents do not increase the risk of bleeding into the brain. Bevacizumab (an anti-VEGF agent) is undergoing investigation in clinical trials on brain metastases from NSCLC, breast cancer and melanoma. Sunitinib, a multitarget small molecule tyrosine kinase inhibitor, is a promising agent in brain metastases from renal cell cancer. The EGFR inhibitors gefitinib and erlotinib have a definite activity in brain metastases from NSCLC with activating EGFR mutations. Regarding HER2 positive breast cancer patients with established brain metastases, lapatinib (small molecule tyrosine kinase inhibitor) seems particularly active in association with capecitabine. Lapatinib alone is attractive in the prevention setting. Brain metastases from melanoma with BRAF V600E mutations respond a specific inhibitor, such as vemurafenib. The immunomodulator ipilimumab is also active on brain metastases from melanoma.

No conflict of interest.

375 INVITED

Medulloblastoma: Next-generation diagnostics entering the clinical stage

S.M. Pfister[1]. [1]*DKFZ − German Cancer Research Center, Division of Pediatric Neurooncology, Heidelberg, Germany*

It is well established now, that the morphological diagnosis “medulloblastoma” is in fact a mixture of several distinct biological entities. In a consensus process between the leading medulloblastoma groups worldwide, these subgroups have been termed WNT, SHH, group 3 and group 4 in an attempt to unify terminology. Recent advances in genome and epigenome sequencing have revealed fundamental new insights in recurrently mutated genes and pathways both somatic and in the germline, many of these in a subgroup-specific manner. Interestingly, novel genetic patterns have been identified in subsets of tumors including tetraploidy as an early event in group 3 and 4 tumors, which is potentially a durggable hit, and chromosome shattering in Li-Fraumeni associated MBs. Furthermore, the genetic landscape of SHH-driven medulloblastoma has been deciphered, which is of central importance for clinical trials targeting the SHH pathway at teh level of Smoothened.

Im summary, this talk will focus on genomic and epigenetic hits in medulloblastoma that confer important information for the clinics and highlights ways of translating these findings to the benefit of our patients.

No conflict of interest.

Scientific Symposium (Tue, 1 Oct, 09:00−11:00)
The Future of Paediatric Oncology in Europe

376 INVITED

Re-enforcing integration of research and care in childhood and adolescent cancer: A new role for clinical epidemiology in outcomes research?

K. Pritchard-Jones[1]. [1]*University College London, Institute of Child Health, London, United Kingdom*

In high-income countries, survival from childhood cancer has reached 80% through a continuous focus on the integration of clinical research into front-line care for nearly all children affected by malignant disease (1). The early successes of international, collaborative clinical trials led to the recognition that such trials were the basis for rapid improvements in survival and should be viewed as best practice (2). However, amongst children with the most excellent survival rates, approaching 90%, (e.g. localised low and intermediate risk Wilms tumour, localised embryonal rhabdomyosarcoma at favourable anatomical sites, extra-cranial germ cell tumours, approximately one third of childhood acute lymphoblastic leukaemia and some lymphomas), continuation of a full portfolio of clinical trials is becoming unaffordable both in terms of financial resources and competing priorities for academic investigator time, when there remain hard to treat sub-groups. Hence, new approaches are needed to continue high quality prospective clinical research. These must capture detailed clinical information on patients treated on standard protocols, allow biological sampling with appropriate consent, monitor outcomes including relapse and generate large cohorts of patients to improve risk stratification through a biology-driven approach and adequately study long-term side effects.

The European Network for Cancer research in Children and Adolescents (ENCCA) has dedicated a specific workpackage to developing mechanisms to conduct prospective clinical studies that do not fall within the definition of a clinical trial testing an investigational medicinal product (IMP). At present, this is focusing on working with existing cancer registration processes at a national level to define what data could be collected routinely and to test the feasibility and resource implications of collecting an enhanced dataset that could be used to continuously monitor the success rates of front line therapy. This will build on the long standing collaboration between cancer registries in the ACCIS and EUROCARE projects, and is being co-ordinated by Dr Steliorova-Foucher at IARC, Lyon.

In parallel, the European paediatric renal tumours study group (SIOP-RTSG) is setting up a prospective registration study with consent, that introduces rapid radiology review and consent for Omics testing as a prelude to more biomarker driven personalized risk stratification for good risk tumours and earlier signposting of patients with very high risk tumours to appropriate targeted therapy trials. This has already highlighted the differences in consent processes for parents to give permission for genomic testing of their child’s tumour and also how this complies with data protection legislation across the EU.

Progress (and barriers to progress) in both of these areas will be discussed.

No conflict of interest.

377 INVITED

Risk adapted therapies for personalising medicine for children and adolescents with cancer

M. Schrappe[1]. [1]*University Medical Center Schleswig-Holstein, Pediatrics, Kiel, Germany*

Systematic recruitment of children and adolescents with leukemia and cancer into clinical trials is one of the largest achievements in oncology and pediatrics. This unique process established profound knowledge on clinical and biological prognostic parameters in all entities of cancer in childhood and adolescence. The clinical trials in Pediatric Oncology comprising combination therapies of all kinds have significantly reduced the risk of disease recurrence but also that of acute and late side effects. One can simply state that in 2013 more children are cured but in most entities with less or different therapy than 20 years ago.

Identification of risk groups has been the main focus of the past years. In childhood leukemia, some distinct unfavourable subgroups were identified in which treatment success is less frequent while others have been shown to benefit from novel strategies. In acute lymphoblastic leukemia, high tumor load (WBC), lack of response, age under one year, or beyond 10 years (more pronounced beyond 15 years), and (rare) cytogenetic subtypes such as translocations t(9;22), or t(4;11), or the presence of *IKZF1* may characterize a significant proportion of children and adolescents with high risk (HR-) ALL. This example may also serve to demonstrate a dilemma which is reflected by the fact that the majority of relapses may occur among so-called intermediate risk patients. Thus, quite frequently, specific characteristics to identify the patient at risk to relapse have been missing. Recently, genetic signatures in various tumors were described which may further characterize high relapse risk patients. Careful response assessment preferably by detection of minimal residual disease (MRD) has become mandatory in leukemia to identify patients at risk to relapse but also those who can be spared intensive therapy. MRD monitoring may also contribute to determine the activityof novel therapies, such as functionally targeted or immunotherapeutic strategies, or it may be used to monitor the efficacy of allogeneic hematopoetic stem cell transplantation. In solid tumors, monitoring of treatment response by MRD detection may be difficult, therefore, the imaging techniques and specific biomarkers play the more important role to assess the efficacy of novel therapies. Eventually, more specific and molecularly targeted therapies may enter clinical practice if the toxicity is acceptable, in particular with regard to specific pediatric aspects, such as growth, organ functions, and mental development.

No conflict of interest.

378 INVITED

Improving access to innovative therapies across Europe

Abstract not received.

379 INVITED

What policy for sustainability of pediatric oncology research in Europe?

Abstract not received.

Scientific Symposium (Tue, 1 Oct, 09:00−11:00) **Enhancing Conventional Oncological Treatments With New Technologies**

380 INVITED

Light-activated multimodal nanoparticles

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Multifunctional nanoparticles (NPs) that interact with light provide a unique opportunity for applications in image-guided therapy. These NPs have a strong and tunable surface plasmon resonance absorption in the near-infrared (NIR) region, which can also carry diagnostic and therapeutic agents. These novel nanostructures home in on solid tumors either via passive targeting mechanism or active targeting facilitated by ligands bound on their surfaces. Once they reach their target tissue, their activity can then be turned on using NIR laser for photothermal ablation therapy (PTA). However, PTA is only effective on a very confined region and is also unlikely to kill all tumor cells when used alone. NPs can also efficiently trigger the release of drugs and activate RNA interference. A multimodal approach, which permits simultaneous PTA therapy, chemotherapy, and therapeutic RNA interference, has the potential to completely eradicate residual diseased cells. In this presentation, an up-to-date review of the synthesis and characterization, functionalization, and in vitro and in vivo evaluation of NIR light activatable multifunctional gold-based nanostructures used for imaging and therapy will be provided. Emphasis will be given on our research on hollow gold nanospheres and magnetic core–shell gold nanoshells.

No conflict of interest.

381 INVITED

Radiosensitisation by gold nanoparticles at megavoltage radiation energies

F.J. Currell[1]. [1]*Queen's University, School of Maths and Physics, Belfast, United Kingdom*

Background: Radiation enhancement by targeted nanoparticles containing a heavy atom species (e.g. gold) has great potential to improve cancer therapy. Based on readily available physical parameters, predictions can be made in terms of the physical dose enhancement. These predictions indicate that treatment of a number of cancers that could benefit from this approach. However, *in vitro* dose enhancements, particularly at megavolt energies, have been observed to be far larger than those arising from these simple physical predictions. The purpose of this study was to reconcile this discrepancy.

Material: Radiation track structure calculations were made concerning the irradiation of gold nanoparticles under various conditions. Drawing on concepts of local dose effects drawn from the heavy ion therapy community these simulations were processed to provide a prediction of the cell killing. Also a number of radiochemistry experiments were conducted whereby nanoparticle-doped aqueous samples were irradiated with the production of the hydroxyl radical being assayed.

Results: The predictions display excellent agreement with measurements, showing the importance of considering the nanoscale effects of radiation in the presence of heavy-atom nanoparticles. The measurements of the hydroxyl radical production show very large enhancements when gold is added. The enhancement is too large to be explained by the localised electron emission mechanism used to explain the cell killing.

Conclusion: Both the simulations and the experimental measurements suggest the targeted use of heavy atom nanoparticles in conjunction with radiotherapy should be applicable to a wider range of cancers. Whilst these are positive indicators for the clinical application of such nanoparticles, basic questions still remain pertinent to the wider field of applying nanotechnology to cancer. The measurements suggest radiation chemistry ideas will need to be reviewed significantly to account for the situation when nanoparticles are present in the system − this then has impact on the whole field of cancer nanotechnology since it is unthinkable that clinical practice will abandon the diagnostic use of X-rays. As well as making the case for heavy atom nanoparticle therapy, this talk will outline the emerging need for basic data, modelling and measurements as nanotechnology becomes more broadly applied to cancer therapy.

No conflict of interest.

382 INVITED

Effectiveness of electrochemotherapy in brain tumours

J. Gehl[1]. [1]*Copenhagen University Hospital, Department of Oncology, Herlev, Denmark*

Brief electric pulses that exceed the electric capacitance of the cell membrane may be used to transiently cause cell permeabilisation (electroporation), enabling direct access to the cell cytosol. The cytotoxicity of e.g. bleomycin may be enhanced several hundred fold in the area subjected to electric pulses (electrochemotherapy). The dramatic increase in cytotoxicity allows treatment of all cancer histologies, and electrochemotherapy is now routinely used for cutaneous metastases from e.g. breast cancer and malignant melanoma with very high local response rates. Electrochemotherapy is currently being pursued for tumors in internal organs, and here we summarize development of an expandable electrode device, as well as preclinical studies and a phase I clinical trial.

First, a novel electrode device able to go through a single insertion point (e.g. burr hole) and deploy electrodes at the location of the tumor, was designed and produced, along with a 'mini-model' for use in experimental rat brain tumor studies.

Preclinical data (Agerholm-Larsen et al, Cancer Research 2011) showed that electrochemotherapy highly efficiently could eliminate rat brain tumors and that side effects were very modest in this experimental model. This first study using intracranial injection of bleomycin followed by electroporation was succeeded by a study using iv bleomycin, and the results here showed similarly impressive responses, and with more favorable effect on normal tissue evaluated by histology (Agerholm-Larsen et al, abstract 2069, Journal Clinical Oncology 2012).

Magnetic resonance imaging (MRI) on a rat brain model (Mahmood et al, J. Membrane Biology 2011) showed that apparent diffusion coefficient (ADC) was very useful in elucidating the treatment area due to changes in diffusion after permeabilisation.

Finally, a clinical study for patients with brain metastases from any histology, where whole brain irradiation and all other relevant treatments had failed, was initiated (clincaltrials.gov NCT01322100). The first patient has been treated, indicating that electrochemotherapyin the brain using the designed electrode device was feasible and safe. After localisation of the target lesion, the patient was anesthetised and in an interventional CT-scanner, a burr hole was made after which the electrode device was inserted to the correct point and the electrodes expanded. Bleomycin (15.000 IU/m^2) was infused iv, and electric pulses were administered over a few minutes, after which the device was folded back and retracted. The patient suffered progression of systemic disease which shortened follow-up, but MRI at 5 weeks indicated progression of untreated metastases whilst the treated metastasis was reduced in size.

In conclusion, a novel electrode device for electrochemotherapy in the brain was designed and preclinical data as well as very early clinical data are promising. This electrode device could potentially be used for primary brain cancers as well as other soft tissue tumors.

Conflict of interest: *Other substantive relationships: Julie Gehl is an inventor of patents related to the electrode device.*

383 INVITED

Multicomponent nanoparticles for enhanced delivery of chemotherapy

S. Jain[1]. [1]*Centre for Cancer Research and Cell Biology Queen's University Belfast, Cancer Centre, Belfast, Ireland*

Nanotechnologies have tremendous potential to improve cancer treatment. The efficacy of systemic anti-cancer therapy is often limited by normal tissue toxicity leading to sub-therapeutic intratumoural drug concentrations. The development of drug nano-conjugates has enabled more targeted delivery of systemic therapies, with several agents improving patient survival in well-conducted Phase III clinical trials. Beyond simple conjugates, many multifunctional nanoparticles have been developed which have been shown to overcome aspects of traditional drug resistance including targeting, cellular entry, nuclear entry, tumour hypoxia and drug efflux. Preclinical and clinical examples will be discussed. In the era of stratified cancer medicine, drug libraries are being developed based on standard core preparations. Similarly, it is clear that the clinical utilisation of many multifunctional nanoparticles is limited by consistency and reproducibility of manufacture and batch-to-batch variability which can dramatically alter drug function. Some of these limitations will be addressed in this overview.

No conflict of interest.

Special Session (Tue, 1 Oct, 11:30−12:30)
Personalising Adjuvant Treatment in Early Breast Cancer

384 INVITED

Is optimum management of early breast cancer now dependent on molecular profiling?

Abstract not received.

385 INVITED

The pathologists' contribution to personalised treatment

Abstract not received.

386 INVITED

Is it safe to omit systemic therapy in small Her2+ node negative breast cancers?

Abstract not received.

Special Session (Tue, 1 Oct, 11:30−12:30)
The Pathology of Lung Cancer and its Clinical Implications

387 INVITED

Lung Adenocarcinoma − from pathology to therapeutic implications − Pathologist viewpoint

W. Travis[1]. [1]*Memorial Sloan Kettering Cancer Center, Department of Pathology, New York, USA*

The new IASLC/ATS/ERS Lung Adenocarcinoma classification provides for the first time, standardized terminology for lung cancer diagnosis in small biopsies and cytology (Table 1), as this was not primarily addressed by previous WHO classifications.

Table 1.

2004 WHO Classification including updated IASLC/ATS/ERS terminology	Morphology/Stains	IASLC/ATS/ERS Terminology
ADENOCARCINOMA Mixed subtype Acinar Papillary Solid Micropapillary	Morphologic adenocarcinoma patterns clearly present	Adenocarcinoma (describe identifiable patterns present)
Lepidic (nonmucinous)		Adenocarcinoma with lepidic pattern (if pure, add note: an invasive component cannot be excluded)
Lepidic (mucinous)		Invasive mucinous adenocarcinoma (describe patterns present; use term mucinous adenocarcinoma with lepidic pattern if pure lepidic pattern − see text)
No 2004 WHO counterpart − most will be solid adenocarcinomas	Morphologic adenocarcinoma patterns not present (supported by special stains, i.e. +TTF-1)	Non-small cell carcinoma, favor adenocarcinoma
SQUAMOUS CELL CARCINOMA	Morphologic squamous cell patterns clearly present	Squamous cell carcinoma
No 2004 WHO counterpart	Morphologic squamous cell patterns not present (supported by stains i.e. +p40)	Non-small cell carcinoma, favor squamous cell carcinoma
LARGE CELL CARCINOMA	No clear adenocarcinoma, squamous or neuroendocrine morphology or staining pattern	Non-small cell carcinoma, not otherwise specified NSCLC-NOS

Until recently there have been no therapeutic implications to further classify NSCLC, so little attention has been given to the distinction of adenocarcinoma and squamous cell carcinoma in small tissue samples. This situation has changed dramatically in recent years with the discovery of several therapeutic options that are only available to patients with adenocarcinoma or NSCLC-not otherwise specified (NOS), rather than squamous cell carcinoma. This includes recommendation for use of special stains as an aid to diagnosis, particularly in the setting of poorly differentiated tumors that do not show clear differentiation by routine light microscopy. A limited diagnostic workup is recommended to preserve as much tissue for molecular testing as possible. Most tumors can be classified using a single adenocarcinoma marker (e.g. TTF-1 or mucin) and a single squamous marker (e.g. p40 or p63) NOS carcinomas that stain with adenocarcinoma markers are classified as *NSCLC, favor adenocarcinoma* and tumors that stain only with squamous markers are classified as *NSCLC, favor squamous cell carcinoma*. Carcinomas lacking clear differentiation by morphology and special stains are classified as *NSCLC, NOS*. The need for every institution to develop a multidisciplinary tissue management strategy to obtain these small specimens and process them, not only for diagnosis but also for molecular testing and evaluation of markers of resistance to therapy, is emphasized.
No conflict of interest.

388 INVITED

Adenocarcinoma − from pathology to therapeutic implications − clinician's viewpoint

D. Camidge[1]. [1]*University of Colorado Cancer Center, Medical Oncology Developmental Therapeutics, Aurora Colorado, USA*

Approximately 60% of adenocarcinomas of the lung harbor a dominant driver oncogene based on recent large US and European sequencing initiatives. Most but not all of these abnormalities appear mutually exclusive. Notable clinical successes utilizing specific small molecule inhibitors in defined molecular subgroups of adenocarcinoma include a range of EGFR tyrosine kinase inhibitors (TKIs) in EGFR mutant disease, crizotinib in ALK rearranged and ROS1 rearranged disease and, most recently, BRAF inhibitors in V600E mutant disease and RET inhibitors in those with RET rearrnagements. Early data suggest MET gene amplifcation may also be an actionable primary abnormality although as gene copy number is a continuous variable the challenge will lie in determining the relevant cutpoint for determining appropriate predictive potential. Because most dominant drivers occur early in carcinogenesis, heterogeneity is unlikely to be a factor in determing which initial lesion to biopsy. Several other rare abnormalities continue to be described although simple sequence abnormalities may, ultimately, not reveal drivers in all cases and the mechanism driving 'pan-negative' cancers continues to be explored. The clincial significance of 'double mutants', similarly, continues to be explored. Following successful targeted treatment, acquired resistance generates additional clincially relevant diversity which is now also starting to be addressed for EGFR and ALK in clincial trial successes.
No conflict of interest information specified.

389 INVITED

Squamous cell carcinoma − from pathology to therapeutic implications − pathologist's viewpoint

E. Brambilla[1]. [1]*Institut Albert Bonniot, Groupe de Recherche sur le Cancer du Poumon, La Tronche Cedex, France*

Squamous cell carcinoma (SCC) accounts for a approximately 20 % of all lung cancers in the United States and 30 % in Europe. The frequency of peripheral lung involvement has increased as compared to central squamous cell carcinoma. Morphologically, squamous differentiation is identified by inter-cellular bridging, squamous pearl formation and individual cell keratinisation. The intensity of these features characterizes well differentiated squamous cell carcinoma, versus poorly differentiated tumors that lack clear squamous morphology, are more difficult to differentiate from large cell carcinoma or from non cell lung carcinoma on small biopsies, deserving the molecular marker P63 and/or P40, and negativity of TTF1 for a tumor to be classified as SCC. In addition to well and poorly differentiated squamous cell carcinoma, basaloid carcinoma represent a third class recently identified as a specific molecular entity among SCC on gene expression profiling (E. Brambilla, *submitted 2013)*. Expression cluster of basaloid carcinoma retrieve the more dismal prognostic among squamous cell carcinoma cases from worldwide data sets. Recently significant knowledge of genomics of SCC has been provided by comprehensive analysis of genetic alteration as part of the cancer gene genome atlas (TGA)which transformed the landscape of genomic and epigenomic alterations. Among specific genetic alterations discovered as driver oncogenes targetable by specific therapies, FGFR1 amplification to 25 % of SCC even smokers restricted to those cases exposed to tobacco carcinogens (upper and lower airways) exclusively, DDR2 mutation accounting for 3 % of SCC targetable by dasatinib; PIK3 amplication (PIK3CA inhibitors). The PIK3CA is amplified in 20−30 % of SCC. In addition, frequent mutation has been discovered on CDKN2/P16 gene, PTEN, PIK3CA, KEAP1 and MLL2, as well as significant copy number alterations including amplifications on SOX2 and deletion of CDKN2/P16. Many of the somatic alterations identified in SCC were drivers of pathway important for initiation and tumor progression.
Therapeutic targets are ready for DDR2 mutation (dasatinib) and FRGR1 amplification (FGFR1 TKI) with anticipated approval for a target for PIK3CA.

All together about 50 % of squamous cell carcinoma are potentially targetable with specific therapies.
No conflict of interest.

390 INVITED

Squamous cell carcinoma − from pathology to therapeutic implications − clinician's viewpoint

J. Soria[1]. [1]*Institut Gustave Roussy, Medical Oncology/Lung Unit, Villejuif, France*

NSCLC is segmented on the basis of modern molecular portraits that allow the identification of new molecular subtypes.
Squamous-cell carcinoma (SCC) of the lung is the second most frequent histology in non-small cell lung cancer. Advances in the understanding of the biology of SCC have also been made and this may pave the road to develop targeted therapies.
Fibroblast growth factor receptor 1 (FGFR1) is a transmembrane tyrosine kinase receptor that plays a role in normal physiological functions and there is evidence of deregulated signals in the pathogenesis of many different cancer types including in lung SCC.
The discoidin domain receptor 2 (DDR2) is a tyrosine kinase that binds collagen as its endogenous ligand and following its activation it interacts with Src and Shc, and can be rarely mutated in SCC of the lung (1 to 2%).
The deletion of exon 2−7 of EGFR is known as variant III mutation of EGFR which is more frequent in SCC of the lung (5%). Amplifications of EGFR are common in SCC but it has not been addressed yet if they confer sensitivity to treatment with EGFR kinase inhibitors or antibodies. Mutations in ERBB2 gene are rare (1%) in SCC.
PIK3CA copy number gains are more frequent in SCC (33.1%) than in adenocarcinoma (6.2%). In lung SCC PTEN mutations are described in 10% of samples, being more frequent than in adenocarcinoma (2%). At genomic level PTEN loss is seen in 8−20% both for SCC and adenocarcinoma.
Somatic activating B-RAF mutations in melanoma are highly prevalent (~60%), and usually involve a single substitution (V600E. In SCC of the lung the mutation prevalence is of 2%.
PDL1 expression is reported to be in the range of 50% in NSCLC and notably SCC of the lung. PDL1 appears as potential predictor of the efficacy of new immune checkpoint modulators.
The table below provides a summary of specific alterations, their frequencies and their potential corresponding molecular targeted interventions.

Molecular alteration	Frequency in adenocarcinoma	Frequency in squamous cell carcinoma	Potential drugs
EGFR mutation	10−40%	2−5%	Gefitinib Erlotinib Afatinib PF-00299804
EML4-ALK translocation	5−7%	Rare	Crizotinib New ALK-inhibitors HSP90 inhibitors
HER2 mutation or amplification	2% 6%	Rare 2%	Trastuzumab Lapatinib PF-00299804 Afatinib
PI3K mutation or amplification	5% <10%	5% <10%	GDC-0941 XL-147 XL-765 PX-866 BEZ-235 BKM120 PF-05212384
MET amplification	<10%	<10%	XL184 ARQ917 MetMab
RAS mutation RAF mutation	10−30% 3%	5% 2%	Sorafenib Selumetinib GSK1120212; AS703026, RO4987655
FGFR1 amplification	5%	10−20%	BJG398, AZD4547, TKI258 EOS3810
PDL1 expression	40−50%	50%	Lambrolizumab Nivolumab MPDL3280A

Conflict of interest: *Consultancy fees from: Abbott, Amgen, AstraZeneca, BMS, EOS, GSK, Lilly, Merck-Serono, MSD, Pfizer, Roche-Genentech, Servier, Sanofi.*

Special Session (Tue, 1 Oct, 11:30−12:30) **Castration Resistant Prostate Cancer: New Therapies**

391 INVITED

Molecular pathways of castration resistance in prostate cancer

J. Schalken[1]. [1]*Radboud University Nijmegen Medical Centre, Urology Research Laboratory, Nijmegen, Netherlands*

The role of the androgen receptor in advanced prostate cancer has regained considerable attention in the past decade. The true importance of some (very) old observations is now generally acknowledged.
These observations are that in endocrine therapy resistant PrCa. − still significant levels of DHT can be measured, and that − at this stage of the disease cancer cells express high evels of nuclear Androgen Receptor. We, therefore, now refer to this stage as Castration Resistant Prostate Cancer. Despite castrate levels of circulating testosterone, the AR in cancer cells is active.
Various mechanism can lead to the adaption to low levels of circulating androgens. Mutations (therapy induced) leading to constitutively active and/or promiscuous AR occur, albeit in a low frequency,in CRPCs(<10%). The most common mechanism of adaptation is by over expressing the AR and/or by AR gene amplification (50−85%). Recently, also splice variants leading to a constitutively active AR, have been reported. Another mechanism, illustrating the versatility of cancer cells is by increasing intra-tumoral steroidigenesis. The recently approved endocrine therapies are targeting these adaptive changes, by interfering with CYP17 associated steroidigenesis (abiraterone acatetate) and by a strong antagonist of androgen receptor signaling (enzalutamide). These interventions, may be more effective in earlier stage disease, however, only appropriately designed clinical trials can test this hypothesis.
We have to anticipate to a mechanism of cancer progression where a cell type is involved that drives the adaptive changes, yet for its survival isn't dependent on the AR. The new endocrine therapies, would then more clearly 'unmask'/reveal this putative (cancer initiating) cell population. The cellular basis of progression under endocrine therapy and the molecular understanding of this cell type, should provide the a model for new targets for therapy.
Conflict of interest: *Advisory board: Astellas, Medivation, Jansen Cilag, Takeda*

392 INVITED

Androgen receptor (AR) and AR-signaling directed therapies in the age of precision medicine

H. Scher[1]. [1]*Memorial Sloan-Kettering Cancer Center, Department of Medicine Sidney Kimmel Center for Prostate and Urologic Cancers Genitourinary Oncology Service, New York NY, USA*

Background: Precision medicine enables the selection of treatments to which patients are most likely to benefit, reducing the chance of exposing individual patients to ineffective, potentially toxic, and costly treatments. Molecular profiling and laboratory studies have shown reactivation of AR and AR signaling to be a key driver of castration resistant prostate cancer (CRPC) growth and survival, informed the successful development of the androgen biosynthesis inhibitor abiraterone acetate (AA), the androgen receptor (AR) signaling inhibitor enzalutamide and newer AR-directed therapies. Not all patients respond, suggesting the presence of predictive biomarkers of sensitivity.
Material and Methods: A key focus now is to understand and target mechanisms associated with both intrinsic and acquired resistance to these agents. Proposed mechanisms include reciprocal feedback between the PI3K/PTEN and AR signaling pathways, AR splice variants, mutations in the ligand binding domain, and activation of glucocorticoid receptor signaling.
Results: Trials targeting the AR and the PI3K/PTEN signaling axes, alone or in combination are ongoing in which analysis of tumor material from patients is planned. Limitations to implementation of a precision medicine paradigm include the lack of analytically and clinically validated assays for the predictive biomarkers proposed, and the availability of tumor material at the time treatment is considered. Disease heterogeneity is another major limitation.
Conclusions: A variety of blood and tissue based biomarkers are under development through a multidisciplinary assay validation program to address the unmet need for integral biomarkers to guide treatment

selection. Co-development of integral biomarker assays is a practical strategy for investigating the next generation of promising AR-directed therapies.
No conflict of interest.

393 INVITED

Non-androgen receptor (AR) targeted approaches for managing castration-resistant prostate cancer (CRPC)

M. Smith[1]. [1]*Massachusetts General Hospital, Harvard Medical School, Boston MA, USA*

The treatment landscape for metastatic CRPC has been transformed by the development of both AR targeted and non-AR targeted therapies. Abiraterone acetate and enzalutamide increase progression-free and overall survival in metastatic CRPC. While the efficacy and safety of these AR-targeted therapies are favorable, not all patients benefit from treatment. Many patients with CRPC do not respond to new AR-targeted therapies and most responding patients develop overlapping resistance. Accordingly, non-AR targeted therapies will continue to have an important role in the management of metastatic CRPC. Cabazitaxel improves progression-free and overall survival for patients with disease progression after docetaxel; an ongoing randomized controlled trial will evaluate the comparative effectiveness of these agents as first line chemotherapy. For patients who are not candidates for chemotherapy or experience disease-progression after docetaxel, radium-223 improves overall survival and delays onset of skeletal-related events. Several investigational drugs have novel mechanism(s) of action. Cabozantinib, for example, is an orally bioavailable tyrosine kinase inhibitor with activity against MET and VEGFR2. In phase 2 clinical trials, cabozantinib was associated with high rates of bone scan improvement, decreases in measurable disease, and reductions in bone biomarkers and circulating tumor cells. Two ongoing randomized controlled trials (COMET-1 and COMET-2) will evaluate the effects of cabozantinib on overall survival and cancer-related pain for patients with metastatic CRPC and disease progression despite docetaxel and abiraterone acetate (and/or enzalutamide).
Conflict of interest: *Advisory board: Amgen, Bayer, Exelixis, Sanofi. Corporate-sponsored research: Amgen, Bayer, Exelixis, Sanofi*

Special Session (Tue, 1 Oct, 11:30−12:30)
Autophagy in Cancer and Cancer Therapy

394 INVITED

Signalling pathways controlling autophagy and its crosstalk with apoptosis

A. Kimchi[1], I.K. Koren[1], A.D. Rubinstein[1], Y. Ber[1], R. Shiloh[1]. [1]*Weizmann Institute of Science, Faculty of Biochemistry, Department of Molecular Genetics, Rehovot, Israel*

Autophagy, a catabolic process responsible for the degradation of cytosolic components, is induced when nutrient supplies are limited, as well as in response to other stress conditions. While in various stress conditions this process contributes to continuous cell survival, under some circumstances it induces cell death, either by 'self eating' of the vital components of a cell or by triggering apoptosis. We focus on the discovery of novel signaling pathways which negatively or positively regulate the autophagic flux and on the identification of new points of interface between autophagy an apoptosis. We found that DAP1, a conserved proline rich adaptor protein, which is a direct substrate of mTOR, acts as an inhibitor the autophagic flux. mTOR phosphorylates DAP1 on two critical serine residues which inactivate its function. Thus, mTORC1 inhibition activates simultaneously autophagy and a specific brake which limits the intensity of autophagic activity to prevent harmful effects when over activated. Additionally, a few novel positive pathways accelerating the autophagic flux have been identified in our lab. These pathways are initiated by members of the DAPK family of calcium-regulated Ser/Thr kinases, including DAPK1 and DAPK2. In parallel, points of interface between autophagy and apoptosis were recently discovered in our lab by applying unbiased siRNA screens. We identified the essential autophagy protein Atg12 as a positive mediator of mitochondrial apoptosis, and showed that Atg12 directly regulates the apoptotic pathway by binding and inactivating the pro-survival Bcl-2 family members. The binding requires a BH3-like motif in Atg12. The interaction between Atg12 and Bcl-2 family members may thus constitute an important point of convergence between autophagy and apoptosis in response to specific signals.
No conflict of interest.

395 INVITED

The importance of autophagy in cancer

K. Ryan[1]. [1]*The Beatson Institute for Cancer Research, Tumour Cell Death Laboratory, Glasgow, United Kingdom*

For over 50 years, preservation of genomic integrity has been considered a cornerstone in the body's defence against cancer. It must be remembered, however, that a DNA mutation will only have an impact if it encodes for a damaged species within the cell. As such, damaged proteins or organelles constitute non-heritable 'mutations' if they are not removed and if these proteins lie in critical cellular pathways, then these cells will have a higher propensity for aberrant function. Therefore in addition to genomic integrity, protein and organelle integrity are also critically important for protecting us against various forms of human disease including cancer.
Autophagy is a cellular trafficking process that serves to degrade cellular constituents in lysosomes. It is major mechanism for the degradation of long-lived proteins and protein aggregates and it is the only process for degrading organelles. As a result, it is a major catabolic process within the cell which acts to preserve cellular homeostasis and integrity. It has recently become clear the autophagy plays an important role in tumour development and may also be an important target for cancer therapy. It seems, however, that autophagy has dual roles in cancer. On the one hand, it is clear that autophagy can keep cells alive and in the context of the cancer cell, this aspect of autophagy can be considered oncogenic. Conversely, several reports have also shown that autophagy can contribute to tumour suppression. Although several clinical trials are underway to target autophagy therapeutically, it seems critical to understand in which cancers and at what stage, autophagy in oncogenic versus tumour suppressive if we are to consider targeting this pathway effectively.
We have been studying the role of autophagy in the context of various aspects of tumour development both in vitro and in vivo. We will present our findings and discuss how they fit with published studies to convey what we currently understand about how this fundamental process contributes to tumour development and how it could be an avenue for the development of novel chemotherapeutic drugs.
Work in our laboratory is supported by Cancer Research UK and The Association for International Cancer Research.
No conflict of interest.

396 INVITED

Fundamental mechanisms in autophagy

S. Tooze[1], H. Dooley[1], H. Jefferies[1], J. Joachim[1], C. Lamb[1], F. McAlpine[1], M. Razi[1], M. Wirth[1]. [1]*Cancer Research UK, London Research Institute, London, United Kingdom*

Background: Autophagy is a highly conserved cell survival pathway that is essential for cell health and homeostasis. Autophagy is a membrane-mediated lysosomal degradation process that can be acutely induced by withdrawal of amino-acids, and more chronically by withdrawal of glucose, growth factors or stressful environmental conditions. Induction by amino-acid starvation has been fundamental in the identification of the 35 or more autophagy-related (Atg) genes first in yeast, and more recently in mammals.
Material and Methods: We use 2 hours amino-acid withdrawal to induce autophagy, followed by morphological and biochemical approaches to study protein localization and protein-protein interactions in a variety of cells.
Results: We are interested in how the autophagosome forms, and study a set of these Atg proteins and regulators required for formation. In particular, we are studying the PI3P effector WIPI2, and the transmembrane protein Atg9, both of which make important contributions at early stages of the pathway by sensing lipids and delivering vesicles. Furthermore, we have identified a RabGAP and associated effectors that mediate ULK1-dependent transport from the recycling endosome to the early autophagosome, also contributing to the early stage expansion of the autophagosome. Starvation-induced autophagy is negatively regulated by mTORC1. ULK1 and ULK2 (mammalian Atg1 homologues) are found in association with mTORC1 in fed cells and negatively regulated by active mTORC1. Activation of the ULK1/2 complex by inhibition of mTORC1 initiates the formation of phagophores, autophagsosome precursor membrane structures. At, or on, these membranes ULK1/2, its complex members FIP200, Atg13 and Atg101, and at least seven other Atg proteins assemble and together mediate the formation of the double membrane autophagosomes on ER-associated membranes. The class III PI 3-kinase complex is also required for initiation, producing an autophagy-specific pool of PI 3 phosphate (PI3P) which is recognized by the effector WIPI2. Using ULK1/2 double knock out MEF cell lines we have found that both amino acid withdrawal-induced PI3P production, and autophagosome formation requires both ULK1 and ULK2. However, while glucose-withdrawal induced autophagy required both ULK1 and ULK2 it

did not require PI 3P production on the phagophore as detected by WIPI1 and WIPI2 puncta formation.
Conclusions: Our current data and the pathways leading to the regulation and formation of autophagy will be discussed.
No conflict of interest.

Special Session (Tue, 1 Oct, 11:30−12:30) **Stem Cell Therapy for Preventing Salivary Gland Toxicity**

397 INVITED

Kit+ progenitor cells regenerate the branching architecture of salivary glands

I. Lombaert[1], S. Abrams[1], M. Hoffman[1]. [1]*National Institutes of Health, Nidcr, Bethesda, USA*

Irradiation damage to salivary glands during cancer treatment often leads to a permanent loss of saliva production. Regeneration of irradiated submandibular glands (SMGs) in mice can occur after transplantation of SMG epithelial Kit+ progenitors. However, the mechanism by which Kit+ progenitors regenerate the tissue is not well understood. Using fetal SMG development, we show that signals from the mesenchyme stimulate both Fgfr2b and Kit signaling to expand the Kit+ progenitors. These progenitors in turn produce neurotrophic factors that promote neuronal innervation, which influences a separate population of K5+ epithelial progenitors that form ductal structures. Ultimately, reiterative rounds of this multicellular communication establish the branching architecture of the developing organ, and a similar molecular mechanism maintains adult tissue homeostasis. This model of organogenesis provides a template for regenerative medicine and may also have implications for targeting receptor kinases of SMG cancer stem cells.
No conflict of interest.

398 INVITED

Stem cell therapy for prevention of radiation-induced salivary gland toxicity

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Hyposalivation and its consequence xerostomia are sequelae of salivary gland (SG) functional ablation, commonly caused by radiotherapy (RT) treatment for head and neck cancers. 40% of the patients treated for head and neck cancer suffer from oral dryness leading to impaired speech, chewing, taste and swallowing, higher susceptibility for infections, and caries. These sequelea severely affect the patients' wellbeing and quality of life. A lack of viable stem cells able to maintain glandular homeostasis underlies age and radiotherapy induced SG dysfunction. Therefore, stem cell therapy could ameliorate xerostomia. Indeed, recently we showed that transplantation of mouse stem cells can rescue murine SG from radiation damage. Currently, we are translating our findings in mice to the human situation. Using human submandibular and parotid biopsies material we are able to culture human primary salispheres (hS) from which single cells could be obtained that were able to self-renew for $\geqslant$5 passages *in vitro*. Moreover, single hS cell derived salispheres could be stimulated to develop into an organoid with cells differentiating in ductal and acinar lineages as indicated by the expression of cytokeratins (Cyt^{+}) and aquaporin-5 ($AQP5^{+}$), respectively. These results indicate that in vitro we can obtain cells that are able to self-renew and differentiate into salivary gland lineages, two prerequisites of tissue stem cells. When xeno-transplanted into a mouse model of radiation-induced hyposalivation, hS cells proliferate extensively and were found to differentiate into human salivary gland structures within the mouse. Moreover, human proteins were detected into the saliva collected from the mice.
We believe hS cell transplantation represents a logical, long-term option for the management of RT-induced xerostomia. We are currently working on the translation of our hS knowledge towards GMP standards, optimization of our cell delivery technique, and the ultimate realization of an hS cell therapy for xerostomia.
No conflict of interest.

399 INVITED

Parotid deformation during IMRT correlates with clinical and dosimetry information

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The rapid spread of integrated delivery and image-guidance systems in combination with accurate morphological and functional imaging techniques opened the possibility of adapting the treatment to take into account modifications occurring during the course of radiotherapy. Another issue of paramount importance concerns how organ deformation during radiotherapy may predict acute and subacute/late toxicity. The detection of anomalous deformation may be a signal of a potentially high risk of toxicity; consequently, early detection could permit the selective adaptation of the treatment in order to reduce the risk of toxicity or, if adaptation is not feasible, to better/timely manage the toxicities and the supportive therapies. Within our group we have investigated the role of both deformation and density variation of parotids as surrogates of long term functional changes. Regarding the former, elastic registration was applied in quantitatively estimating entity and direction of deformation occurring during treatment; in a preliminary study, elastic matching was validated for the parotid glands. In this study, the entity of deformation (in terms of compression of expansion of each single voxel) was expressed by the Jacobian (Jac) of the deformation field, and the Jac was used to quantify inter-fraction anatomical changes. The Jac analysis showed correlation between the low-dose bath (around 10−15 Gy) and a larger fraction of voxels subject to large compression. In a follow up study on 84 pts, the Jac mean value (Jac_mean) was found to be correlated to pretreatment dosimetric parameters, particularly V10 and V40.
Regarding parotid density changes, we assessed the predictive power of parotid gland early variations on final deformations at the end of therapy and, possibly, on peak xerostomia during IMRT for head-neck cancer by considering 92 parotids. For 24 patients prospectively collected toxicity data (CTCAE v3.0) during treatment were analyzed. Kinetics of the changes during treatment were described by the daily rate of density ($r\Delta\rho$) and volume ($r\Delta vol$) variation and the mean Jac (Jmean). A larger $r\Delta\rho$ was observed at the beginning of the treatment, compared to the end ($p = 0.0001$). Both early $r\Delta\rho$ and $r\Delta vol$ predicted for mean acute xerostomia$\geqslant$median population value (1.57;p-value=0.01,logistic regression). Therefore, a larger longitudinally assessed score of acute xerostomia is well predicted by larger $r\Delta\rho$ and $r\Delta vol$ in the first two weeks of treatment.
No conflict of interest.

Special Session (Tue, 1 Oct, 11:30−12:30) **Retroperitoneal Sarcomas**

400 INVITED

Surgical aspects of retroperitoneal sarcomas

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Retroperitoneal sarcomas expose to a high risk of local recurrence compared to limbs. Their extra compartmental expansion, adjacency to vital structures, and significant size at diagnosis challenging one bloc surgery, represent the main reasons. In low and intermediate grades, death is mainly related to local recurrences that eventually become non resectable. Concerning primaries; two teams initiated compartmental resection (CR) in order to limit the areas of close margins, by assimilation to other soft tissue sarcomas. Their studies provided a local benefit, reporting greater than 75 % local control at 5 years. CR has been accepted by many other teams, especially in Europe. However, it is difficult to demonstrate an impact on overall survival, knowing that patients who have had a simple resection for a low grade may have been operated several times and that high grade sarcomas expose to visceral metastasis. This is one of the reasons why there is still a debate about best indications of CR.
Best indications of CR are represented by potentially curative situations. This includes primary tumors (especially when a previous piecemeal resection was performed: it exposes to peritoneal seeding), unifocal sarcomas (6), and those with the lower metastatic risk. However, many WD/DD liposarcomas seem to be multifocal, while they're a single tumor, made by several different components. This apparent multifocality may be the result of a non-compartmental surgical approach, which does not visualize the contiguous areas. Decision making is finally balanced according to expected morbidity of accumulated resections and patient's co morbidities. Morbidity is around 10%, comparable to other high risk visceral surgery. Experience of the surgeon is also another prognostic factor and CR should be performed in referential centers (2).

Many retrospective studies suggest a benefit of adding radiation therapy, even with CR (8). The pre-operative radiotherapy timing appears to display less toxicity. There is currently a randomized study of EORTC (protocol 62092–22092, ClinicalTrials.gov Identifier: NCT 01344018) to evaluate the benefit of pre operative radiotherapy (28 daily fractions of 1.8 Gy (5 fractions per week) for a total dose of 50.4 Gy). Of course, limits of preoperative radiotherapy are tumor size (too large fields are not possible) and growth kinetic. Patients must be both resectable and suitable for radiotherapy. Chemo sensitive sarcomas (such as rhabdomyosarcomas, PNET or other small round blue cells sarcomas) and visceral sarcomas should not be included in this trial.
There are currently too much redundant literature and too many hasty conclusions drawn from retrospective studies, sometimes limited, and we can emphasize the importance of prospective and controlled studies or registry.
No conflict of interest.

401 INVITED

The role of radiotherapy in retroperitoneal sarcoma

R. Haas[1]. [1]*The Netherlands Cancer Institute, Radiotherapy, Amsterdam, Netherlands*

Retroperitoneal sarcomas (RPS) are rare. They comprises about 15% of all soft tissue sarcomas. RPS are diagnosed at a median size of 15−18 cm, because they remain asymptomatic for a relatively long period. The majority (70%) of RPS is either a liposarcomas or a leiomyosarcomas and predominantly of high grade histology.
The chance to obtain negative margins in these large tumors is small. In a substantial proportion of cases the surgeon has to leave macroscopic tumor behind (R2 resections). This results into a local failure rate of 52−60% at 5 years. Predictive factors for local recurrence are grade, margin status, the fact whether patients have been operated upon in reference centers and whether or not radiotherapy (XRT) has been applied.
The cause of death in patients with extremity sarcomas (ESTS) is most often metastatic disease. In contrast, most RPS patients die due to local failures. In order to obtain the highest probability of abdominal control complete resection with gross negative margins and aggressive en bloc resection of the primary disease is now considered standard of surgical care.
What is the role of XRT in RPS and are aspects from XRT in ESTS applicable to RPS? In contrast to ESTS it is almost impossible to perform postoperative XRT due the high complication rates of the small intestines, kidneys and liver. Possibly the best timing of XRT is preoperative. In the presentation XRT trials and studies focused on RPS are discussed.
No conflict of interest.

402 INVITED

The role of chemotherapy

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A third of all retroperitoneal tumors are sarcomas, and 10−15% of all sarcomas are located in the retroperitoneum, with liposarcoma (70%) and leiomyosarcoma (15%) being the two most frequent histologies.
Surgery is the mainstay of treatment for retroperitoneal sarcomas. Location and extent of the disease pose significant challenges, but an aggressive surgical approach improves survival. Radiotherapy is often part of the treatment plan to achieve better local control, as recurrences are frequent and cause significant morbidity and mortality.
Chemotherapy has been used in the metastatic and adjuvant, and more recently in a preoperative setting.
While it has been recognised that the role and effect of any treatment depends on the histological or molecular sarcoma subtype, matching a disease subtype with an effective drug is complicated by the lack of (trial) data. Furthermore, the identification of oncogenic targets or pathways has just started.
For unresectable retroperitoneal leiomyosarcomas or liposarcomas the role of trabectedin has been established in the past years, but only recent reports suggest that a preoperative use might be of benefit in selected patients.
Reviewed will be potential oncogenic targets, and the role of chemotherapy and molecular agents in retroperitoneal sarcoma.
No conflict of interest.

Special Session (Tue, 1 Oct, 11:30−12:30)
Advanced Practitioner Roles in Cancer Care: Where Next?

403 INVITED

Developing appropriate education programmes in advanced nursing practice: The Irish experience

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Background: Advanced practice in nursing and midwifery has developed internationally and nationally. In Ireland the Commission on Nursing recognised that promotional opportunities should be open to nurses and midwives wishing to remain in clinical practice and accordingly recommended a clinical career pathway leading from registration to clinical specialisation and to advanced practice (Government of Ireland 1998). In 1999 the establishment of the National Council for the Professional Development of Nursing and Midwifery enabled nurses to be approved and accredited as Advanced Nurse Practitioners (ANP). A framework for Advanced Practice was developed with criteria to become an ANP and the attainment of Core Competencies.
In 2010 the Department of Health in Ireland transferred the area of Advanced Practice to the Nursing and Midwifery Board of Ireland and Advanced Practice became a registration qualification.
What do ANPs in Ireland do? ANPs are experienced nurses who are educated to a Master's Degree or above, are at least 7 years post-registration and have a minimum of 5 years working in their speciality area of practice, such as cancer care, palliative care, diabetes. These ANPs promote wellness, offer healthcare interventions and advocate healthy lifestyle choices for patients/clients, their families and carers in a wide variety of settings in collaboration with other healthcare professionals, according to agreed scope of practice guidelines. They utilise advanced clinical nursing knowledge and critical thinking skills to independently provide optimum patient/client care through caseload management of acute and/or chronic illness, such as cancer care.
Evaluation of ANP Programme in UCD: In 2001 University College Dublin (UCD) commenced an Advanced Practice education programme. Preparation and education for Faculty was undertaken in University of Pennsylvania, Philadelphia, USA. Eleven years later this programme was evaluated by a research team in UCD. Two questionnaires were used to evaluate the education programme undertaken by nurses and midwives to prepare them for advanced nursing practice. The first, entitled the *Outcomes Evaluation Questionnaire* (OEQ), evaluated course participants' abilities and understanding of advanced practice as a consequence of the preparation programme. The second, the *Course Evaluation Questionnaire* (PCEQ), evaluated course participants' perceptions of the quality of their preparation programme. This presentation will conclude with preliminary results from a national survey of nurses who undertook their Advanced Practice education at University College Dublin, Ireland.
No conflict of interest.

404 INVITED

The role of advanced nursing practice in teenage and young adult cancer care

S. Smith[1]. [1]*Teenage Cancer Trust, London, United Kingdom*

Background: It is now over twenty five years since the first Teenage Cancer Trust Unit opened in London. Teenage and Young Adult (TYA) cancer care has gained recognition as a specialty within its own right and the UK are seen as worldwide leaders in TYA cancer care. Development of TYA nursing expertise has largely been organic through the experience of specialist nurses working in this field. TYA "expert" nurses have evolved over time and range from Clinical Nurse Specialists, Lead Nurses and Nurse Consultants. These nurses have led developments in TYA cancer care in the UK and Internationally.
Material: The best standard of care for TYA patients is undoubtedly provided by staff who have been specifically trained to care for them. The UK has developed TYA cancer care for twenty years and has captured their expertise in delivering age-appropriate, multidisciplinary and nursing care within A Blueprint of Care (2012). Alongside the development of TYA cancer nursing and services the UK has developed multidisciplinary education programs for staff working in this field through both pre and post graduate education.
Results: We are now in a position to define and describe TYA cancer care nursing from foundation level to expert and advanced practice. The UK is in the process of formally capturing and describing the knowledge, skills, competences and education requirements for nurses working in this specialty through a project and publication supported by the Royal College

of Nursing. This will enable TYA specialist nursing care in the future to be delivered by a competent and knowledgeable nursing workforce.
Conclusions: TYA cancer nursing expertise is largely confined to a small number of nurses in the UK and even fewer internationally. However, TYA cancer care is rapidly evolving internationally and it is crucial that care is delivered by a skilled and appropriately trained workforce of which nursing skills and competencies are the cornerstone for specialist age appropriate care delivery. The UK are in an ideal position to share practice and collaborate with international colleagues who are now developing specialist nursing care for this patient group. Defining TYA Cancer Nursing competencies will provide a framework for both the UK and International colleagues to educate and develop a knowledgeable nursing workforce and embed the philosophy and principals of age appropriate care for TYA's with cancer.
No conflict of interest.

405 INVITED
Advantages of nurse-led follow up

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The cancer incidence in Europe is increasing, caused by factors as the aging population. As a result of this more people will need treatment and follow up in a curative or palliative setting.
Due to the fact that cancertreatment is often very successful, the group cancer survivors will also increases and conventional follow-up will have a major impact on outpatient services. So new strategies for follow up are needed.
Follow up normally contains inventigating possible recurrence, support for treatment related side effects (immidiate or late) and psychosocial support. The European commission has estimated a shortage of physicians in 2020 of 13%, what results in a challenge to cover the increasing demand for specilized care and physician led follow up. We have to face this and reorganize our care. Nurse-led follow up is a promising alternative.
Although the evidence is limited, there is already more then enough experience in breast-, lung- and prostate cancer, that nurse led follow up is a part of daily routine in a lot of countries and institutions. A few randomised controlled trials can be identified were no statistically significant differences in survival, recurrence or psychological morbidity were found in nurse led follow up. Some studies even showed a better quality of live measures.
Although the level over basic nursing education differs in European countries, more and more nurses have the ability to follow specilized oncology training as a bachelor or master program. In a lot of European countries well trained specialized oncology nurses and/or clinical nurse specialists/nurse practitioners take over originaly physicians tasks in patients follow up. For nurses this is also a possibility to develop themselves an extent their responsabilities and specialized role.
An other aspect is the increasing health care costs, wich gives us the responsibility to organize the care as cost effective as possible. Nursing-led follow is less expensive without a decrease of quality and is therefore a good and save way of organizing care. Also alternative follow-up strategies have to be considered, for example telephone follow up.
The available studies and experiences from the field show that patients appeared satisfied with nurse-led follow-up. Patient-initiated or telephone follow-up could be practical alternatives to conventional care. However, more well-conducted research is needed before equivalence to physician-led follow-up can be assured in terms of survival, recurrence, patient well-being and cost-effectiveness.
No conflict of interest.

Special Session (Tue, 1 Oct, 11:30−12:30)
Outcome Issues for the Older Patient

406 INVITED
Which outcomes for older cancer patients

M. Janssen-Heijnen[1]. [1]*VieCuri Medical Centre, Clinical Epidemiology, Venlo, Netherlands*

Background: Presently, almost 30% of newly diagnosed cancer patients are aged 75 years or older. Treatment of older cancer patients is challenging, since it is often complicated by comorbidity, poor performance status, or social or psychological factors. Elderly patients are often excluded from clinical trials and therefore evidence is scarce about predictors for the risks and benefits of treatment. Although mortality reduction is important for patients of all ages, additional endpoints, such as toxicity and completion of planned treatment, and the ability to live independently and with a high quality of life, may be equally (or more) important for older patients.
Material and Methods: An overview of current literature concerning important outcomes for elderly cancer patients as well as evidence for predictors of outcome.
Results: Survival time, response and toxicity are often included as endpoints in clinical trials, but quality of life and geriatric assessment scores such as independency are seldom included. It is unknown whether outcomes from clinical trials are valid for everyday clinical practice, because elderly and those with serious comorbidity or poor performance status are often excluded.
Population-based observational studies have shown that despite high toxicity rates in elderly and poor treatment completion rates, those who received standard treatment had a significantly better survival. Unfortunately, results on predictors for outcome of treatment in observational studies cannot be fully adjusted for the fact that the fittest patients are selected for (aggressive) treatment.
There is an urgent need to identify patient characteristics that are predictive for the relevant outcomes in elderly. Some prediction models for toxicity of chemotherapy, postoperative mortality or hospital stay have been developed. However, the geriatric predictors that were identified differ significantly between the models and outcome measures.
Conclusions: Elderly cancer patients experience competing events which interfere with the disease-specific outcome of interest. It is important to avoid discomfort (loss of functionality or autonomy, deterioration of quality of life, time spent in the hospital). This means that, besides traditional outcomes as survival time, it is important to include other outcomes as preservation of independency and quality of life in older-specific clinical trials.
No conflict of interest.

407 INVITED
New targeted outcomes for colorectal cancer in older patients

G. Liefers[1], on behalf of the Geriatric Oncology Group. [1]*Leiden University Medical Centrum, Surgery, Leiden, Netherlands*

Elderly colorectal cancer patients have worse prognosis than younger patients. Age-related survival differences may be cancer or treatment related, but also due to death from other causes. Elderly colorectal cancer patients who survive the first year have the same cancer-related survival as younger patients. Therefore, decreased survival is mainly due to differences in early mortality. The 30-day mortality rate highly underestimates the risk of dying in the first year after surgery, with excess 1-year mortality rates varying from 15 to 30%. This excess mortality is especially prominent in patients with comorbidities, higher stages of disease, emergency surgery, and postoperative surgical complications. Treatment of elderly colorectal cancer patients should focus on perioperative care and the first postoperative year. In this presentation we will discuss the differences between young and older patients with regard to outcome and highlight the potential design of studies to improve treatment of this vulnerable and growing group of patients.
No conflict of interest.

Special Session (Tue, 1 Oct, 11:30−12:30)
Repainting and Tracking in Ion Beam Therapy

408 INVITED
Motion mitigation using scanned beams with moving targets

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Currently newly built particle therapy centers are mostly equipped with scanning beams, since they provide highly conformal dose distributions when treating static targets. However, scanned beams face significant challenges when applied to moving targets. To mitigate motion effects, different approaches have been suggested.
In this talk, we would like to concentrate on a motion mitigation technique that exploits the characteristics of scanning, namely rescanning. The idea of rescanning is to statistically average out dose heterogeneities by repeatedly delivering the planned dose to the target with an accordingly reduced number of particles per scan. For a successful application of rescanning it is therefore essential to choose the right "flavor" of rescanning.
Before going into different rescanning flavors one should be reminded that scanning itself can be performed in many different ways. Lateral as well as depth (energy) beam adjustments can be undertaken in a discrete or continuous manner. Furthermore, the dose grid points within the target can be visited in different orders. Also it has been suggested to vary the beam spot size during one scan, using small sizes at the boarder of the volume to closely conform the dose to the target and large sizes in the center of the volume to minimize dose inhomogeneities due to misspositioned spots.

In addition, rescanning can be performed in a layered or a volumetric way. In the layered approach, N rescans are applied to an iso-energy-layer before a change in depth is done. In the volumetric approach each dose grid point of the entire volume will be visited once, before the next rescan is started. Finally, also different flavors of beam weighting can be chosen. Such as scaled, where each spot weight is divided by the number of rescans and alternatively iso-layered, where the weight per spot visit is kept below an upper limit.
Each specific way of scanning and each flavor of rescanning has its own characteristic delivery-time-line which is machine specific. In this presentation, we will show examples to emphasize that for a successful application of rescanning it is important to choose a way of scanning and a flavor of rescanning appropriate for your specific facility and adapted to the characteristics of each specific patient.
Finally, we will introduce the “slow tracking” approach which in our opinion is currently the most practical way to treat moving targets with scanned beams. In this approach, each treatment fraction would be delivered during several breath-holds, within which the tumour position would be verified and the beam parameters would be adjusted to compensate for inter-breath-hold positioning changes. Ultimately this procedure could be combined with rescanning to smooth out any interplay effects resulting from residual motions during the breath-holds.
No conflict of interest.

409 INVITED

Motion mitigation in scanned carbon beam therapy

C. Bert[1]. [1]*University Clinic Erlangen, Radiation Oncology, Erlangen, Germany*

Scanned ion beams interfere with intra-fractional organ motion potentially leading to underdosage of the clinical target volume (CTV). Several techniques are proposed to overcome that challenge, including beam tracking, gating, rescanning and potentially 4D optimized treatment plans. The talk focuses on latest developments in motion mitigation with a scanned carbon beam with an emphasis on beam tracking and 4D optimization.
Beam tracking aims at compensating intra-fractional target motion by adapting the scanned pencil beam during treatment delivery. 4D treatment planning data, i.e. compensation vectors that are based on information from 4D computed tomography (4DCT) + deformable registration, and a precise motion monitoring system are essential. In addition, a dedicated delivery system is needed. For beam tracking, 4D treatment planning is already based on 4DCT data but does not include the temporal domain in the plan optimization. Dedicated routines were developed that use target motion as an additional degree of freedom within the optimization process. In addition, these data can be used for precise internal target volume (ITV) definition.
Based on experimental and simulation data acquired at GSI in cooperation with several partner institutes the current status of the above mentioned techniques will be presented. Beam tracking is at the verge to a clinically applied method. Experiments with complex phantoms showed the feasibility of the complete technical workflow. Bottleneck will be 4DCT validity which can be overcome by treatment plan (adaptation) briefly before treatment delivery. 4D treatment plan optimization is feasible. Data of in-silico studies with 9 NSCLC patient showed feasibility. Also 4D optimized plans need a refined treatment delivery control. The GSI systems has been updated accordingly and first results show that treatment plan application is possible with acceptable delivery times.
In conclusion, beam tracking and 4D optimized treatment plans are feasible candidate techniques to enhance the possibilities of treatments for intra-fractionally moving tumors with scanned ion beams. Especially 4D optimization requires more research prior translation to clinical use can start.
Conflict of interest: *Corporate-sponsored research: Part of our research was sponsored by Siemens AG*

Scientific Programme
Proffered Papers

Proffered Papers Session (Sun, 29 Sep)
Basic Science/Translational Research

500 ORAL

Distinct chromatin binding patterns for estrogen receptor and histone marks classify aromatase inhibitor resistant breast cancer

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Background: Estrogen receptor-positive breast cancer patients receive endocrine treatment, however, resistance is common. To date, few tumor tissue specimens have been evaluated for their global binding patterns of the estrogen receptor to DNA in patients. The goal of this study is to identify chromatin binding events of the estrogen receptor and epigenetic histone marks that associate with endocrine therapy resistance.
Methods: Using chromatin immunoprecipitation followed by high-throughput sequencing (ChIP-seq), we analyzed primary tumor specimens from breast cancer patients with metastatic disease treated with first-line aromatase inhibitors, and mapped the genome-wide chromatin binding patterns of the estrogen receptor alpha (ERa) and epigenetic histone 3 modifications H3K4me3 and H3K27me3 for activation and suppression of gene expression, respectively.
Results: Differential binding patterns of all three markers were found between patients with a good and poor outcome after aromatase inhibitors, where altered ERa binding patterns were not accompanied by changes of epigenetic marks. Integrating these findings with array-based gene expression and progression-free survival data enabled us to identify distinct gene expression profiles linked to these altered binding events of ERa and H3K27m3 that associate with outcome upon aromatase inhibitors (ERa (HR = 5.02, 95% CI: 2.41–10.5; $p < 0.001$) and H3K27me3 (HR = 2.25, 95% CI: 1.19–4.24; $p = 0.013$)). Both ERa and H3K27me3 ChIP-seq based expression profiles remained significant in an independent cohort of specimens and in multivariate analyses with known clinical markers but did not correlate with progression-free survival upon first-line tamoxifen, illustrating a treatment-selective classification.
Conclusion: We applied a novel approach in primary tumor tissue specimens by integrating ChIP-seq with mRNA expression profiling. Above findings indicate that poor outcome after aromatase inhibitor therapy is accompanied by distinct ERa and H3K27me3 binding patterns. These altered binding patterns result in differential gene expression profiles that associate with outcome after aromatase inhibitors but not after tamoxifen in independent sets of specimens.
No conflict of interest.

501 ORAL

The stem cell-associated transcription factor TCF3 promotes breast tumor initiation and growth

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Background: Regulatory factors controlling stem cell identity and self-renewal are often active in aggressive cancers and are thought to promote their growth and progression. TCF3 is a member of the TCF/LEF transcription factor family that is pivotal in regulating epidermal and embryonic stem cell identity. We found that TCF3 is highly expressed in poorly differentiated human breast cancers, preferentially of the basal-like subtype. This suggested that TCF3 is involved in the regulation of the breast cancer cell differentiation state and tumorigenicity.
Methods: We set out to characterize the role of Tcf3 in breast cancer and in normal mammary stem cells. We silenced or overexpressed TCF3 in breast cancer cells as well as in the normal mouse mammary gland, relying on a combination of shRNA and transgenic tools.
Results: Silencing of TCF3 in basal-like breast cancer cell lines disrupted cell proliferation and morphology, and TCF3-silenced cancer cells formed smaller and less invasive tumors. We found that TCF3 enhances cancer stem cell-associated traits, including mammosphere formation and the $CD44^{high}/CD24^{low}$ marker profile. Importantly, tumor initiating capacity upon implantation in mouse mammary glands was dramatically reduced in TCF3-silenced cells, indicating that TCF3 is required both for the initiation and the growth of breast cancers. TCF3 is known to suppress Wnt target genes and self-renewal in ES cells; in contrast, we found that in breast cancer cells TCF3 binds and activates a subset of Wnt target genes while suppressing a distinct set of Wnt targets. Moreover, upon stimulation with Wnt3A, cells silenced for TCF3 showed reduced mammosphere formation ability compared to treated controls, suggesting that TCF3 can act also as a positive regulator of the Wnt signaling. Tcf3-silenced mouse mammary epithelial cells formed fewer mammospheres and showed reduced tissue reconstitution ability, while transgenic Tcf3 overexpression disrupted mammary ductal growth, revealing that Tcf3 is necessary for normal mammary stem cell function.
Conclusions: Our results identify TCF3 as a key regulator of breast cancer growth and initiation, and a novel link between stem cells and cancer.
No conflict of interest.

502 ORAL

Moving beyond in vitro models: Addressing the challenges of pooled RNAi screens in xenografts

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To date, several groups have successfully run genome-wide *in vitro* RNAi screening using pooled libraries expressing a complex diversity of shRNA molecules. Integral to obtaining reliable and robust results with this technique has been the use of quantitative next generation sequencing to accurately assay hairpin representation levels in the endpoint populations of cells transduced with an shRNA library. However, there are significant challenges in adapting the current pooled RNAi screening approaches to more sophisticated cell model systems, such as *ex-vivo* xenograft models. Our studies tracking the fates of thousands of individually barcoded implanted cells found that xenograft growth is characterized by a small subset of cancer cell sub-clones that ultimately produce the bulk of the resulting tumor mass. This phenomenon significantly impacts the ability to reliably detect shRNA-induced growth inhibition in these systems. To address this problem, we have developed a novel approach to constructing pooled shRNA libraries that enables effective viability screening in systems in which external parameters strongly influence cell growth rates, such as xenograft tumors. We will present preliminary data using this approach, as well as data from more conventional *in vitro* 'drop-out' lethality screens, to identify genes essential for cell proliferation. The results demonstrate that complex pooled shRNA libraries offer an efficient and flexible tool for both *in vitro* and *in vivo* screens aimed at discovering potential cancer therapy targets.
Conflict of interest: *Ownership: Cellecta, Inc.*

503 ORAL

Genome-wide identification of stromal metastasis regulators in breast cancer mouse models (Winner of ECCO/EJC Young Investigator's Award)

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Background: Metastasis is the leading cause of death in breast cancer patients and its molecular mechanisms remain largely elusive. In addition to the many genes that have been identified in cancer cells to regulate metastasis in a tumor cell-autonomous way, it has become increasingly recognized that the host stroma including vasculature, immune cells, and extracellular matrix plays a critical role as well. Unfortunately, to date no experimental systems exist that allow for the unbiased identification of stromal metastasis regulators on a genome-wide scale.
Methods: We have set up a genetic approach to map variants in host genes associated with metastasis. To this end, we orthotopically injected a genetically diverse mouse population with a metastatic mouse mammary carcinoma cell line and quantified lung metastasis. We then searched for associations of metastasis and other phenotypes with allelic variants in a genome-wide Quantative Trait Loci (QTL) analysis. As a genetic panel, we used the Diversity Outbred (DO) heterogeneous stock, recently developed by the Jackson Laboratory. These mice have a highly mosaic genetic background from eight different strains.
Results: To avoid immune rejection of the implanted breast cancer cells, we injected 150 F1 female progenies from a DO $\times$ FVB cross with FVB-derived Mvt-1 mammary carcinoma cells. 13 mice did not develop tumors, suggesting the presence of tumor-suppressive stromal factors at the

primary site. Genotyping with the 77,8k MEGA-MUGA BeadChip SNP array and generating haplotype structures using Haploview and PHASE software revealed 148 QTLs associated with stromal tumor suppression at a false discovery rate (FDR) <0.05. The other 137 tumor bearing mice were analyzed for metastasis and presented between 0 and 147 macroscopic tumor nodules on the surface of the lungs, uncovering 15 statistically significant QTLs. 14 mice displayed also tumor cell dissemination to kidneys, associated with another 3 QTLs. Several drug-amenable candidate genes could be identified within the mapped loci (interval sizes 1.7kb − 497.3kb).
Conclusions: Our approach represents a novel model system that screens for host-specific regulators of metastasis in an unbiased manner. We demonstrate that with the state-of-the-art genetic tools available, QTL mapping is feasible to identify candidate stromal metastasis regulators that can be further validated as prognostic markers and novel therapeutic targets for metastatic breast cancer.
No conflict of interest.

504 ORAL

Integrative analysis of genomic and transcriptomic data reveals the presence of a novel molecular class of biomarkers shared by all cancer entities

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Recent approaches to the classification of human tumour types have mainly been based on clinical, pathological, as well as molecular parameters. By contrast, gene expression patterns reflecting the sum of genetic aberrations in individual tumours have not been fully explored. We hypothesized that similar sets of common, tumour-specific properties exist which are independent of any histologic, clinical or single molecular parameters. In an attempt to uncover such prominent and common molecular features, we developed a novel, unbiased and integrative approach.
We first analysed matched pairs of normal and tumour DNA of 45 renal cell carcinoma (RCC) patients, unbiased from current clinico-pathological, genetic and biological valuations, using SNP microarrays. Based on the hypothesis that genomic alterations impact on the expression of a broad array of genes, we integrated these results into a novel workflow by combining data from *in silico* data mining tools, gene expression and tissue microarrays (TMA). Finally, we used our Artificial Intelligence platform (Q-USD™) to screen for systematics identified in RCC and potential novel ones in 12 additional human tumour types encompassing more than 3000 individual samples.
We have identified five possible global constellations of genetic relationships within the tumours that we call the 'Cancer States.' These Cancer States split the entire patient cohort into up to five homologous molecular subgroups, which appear independent of any currently used pheno- or genotypic classification. Translating these results into applied tumour pathology, we demonstrate that Cancer States represent a novel view for classifying human cancer. Ongoing clinical investigations suggest Cancer States as independent predictors of overall patient survival in RCC. Tamoxifen treated breast cancer patients with Cancer State A were found to have a better prognosis compared to patients with all other Cancer States. Thus, Cancer State A clearly identifies a distinct responder subpopulation among the entire cohort of treated patients.
In summary, Cancer States are reflecting global-mRNA-represented systematics as recurrent features in human cancer. We suggest that the sum of individual molecular alterations in a given tumour represents an intrinsic roadmap to establish one out of the five Cancer States.
No conflict of interest information specified.

505 ORAL

Tumor associated copy number changes identified by whole-genome sequencing in the circulation of patients with prostate cancer

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Background: Patients with prostate cancer may present with metastatic or recurrent disease despite initial curative treatment. The propensity of metastatic prostate cancer to spread to the bone has limited repeated sampling of tumor deposits. Hence, considerably less is understood about this lethal metastatic disease, as it is not commonly studied. Here we explored whole-genome sequencing of plasma DNA to scan the tumor genomes of these patients noninvasively.
Methods: We wanted to make whole-genome analysis from plasma DNA amenable to clinical routine applications and developed an approach based on a benchtop high-throughput platform, i.e. Illuminas MiSeq instrument. We performed whole-genome sequencing from plasma at a shallow sequencing depth to establish a genome-wide copy number profile of the tumor at low costs within 2 days. In parallel, we sequenced a panel of 55 high-interest genes and 38 introns with frequent fusion breakpoints such as the *TMPRSS2-ERG* fusion with high coverage. After intensive testing of our approach with samples from 25 individuals without cancer we analyzed 13 plasma samples derived from 5 patients with castration resistant (CRPC) and 4 patients with castration sensitive prostate cancer (CSPC).
Results: The genome-wide profiling in the plasma of our patients revealed multiple copy number aberrations including those previously reported in prostate tumors, such as losses in 8p and gains in 8q. High-level copy number gains in the *AR* locus were observed in patients with CRPC but not with CSPC disease. We identified the *TMPRSS2-ERG* rearrangement associated 3-Mbp deletion on chromosome 21 and found corresponding fusion plasma fragments in these cases. In an index case multiregional sequencing of the primary tumor identified different copy number changes in each sector, suggesting multifocal disease. Our plasma analyses of this index case, performed 13 years after resection of the primary tumor, revealed novel chromosomal rearrangements, which were stable in serial plasma analyses over a 9 months period, which is consistent with the presence of one metastatic clone.
Conclusions: The genomic landscape of prostate cancer can be established by non-invasive means from plasma DNA. Our approach provides specific genomic signatures within 2 days which may therefore serve as 'liquid biopsy'.
No conflict of interest.

Poster Session (Sat, 28 Sep)
Basic Science

506 POSTER

Temporal dynamics of the unfolded protein response and chemoresistance in hepatocellular carcinoma

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Background: Hepatocellular carcinoma (HCC) ranks as the fifth most common cancer worldwide. HCC is a chemoresistant tumour. Systemic therapy with cytotoxic drugs yields low response rates. Medications influencing the chemosensitivity profile are therefore needed. The unfolded protein response (UPR) is implicated in the pathophysiology of several diseases including cancer and endoplasmic reticulum (ER) stress could be a cause of the chemoresistance in HCC. To investigate these phenomena in HCC, we examined the presence and time-dependent alterations of ER stress and multidrug resistance (MDR) in a mouse model of HCC in order to have an in vivo method for the evaluation of UPR manipulation strategies as future cancer therapy.
Material and Methods: The in vivo study design was a diethylnitrosamine (DEN)-induced mouse model for HCC. Mice (6 groups of n = 14) where sacrificed after 20, 25 and 30 weeks of DEN or saline administration. The activation pattern of the UPR and the expression of MDR-related efflux pumps were determined by qRT-PCR, Western blot, ELISA and immunohistochemistry. The histology of the HCC nodules was examined by H/E, Sirius red, F4/80 and reticulin staining. Small animal imaging by dynamic-contrast-enhanced MRI and choline PET was performed.
Results: After 25 weeks of DEN, this model showed MR/PET-positive hepatocarcinogenesis occurring in a background of inflammation and fibrosis. The major MDR-related efflux pumps including mdr1, mrp1, mrp4 and brcp were significantly upregulated in the HCC nodules from 25 weeks. The master regulator of the UPR, bip, was significantly induced on 25 and even more on 30 weeks. Downstream targets of the perk branch (phosphorylated eif2a part: atf4, chop, gadd34 and nrf2 part: gclc, gsta1 and −2) were significantly upregulated after 25 weeks and continued to rise until 30 weeks. Unexpectedly, we could not show an increase in xbp1 splicing, spliced xbp1 targets or ire1a phosphorylation in the HCC nodules compared to the normal liver tissue. Only after 30 weeks, the atf6 pathway and the downstream targets showed significant induction.

Conclusions: Here, we provide the first evidence of the presence and the time-dependent alterations of MDR-related efflux pumps and a specific activation pattern of the UPR in the HCC nodules of a DEN-induced mouse model.
Consequently, this model can be used to manipulate the fine-tuning of the UPR in hepatocarcinogenesis and the related MDR development.
No conflict of interest.

507 POSTER

Constitutive activation of RANK in the mammary gland disrupts luminal and basal cell fate leading to tumorigenesis

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Introduction: RANK pathway controls mammary gland development in mice but its role in mammary stem cell fate remains undefined. The aim of the study is to investigate the role of RANK pathway in mammary morphogenesis and tumorigenesis.
Methods: MMTV-RANK transgenic mice were used in this study. Normal glands and tumors were characterized by expression analysis of keratins and key markers of mammary differentiation. Mammary epithelial populations were analyzed by surface marker expression in flow cytometry. Mammary stem cells and progenitor cells were quantified by mammary repopulating assays and colony forming assays respectively.
Results: We show that constitutive RANK signaling expands luminal and basal mammary compartments including mammary stem and luminal progenitor cell pools and interferes with the generation of CD61+ and Sca1+ luminal cells and Elf5 expression. Impaired mammary cell commitment upon RANK overexpression leads to the accumulation of progenitors such as K14+K8+ bipotent cells and the formation of heterogeneous tumors containing hyperplastic basal, luminal and progenitor cells. RANK expression increases in wild-type mammary epithelia with age and parity, and spontaneous preneoplastic lesions express RANK and accumulate K14+K8+ cells. In human breast tumors, high RANK expression levels are also associated with altered mammary differentiation.
Conclusions: These results suggest that increased RANK signaling interferes with mammary cell commitment, contributing to breast carcinogenesis.
No conflict of interest.

508 POSTER

Traditional chinese medicine BDL301 inhibits stat3 signaling pathway and angiogenesis in colorectal cancer cells in vitro and in vivo

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Background: Signal transducer and activator of transcription 3 (Stat3) and p-Stat3 are overexpressed compared with normal intestinal epithelial tissue in invasive colorectal adenocarcinoma, and they are closely related with tumor proliferation, lymph node metastasis, the depth and degree of tumor invasion in the colorectal cancer. Traditional Chinese medicine BDL301 has significant anti-inflammatory effect. The development of colorectal cancer and chronic inflammation are closely related. We therefore hypothesize that BDL301 might inhibit Stat3 Signaling pathway in colorectal cancer cells mediated by the down regulation of inflammatory pathway.
Material and Methods: Specificity of the BDL301 was demonstrated by High-Performance Liquid Chromatography (HPLC). CT26 and HCT116 were used in this study and treated by BDL301 in Vitro. Stat3, p-Stat3, P65, p-P65, COX2 were assessed by Western Blot, proliferation inhibition was tested by CCK8 (Cell Counting Kit-8) experiments. Cell cycle inhibition was investigated by Flow Cytometry. In Vivo studies were done in the Mouse CT26 Tumor Model. Stat3, p-Stat3, P65, p-P65, CD31, VEGF, SHP1, SHP2, IL-6 were investigated in the control and BDL301 treatment groups by Hematoxylin and eosin (H&E), Immunohistochemistry and Western Blot.
Results: Main components of BDL301 were quantified compared with biological reference preparation (BRP) by Agilent 1200 HPLC System. In Vitro, p-Stat3, p-P65, COX2 were down regulated and proliferation of CT26 cells was inhibited by BDL301, while Stat3, P65 has no significant decrease. In Vivo, p-Stat3, CD31, VEGF, IL-6 were investigated to be lower-expressive in the treatment group than the control, accordingly, SHP1, SHP2 were higher. The implantation tumors Weight and Volume of the Mouse CT26 Tumor Models in treatment group were significantly lower. Moreover, angiogenesis was observed to be obviously inhibited in treatment group whose implantation tumors have more apoptosis and necrosis by H&E staining.
Conclusions: We have demonstrated that BDL301 had a significant inhibition of Stat3 Signaling Pathway and angiogenesis in colorectal cancer cells in Vitro and in Vivo. Down regulation of p-P65, COX2 and IL-6 may be taking an important and active effect in the process that should deserve further (pre)clinical evaluation.
No conflict of interest.

509 POSTER

Study of nephrotoxic effects of vincristine treatment in mice

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Background: Vinca alkaloid drugs such as vincristine and vinblastine are known to disrupt microtubule functions of the cell, especially in the mitotic spindle apparatus leading to arrest of cellular mitotic division in metaphase and apoptosis. Hyperuricaemia may occur in some patients receiving vincristine, especially those with non-Hodgkin's lymphomas or leukaemia. According this adverse reaction we evaluated nephrotoxic effect on mice kidney tissue.
Material and Methods: This study was done on 40 adult male mice. Mice were divided randomly into 2 groups (control and treatment). The treatment group received vincristine as I.P in 3 weeks (single dose in each week). In the end mice were scarified and kidney were gathered and fixed to staining with H&E and Masson's Trichorome. Data were analyzed by T-test and SPSS software. There was also a meaningful relation in the statistical analyses of comparing treatment and control group parameters ($p < 0.05$).
Results: According the observations, this drug, Vincristine, induced necrotic effect on proximal convoluted tubules. Epithelial cells of tubules, were seen with hyper chromatin nucleus and hyper eosinophilated cytoplasm and destructions of Brush borders observed too. Furthermore hyaline droplets were observed in collecting ducts. Additionally membranous glomerulopathy and proliferative glomerulonephritis were seen.
Conclusions: The dangers of prescribing these anticancer agents to patients with impaired liver function are always emphasised but hepatotoxicity of these drugs is often overlooked. Entero-hepatic circulation and subsequent elimination may also account for its prolonged elimination. Approximately 8% of the injected dose was excreted in the urine as unchanged vincristine. It was revealed that nephrotoxic effect of the vincristine was obvious as in renal tissue particularly. The existence of proteinuria after vincristine administration is the major consequences of drug induced glomerulopathy. In the end we recommended the massive water taking and co-administration of urocozoric agent for decreasing of nephrotoxic side effects of vincristine.
No conflict of interest.

510 POSTER

Improving discrimination in the grading of rat mammary tumours using low-dimensional mapping of histopathological observations, and advanced modeling techniques

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The Nottingham Grading System defines three groups for invasive tumors, apart from their global heterogeneity, histogenesis and morphology. On tumors with no clear evidence of invasion, increasing concerns related with the comparison between animal models and humans support a deep interest on enhanced histopathology and its improvement by numerical analysis. In this context, is suggested that principal component analysis (PCA) can be central to find new relations, groups and trends using multiple ranged biological parameters. For each animal model, PCA builds up a low-dimensional map that reflects tumoural heterogeneity. This is useful for making a parallelism between pre-clinical and clinical studies. Statistical estimates based on conditional probability and ordinary least squares and logistic regression allow to relate tumor grade, histological patterns and histological parameters.
48 virgin female Sprague Dawley rats were orally induced with a single dose (65 mg/kg) of 7,12-dimethylbenz(a)-anthracene (DMBA) at 50 days of age. At 27 weeks of experiment and a full necropsy and histological evaluation were performed over multiple ranged microscopic parameters of traditional pathology. Statistical, multivariate analysis was carried out resorting to R (version 2.15.3).
A total of 148 mammary tumors were developed in 75% of rats. In the global set 93% of tumoural lesions are invasive carcinomas. Most of invasive tumors are of low and intermediate grade and 12% are high grade tumors.

All non-invasive tumors (benign and in-situ carcinomas) are of grade I. The number of histological patterns present on a tumor tends to correlate with more malignant features. When tumors were grouped according to the number of histological patterns, most of single pattern tumors were of low grade, two and three pattern tumors were almost equally distributed on low and moderate grade. Four and five pattern tumors were high graded. Cribriform pattern is correlated with grading, *i.e*, tumors having a higher predominance of cribriform pattern are likely to be more malignant. Microcalcifications are present in 12% of tumoural lesions and does not relate with tumoural grade. In contrast, necrosis and haemorrhage intensity relate with more malignant tumors, being the latter in a moderate level. The absence of necrosis is associated with low grade tumors. All high grade tumors have inflammatory infiltrating cells usually lymphocytes and eosinophils, but the intensity of these cell populations as well as secretion does not correlate with malignancy grading.
A characterization of mammary tumors based on the proposed analysis reveals new insights behind the pathology. Malignancy discrimination within a specific grade relies on pertinent parameters related with tumour grading and provide a detailed kaleidoscope map of tumour heterogeneity very useful for mammary comparative oncology and mammary tumour model comparison.
No conflict of interest.

511 POSTER

'Ex vivo' culture of human micro-tumors in unfertilised avian eggs

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Background: The quest for more relevant pre-clinical models for testing cancer drug efficacy is a primary focus of cancer research. Current *in vitro* protocols are poor representations of the cancer microenvironment inside the body. The focus of this research study was to evaluate a novel pre-clinical model involving the culture of tumor cells in unfertilised avian eggs. The choice of this experimental system is based on the hypothesis that the avian egg may represent a pre-clinical model of intermediate complexity between the *in vitro* system and the *in vivo* setting that combines essential elements of the *in vivo* system with the simplicity of a highly accessible, stable and quantifiable *'ex vivo'* system to assess tumor biology and drug sensitivity. Fertilised avian eggs inoculated with human tumor cells have been used to assess tumor neo-angiogenesis of the chorioallantoic membrane; to date, there are no reported studies of tumor cells cultured in *unfertilised* avian eggs.
Materials and Methods: Unfertilised avian eggs were inoculated with tumor cells from glioblastoma and juvenile osteosarcoma cell lines in the following procedure: a 1−2 cm opening in the egg shell and membrane was made by small punctured hole on top of the egg. Egg white (albumen) was removed with a syringe and different amounts of media were replaced. Trypsinised tumor cells or tumor spheroids from suspension culture were inoculated into the albumin portion of the egg. Eggs were covered with sterile gauze pads and placed into the incubator where they were incubated at 37ºC with a atmospheric saturation of 5−10% CO_2 from 4 days to 2 weeks. To assay tumor growth, 1 ml of incubated albumin contents were removed with a syringe and placed onto a monolayer culture plate containing standard culture media. After 24 hours the egg contents were observed. Tumor attachment to culture dish substrate and the trypan blue exclusion assay were used as indicators of viability.
Results: Live cell photo microscopy studies showed that both cell lines were capable of proliferation and micro-tumor formation in the albumin component of unfertilised avian eggs when at least 15−20% of the egg albumen was replaced by complete culture medium (RPMI 1640 or DMEM) supplemented with 10% serum. When cells inoculated into avian eggs were transferred to liquid culture, cells were able to reattach and form small cell masses indicative of micro-tumor formation.
Conclusion: This research has shown that two tumor cell lines of diverse tissue type can be successfully cultured in unfertilised avian eggs. This may be the first series of experiments to show the possible use of this system to support the growth of tumor cells. Future studies will attempt to quantify the growth parameters, biological properties and treatment sensitivity of tumor cell lines cultivate in this novel '*ex vivo*'system.
No conflict of interest.

512 POSTER

Effect of zinc supplementation on the expression of metallothionein and p53 in mus musculus with induced metastatic breast cancer

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Background: Zinc is considered an important regulator of apoptosis, cell cycle and oxidative stress and thus is interesting from the perspective of tumour development. The aim of this study was to evaluate the effect of zinc supplementation on metallothionein 1 and 2, metal-regulatory transcription factor 1 (MTF-1) and p53 gene expression on an animal model with induced advanced breast cancer.
Material and Methods: 40 Balb/c female mice were equally distributed to 2×2 groups according to tumor presence (tumour/control) and zinc supplementation (supplemented/not supplemented). 4T1 metastatic breast cancer cell line was used to induce neoplatic process and total 0.15 mg/g zinc sulphate divided in 4 doses was applied to mice. After 1 month, animals were inducted to anaesthesia, the weight and size of tumor was measured and following organs were isolated: primary tumour, brain, liver, lung, spleen, kidney, blood. RNA was isolated and qRT-PCR was performed with b-actin as housekeeping gene. Following TaqMan probes were used: Mm 00485274_m1 Mtf1; Mm 01731290_g1 Trp53; Mm 00496660_g1 Mt1; Mm 04207591_g1 Mt2. Factorial ANOVA with Bonferroni post-hoc test were used for statistical analysis. Animal experiments were approved by Ethic commission Faculty of Medicine, Masaryk University, Brno, CZ.
Results: The tumour size of zinc-treated animals was 40% smaller ($p = 0.04$) in the end of experiment. Significant differences in the gene expression were observed between organs; while significantly highest levels were observed in liver and kidney, significantly lowest levels were determined in primary tumor, lung and spleen. Brain showed significantly elevated expression of MTF-1 and MT2 only. In mice with tumours, hepatic MT-2 and −1 expression increased 22-fold and 3-fold when exposed to Zn treatment ($p < 0.05$). Animals without Zn supplementation did not show similar trend. In kidney, level of MT1 and 2 was significantly lower in cancer mice. When zinc-treated, MT level increased up to the level as in healthy controls. In other tissues there are no such characteristics changes in MT expression.
Conclusions: Zinc supplementation significantly reduces the progression of breast cancer, most likely through metallothionein-mediated pathways. Liver and kidney are tissues with highest zinc turnover, with MT level being decreased in cancer cases and restored up to control level, when treated with zinc.
Acknowledgment: The work has been supported by CEITEC CZ.1.05/1.1.00/02.0068.
No conflict of interest.

513 POSTER

Evidence for a direct relationship between the metabolic profile of tumor cells and their response to ionizing irradiation

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Background and Aim: The Warburg phenotype identified decades ago describes tumor cells with increased glycolysis and decreased mitochondrial respiration even in the presence of oxygen. This particular metabolism also termed 'aerobic glycolysis' reflects an adaptation of tumor cells to proliferation in a heterogeneous tumor microenvironment. Although metabolic alterations in cancer cells are common features, their impact on the response to radiotherapy is not yet fully elucidated.
Material and Methods: We produced Warburg-phenotype tumor cells with impaired mitochondrial respiration (MD) and after characterization of their metabolism we injected subcutaneaously the cells for tumor xenograft. Mice were then imaged with a small-animal PET system for tumor in vivo characterization before irradiation (16 Gy). Tumor regrowth delay was recorded until mean diameter reached 16 mm. We then determined radiosensitivity in vitro by clonogenic survival, analysis of cell cycle distribution, G2/M checkpoint and gamma-H2Ax assay kinetics.
Results: We first confirmed that MD cells were exclusively glycolytic while WT cells exhibited mitochondrial respiration. We then used these cells for assessing the response of WT and MD tumors to a single dose of radiation and showed that the in vivo tumor growth delay of the MD group was increased, indicating therefore an increased radiosensitivity compared to WT. However, in vitro radiation showed that the ability of both

cell lines to repair radiation-induced DNA damage was similar in terms of clonogenic survival and gamma-H2AX clearance, suggesting that the increased radiosensitivity of MD tumors could at least partially be explained by the impaired oxygen consumption of these cells. Therefore, we tested this hypothesis by using different cell lines irradiated in a closed system and obtained a significant positive correlation between survival fraction and respiratory rate.
Conclusion: Our study highlights the impact of the metabolic profile of a tumor on its response to irradiation. In addition, our study provides a rationale for combining antimetabolic therapeutic strategies to radiotherapy in particular if such therapies focus on decreasing the oxygen consumption of tumor cells.
No conflict of interest.

514 POSTER

Cancer cells switch between glycolytic and nonglycolytic phenotype

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Background: Cancer cells typically exhibit the Warburg effect, i.e., aerobic glycolysis that converts between 80 to 90% incoming glucose to lactate as a metabolic waste. However, because of the poor circulation, glucose concentrations in many solid tumors are very low, e.g., the glucose concentrations in non-necrotic regions of colon and stomach cancer are only ~0.1 and ~0.4 mM, respectively. Conceivably, cancer cells in these tumors cannot afford to constantly waste the very limited source of glucose, which supplies not only energy but also building blocks for biosynthesis. We propose that cancer cell can switch between Warburg and nonglycolytic phenotype (economic utilization of glucose), and that lactic acidosis, a common tumor environmental factor, is responsible for the phenotype switch.
Material and Methods: Cancer cells were incubated in the presence or absence of lactic acidosis (lactate: 0−25 mM, pH:6.7−7.4). The following parameters were measured: the rates of glycolysis, lactate generation, and OXPHOS (oxidative phosphorylation); cell growth; intracellular ATP, ADP, AMP; intracellular mass action ratio ([pyruvate][NADH]/[lactate][NAD]); the effects of pH on the kinetics of glycolytic enzymes.
Results: Without lactic acidosis, cancer cells showed typical Warburg effect, which led to accumulation of lactate and proton, creating a lactic acidosis environment, which then led to a decrease of intracellular pH and an increase of intracellular lactate. While acidic pH inhibited glycolytic enzymes and significantly reduced glycolysis, high lactate concentration led to the mass action ratio ([pyruvate][NADH]/[lactate][NAD] approach to the equilibrium constant of this reaction. As a result, cancer cells did not produce or only produce minimal amount of lactate, instead, cancer cells diverted glucose to OXPHOS and biosynthesis. We further demonstrated that lactic acidosis permitted cancer cells proliferate under moderate glucose deprivation that otherwise was unsupportive for cell survival let alone cell growth, and that eradicating the acidosis component of lactic acidosis by elevating intratumoral pH significantly inhibited tumor growth and promoted tumor necrosis in a mouse breast cancer model.
Conclusion: Cancer cells show dualism of glucose metabolism: typical Warburg and nonglycolytic phenotype in the absence or presence of lactic acidosis. The nonglycolytic phenotype is potentially crucial for cancer cell survival and growth in vivo, as it allows cancer cells to use economically the limited supply of glucose in many solid tumors. This metabolic dualism may allow cancer cells to sustain/obtain growth advantage by adapting to dynamic microenvironments with temporal/spatial fluctuations of glucose, lactate and proton levels.
No conflict of interest.

515 POSTER

Chronic intermittent hypoxia triggers adaptive changes that promote protection against cell death

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Introduction: Hypoxia is a common feature of human solid tumors and is considered as one main biological factor driving malignant progression and promoting tumor cell resistance to chemotherapy and radiotherapy. We showed in previous work that chronic intermittent hypoxia drives the evolution of hypoxia-tolerant lung cancer cells that display increased resistance to stimuli of the intrinsic apoptosis pathway. Aim of the present study was to gain further insight into the molecular changes responsible for hypoxia tolerance and to understand the molecular mechanisms that link hypoxic selection to apoptosis resistance.
Methods: Human lung adenocarcinoma cells (NCI H460) were subjected to up to 25 cycles of severe hypoxia (48 h <0.1% O_2) and reoxygenation (120 h 21% O_2). We analyzed tumor cell growth and sensitivity to dihydroartemisinin [DHA] and ionizing radiation. Moreover, we compared gene expression profiles of hypoxia-selected and control cells under resting and stress conditions by microarray analysis. Cell function was determined by measuring apoptosis (SubG1 population), cell death (Propidium iodide [PI] exclusion), mitochondrial potential (Tetramethylrhodamine, ethyl ester [TMRE]), and reactive oxygen species (Dihydroethidium [DHE]).
Results: The hypoxia-selected cells were characterized by decreased sensitivity to radiation-induced apoptosis. Moreover, the hypoxia-selected cells displayed increased resistance to the reactive oxygen donor DHA when treatment was performed under hypoxic conditions. Death resistance was associated with deregulated expression of genes involved in defense against oxidative stress, metabolic regulation, and mitochondrial function under resting conditions and with differential responses to hypoxia or reoxygenation stress.
Conclusions: We speculate that the adaptive changes observed in our hypoxia tolerant tumor cells act in concert to attenuate oxidative damage thereby decreasing sensitivity to cell death in response to (oxidative) stress.
No conflict of interest.

516 POSTER

Pten loss increases pd-l1 protein expression and affects the correlation between PD-l1 expression and clinical parameters in colorectal cancer

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Background: Programmed death ligand-1 (PD-L1) has been identified as a factor associated with poor prognosis in a range of cancers, and was reported to be mainly induced by phosphatase and tensin homolog (PTEN) loss in gliomas. However, the clinical effect of PD-L1 and its regulation by PTEN has not yet been determined in colorectal cancer (CRC). In the present study, we verified the regulation of PTEN on PD-L1 and further determined the effect of PTEN on the correlation between PD-L1 expression and clinical parameters in CRC.
Material and Methods: RNA interference approach was used to down-regulate PTEN expression in SW480, SW620 and HCT116 cells. Tissue microarray immunohistochemistry was used to detect PD-L1 and PTEN in 404 CRC patient samples. The relationship between the expression levels of PD-L1/PTEN and clinical parameters was analyzed. We also investigated the clinical significance of PD-L1 in a subset of 39 patients with PTEN complete loss to explore whether the effect of PD-L1 in CRC is dependent on PTEN expression.
Results: It was showed that PD-L1 protein, but not mRNA, was significantly increased in cells transfected with siRNA-PTEN compared with the negative control. Moreover, the capacity of PTEN to regulate PD-L1 expression was not obviously affected by IFN-γ, the main inducer of PD-L1. Overexpression of PD-L1 was significantly correlated with distant metastasis ($P<0.001$), TNM stage ($P<0.01$), metastatic progression ($P<0.01$) and PTEN expression ($P<0.001$). Univariate analysis revealed that patients with high PD-L1 expression had a poor overall survival ($P<0.001$). However, multivariate analysis did not support PD-L1 as an independent prognostic factor ($P = 0.548$). Univariate ($P<0.001$) and multivariate survival ($P<0.001$) analysis of 310 located CRC patients revealed that high level of PD-L1 expression was associated with increased risks of metastatic progression. Furthermore, the clinical effect of PD-L1 on CRC was not statistically significance in a subset of 39 patients with no PTEN expression (distant metastasis: $P = 0.102$; TNM stage: $P = 0.634$; overall survival: $P = 0.482$).
Conclusions: PD-L1 can be used to identify CRC patients with high risk of metastasis and poor prognosis. This clinical manifestation may be partly associated with PTEN expression.
No conflict of interest.

517 POSTER

Relationship between rest metabolic rate and nutritional, inflammatory status and cancer stage: A prospective observational study in cancer patients

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Background: In cancer patients (pts), evaluating the rest metabolic rate (RMR) could help to improve early nutritional support. However, it remains poorly documented. This study aimed to investigate the correlation between RMR and pts characteristics.
Material and Methods: This observational prospective unicenter study included chemotherapy-naive cancer pts. Before treatment initiation they underwent indirect calorimetry. We recorded the following data: WHO performance status (PS), weight loss, number of metastatic sites, serum albumin and transthyretin levels, C-reactive protein (CRP), ferritin, α-1 glycoprotein acid (α-1 GPA). A Spearman's test was performed to determine correlation between RMR and these parameters.
Results: 140 consecutive pts were included. Median age was 64 years (20−94), 40% were females. Main primary tumors were: genito-urinary (28%), gastro-intestinal (25%) and lung (18%) cancers. 59% of the pts were metastatic, 35% were PS $\geqslant$2. Median percentage of weight loss was 3.0% kg (−33.9–19.0). Mean RMR was 1711.6 kcal/d (922–2605). Mean RMR was significantly higher in metastatic pts: 1775.0 versus 1628.4kcal/d ($p = 0.012$; unpaired t-test). Significant positive correlations were found between RMR and number of metastatic sites ($r = 0.170$, $p = 0.044$), percentage of weight loss ($r = 0.172$, 95% CI [0.006;0.329], $p = 0.04$), inflammatory serum markers: CRP ($r = 0.311$, 95% CI [0.149;0.457], $p < 0.001$), ferritin ($r = 0.239$, 95% CI [0.072;0.396], $p = 0.006$) and α-1 GPA ($r = 0.223$, 95% CI [0.024;0.404], $p = 0.0292$), as assessed by Spearman's coefficient. There were no relationship between RMR and PS, serum albumin and transthyretin levels.
Conclusion: Inflammation and metastatic stage are determining factors of higher energy expenditure in cancer pts. Early nutritional guidance should be provided according to the cancer stage and the inflammatory status.
Conflict of interest: *Advisory board: Fresenius*

518 POSTER

Glucose induced wnt signalling in cancer

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Background: Nuclear accumulation of β-catenin, a widely recognized marker of poor cancer prognosis, drives cancer cell proliferation and senescence bypass. High levels of sugar in plasma, as present in diabetes increase cancer risk enhance the cancer-associated Wnt signalling pathway and promote nuclear accumulation of b-catenin, but whether other dietary components or metabolic intermediates impact on cancer associated signalling pathways is not known.
Material and Methods: Mouse and human intestinal tumour cells were used to study the influence of metabolic intermediates on cancer-associated pathways. Endogenous gene expression was analysed by RT/PCR and chromatin immunoprecipitation. Mechanistic studies were done using a range of mutants from transduction intermediaries. Fractionated extracts, immunofluorescence and immunocytochemistry were used to assess translocation of essential Wnt components.
Results: Here we show that distinct inhibitors of glucose metabolism block the enhancement of Wnt signalling induced by glucose at different levels, including nuclear translocation or transcriptional activity of β-catenin.
Conclusions: Certain metabolic intermediates or suppressors of glucose metabolism block signalling through the cancer-associated Wnt/β-catenin pathway and may provide new compounds and targets for cancer prevention and anti-cancer therapies.
No conflict of interest.

519 POSTER

Cholangiocarcinoma diagnosis and therapy: in vitro studies contribution

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Background: Cholangiocarcinoma (CC) is the second most frequent primary liver tumor. Surgery is currently the only curative therapy. In most cases the CC diagnosis occurs late and patients are conducted to other therapies such as chemotherapy. However, in majority of the cases chemotherapy is palliative. More recently, new drugs for targeted therapies have been developed, including sorafenib, a tyrosine kinases inhibitor. In the diagnosis of malignant lesions some improvements have also been observed, including the development of new radiopharmaceuticals to use in PET, such as ^{18}F-Fluorocholine. Thus, the objectives of this experimental work were to evaluate the effect of various conventional chemotherapy agents and also sorafenib on cell proliferation of a human CC cell line, and also study the ^{18}F-FDG and ^{18}F-Fluorocholine uptake profiles by the same cell line.
Material and Methods: An human CC cell line, TFK1, was used. Cells were incubated with increasing concentrations of cisplatin, doxorubicin, etoposide, 5-fluorouracil (5-FU) and sorafenib during 24, 48, 72 and 96 hours. After, the effect on cell proliferation was evaluated using the MTT assay, in order to calculate the half maximal inhibitory concentration (IC_{50}). Uptake studies using ^{18}F-FDG and ^{18}F-Fluorocholine were performed.
Results: For all the drugs tested, the effect on cell proliferation was time and concentration dependent. The drug with less potential for cell proliferation inhibition was etoposide, with a IC_{50} after 24 hours of incubation of 407μM and after 96 hours of incubation of 14μM. Sorafenib was the drug that showed the best results for shorter incubation times (IC_{50}(24 h)=23μM), being also the drug with which it has obtained the best fit to the kinetic function, which corresponds to a better pharmacokinetic effect. The radiopharmaceutical with higher uptake by the cell line used was ^{18}F-Fluorocholine.
Conclusion: In general, the CC cell line shown to be highly resistant to the drugs used, what is concordant with the disappointing results that chemotherapy usually presents in patients with CC. However, the results obtained with sorafenib were much better that those achieved with other drugs, indicating that tyrosine kinase inhibitors may be a therapeutic option for CC. On the other hand, ^{18}F-Fluorocholine uptake was higher than ^{18}F-FDG uptake, demonstrated that cell proliferation indicator may be more useful for CC diagnosis than the metabolic activity indicator.
No conflict of interest.

520 POSTER

Role of AML-1a/RUNX1 in TRPV2-mediated transcriptional regulation of glioblastoma stem cell (GSC) proliferation and differentiation

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Background: Astrocyte differentiation occurs through the regulation of a variety of transcription factors. Among these, AML1/RUNX1 has been suggested to play a pivotal role not only in definitive hematopoiesis or in embryonic stem cells but also in the development of stem/neural progenitor cells. Microglia, the resident macrophages of the SNC, are associated with the pathogenesis of many stem cell-derived brain tumours. Ontogenetically they derive from primitive myeloid progenitors, and represent a distinct haematopoietic population in the mononuclear phagocyte system. In this regard, we have recently reported that TRPV2 channel promotes both in vitro and in vivo Glioblastoma Stem Cell-Like (GSC) differentiation and inhibits their proliferation (Morelli MB et al., Int J Cancer 2012). However no findings on transcriptional regulation of TRPV channels during astroglial differentiation of GSCs have been provided so far. AML1/RUNX1 coordinates the proliferation and differentiation of olfactory neuron stem/neural progenitor cells, but to date its involvement on GSC progression has not been elucidated. Aim of this study was to elucidate the role of AML-1a in the regulation of TRPV2 expression during GSCs differentiation.
Materials and Methods: Chromatin immunoprecipitation assay was used to detect the binding of AML-1a with TRPV2 promoter. Short-interfering

RNA was performed to silence AML-1a in GSCs during differentiation and Real Time PCR was performed to verify AML-1a silencing. Western blot analysis and bromodeoxyuridine incorporation assays were used to detect protein expression and cell proliferation respectively.
Results: We demonstrated that AML-1a is efficiently recruited onto TRPV2 target gene promoters following GSC differentiation, indicating that AML-1a is involved in TRPV2-mediated transcriptional regulation during GSC differentiation (Morelli MB et al. Int J Cancer 2012). Indeed, forced down-regulation of AML-1a by gene silencing inhibits transcriptional activity of TRPV2 in response to differentiation and reduces differentiation marker expression level (e.g. GFAP). Moreover, we observed that knockdown of AML-1a increases GSC proliferation.
Conclusions: Taken together, our data suggest that AML-1a is required for the stimulation of TRPV2 in response to GSC differentiation and also provide novel insight into understanding the molecular mechanisms behind TRPV2 transcriptional regulation.
No conflict of interest.

521 POSTER

Strategies targeting fusion machinery of bone marrow derived macrophage may ameliorate intestinal fibrosis after radiation

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Background: Bone marrow (BM) cells could repopulate damaged tissue and contribute to repair in non-hematopoietic tissues. Our previous observations demonstrated that the mitigating effect to intestine after acute radiation damage was achieved through paracrine mediators released by BM cells. Maximal appearance of BM cells, however, occurred long after intestine mucosa recovered from radiation damage. Recent studies revealed cell fusion between BM and somatic cells were enhanced by chronic inflammation. There was a significant role of BM cells in triggering fibrotic responses and contributing to liver and renal fibrosis. We would like to explore the association between cell fusion and intestine fibrosis after radiation.
Material and Methods: Using gender-mismatched BMT and BMT from GFP mice donors, we quantified the fusion phenomenon within intestine of mice after irradiation. By using pravastatin, an HMG Co-A reductase inhibitor, to diminish intestine fibrosis after WBI, we evaluated the proliferation and fusion phenomenon as well as fusion signaling proteins (macrophage fusion receptor (MFR) and CD47) and fibrosis markers (CCN2, fibronectin, collagen). Using immunohistochemical study and isolated CD11b(+) BM cells for BMT, we evaluated the major BM derived cells contributing to the fusion phenomenon. Clodronate liposome was used to deplete macrophage/myelomonocytic cells in mice as BMT donors. Anti-cell fusion strategies including MMP9 inhibitor, Rac 1 inhibitor and MFR RNA silencing were used to suppress fibrotic protein expression of co-culture between intestine stromal and BM cells.
Results: BM cells fused with intestine stromal cells after BMT to mice after WBI. The maximal fusion phenomenon occurred before significant level of fibrosis appeared within intestine of mice after WBI+BMT. Pravastatin suppressed intestine fibrosis and fusion phenomenon of mice. The cell fusion protein expression and the proliferation index within fused cells were also decreased by prvastatin. BM derived macrophage/myelomonocytic cells contributed majorly to the fusion phenomenon. Treatment with MMP9 inhibitor, Rac 1 inhibitor or MFRsiRNA during co-culture between BM and intestine stromal cells suppressed fibrosis protein expression. Intestine mucosa lysates from mice receiving clodronate liposome after WBI and BMT revealed decreased cell fusion and fibrosis in histology as well as in biochemical examination.
Conclusions: Fusion between BM and intestine stromal cells is associated with chronic intestine fibrosis after radiation. The fusion phenomenon can be diminished by anti-fibrosis agent. Intestine fibrosis may be ameliorated by depleting macrophage/myelomonocytic cells as well as strategies against fusion machinery.
No conflict of interest.

522 POSTER

RANK induces epithelial–mesenchymal transition and stemness in human mammary epithelial cells and promotes tumorigenesis and metastasis

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Background: Paracrine signaling through RANK pathway mediates the expansion of mammary epithelia that occurs during pregnancy and activation of RANK pathway promotes mammary tumorigenesis in mice. The objective of this study is to analyze the effect of RANK overexpression in human mammary epithelial cells.
Materials and Methods: Human RANK was overexpressed by lentiviral infection in non-transformed human mammary cells and tumoral BRCA1 deficient cells. Then, we analyzed the role of RANK in:
– Stemness: we analyzed stem cells markers by flow citometry, stem cells transcription factors by QRT-PCR and functionality by mammary reconstitution assays.
– Epithelial–mesenchimal transition (EMT): we measured the levels of epithelial/mesenchimal markers by QRT-PCR and immunofluorescence, EMT transcription factors by QRT-PCR and migration capacity by Wound-Healing.
– Tumorogenesis: we performed in vitro assays like 3D cultures and foci assays, and in vivo assays by injection of these cells in immunodeficient mice.
– Clinical samples: we analyzed RANK and RANKL mRNA expression levels by QRT-PCR in human adenocarcinomas considering their pathological characteristics.
Results: Overexpression of RANK induces the expression of breast cancer stem and basal/stem cell markers in tumoral and normal human mammary cells. High levels of RANK in untransformed MCF10A cells induce changes associated with both stemness and transformation including mammary gland reconstitution, epithelial–mesenchymal transition, increased migration and anchorage independent growth. In addition, spheroids of RANK-overexpressing MCF10A cells displayed disrupted acinar formation, impaired growth arrest and polarization, and luminal filling. RANK overexpression in tumor cells with non functional BRCA1, enhances invasiveness in acinar cultures and increases tumorigenesis and metastasis in immunodeficient mice. High levels of RANK were found in human primary breast adenocarcinomas that lack expression of the hormone receptors, estrogen and progesterone, and in tumors with high pathological grade and proliferation index; high RANK/RANKL expression was significantly associated with metastatic tumors.
Conclusions: RANK promotes tumor initiation, progression and metastasis in human mammary epithelial cells by increasing the population of CD44+CD24− cells, inducing stemness and epithelial mesenchymal transition. These results suggest that RANK expression in primary breast cancer associates with poor prognosis.
No conflict of interest.

523 POSTER

The effect of salinomycin and analogs on breast cancer stem cells

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Background: Agents that selectively target cancer stem cells (CSC), either by selective inhibition or by induction of a phenotypical change, have attracted considerable attention recently as a new venue to minimize recurrence and/or metastasis of cancer. A study by Gupta *et al*. details that out of a library comprising over 16000 compounds, the naturally occurring ionophore antibiotic salinomycin was the most selective in reducing the relative proportion of cells with the CD44+/CD24− phenotype associated with CSC properties. We have synthesized a unique library of presently 30 structurally distinct synthetic analogs of salinomycin. The potency and selectivity against CSCs have been evaluated in JIMT-1 breast cancer cells.
Materials and Methods: Potency was evaluated as the inhibitory concentration 50 (IC50) deduced from dose response curves obtained using an MTT 96-well assay. Selectivity was studied by investigating the effect of treatment with the compounds on the putative CSC CD44+/CD24− cell population by flow cytometry. Selectivity was also investigated by determining the colony forming efficiency (CFE) in a serum free soft agar assay.
Results: Chemical modification of salinomycin resulted in analogs with higher or lower IC50 than salinomycin. The IC50 of salinomycin was 0.59 μM and 0.16 μM for the analog with the highest potency. At a 0.05 μM concentration, salinomycin did not affect the CSC population. On the other hand, some of the analogs reduced the CD44+/CD24− population by almost 80% and the CFE was around 50% of control.
Conclusions: Chemical modification of salinomycin results in analogs with higher potency *i.e*. lower IC50 and increased selectivity to CSCs at a low dose.
No conflict of interest.

524 POSTER

Evidence of an association of mRNA expression of inhibitors of DNA binding 1 and 2 with advanced tumour stage and adverse clinical outcome in human breast cancer

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Background: Inhibitors of DNA binding (ID) are known to have a role in embryogenesis, cancer stem cell renewal, and oncogenesis. In this study, we studied the role of ID1 and ID2 in breast cancer, by assessing associations of mRNA expression with clinicopathological parameters.
Materials and Methods: Breast cancer tissues (n = 152) and adjacent normal tissues (n = 31) underwent reverse transcription and quantitative polymerase chain reaction (qPCR). Transcript levels were correlated with clinicopathological data.
Results: *ID1* mRNA expression was found to be increased in breast cancer samples. Its expression was significantly associated with adverse clinical outcomes. This was highly significant when comparing patients who had no recurrences over a decade of follow-up with those with disease-related mortality ($p = 0.0169$), and when comparing patients who were disease-free with all other patients ($p = 0.0033$).
The Kaplan–Meier plot analysis demonstrated that patients with higher *ID1* mRNA expression had reduced disease-free ($p = 0.001$) and overall ($p = 0.02$) survival.
ID2 expression was also found to be directly associated with breast cancer. *ID2* expression was significantly increased with higher NPI scores (NPI 2 *vs*. 3; $p = 0.0062$).
Mean and median *ID2* copy numbers were also significantly increased with advanced disease. This attained highest significance when comparing patients who were disease-free during follow-up with those with disease related mortality ($p = 0.0004$).
A similar, albeit insignificant, association was seen between *ID2* expression, tumour grade and TNM stage.
This was further illustrated by the Kaplan–Meier plot analysis, in which higher *ID2* mRNA expression was associated with worse disease-free ($p = 0.01$) and overall ($p = 0.005$) survival.
Conclusion: Our findings are suggestive of a role for ID1 and ID2 in human breast cancer as possible prognostic markers and therapeutic targets meriting further validating investigations, including immunohistochemistry and mechanistic studies.
No conflict of interest.

525 POSTER

Cancer stem cells in lung cancer: The resident evil!

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Background: Cancer is a major public health problem affecting millions of new individuals each year. Recent research emphasized the major role of cancer stem cells (CSCs) in the metastatic disease, the main cause of cancer patients' mortality. CSCs drive tumorigenesis and differentiation, contributing to tumors' heterogeneity and to their therapy resistance and eventually relapse. Albeit targeted therapies have been developed, CSCs can reemerge by stromal-induced dedifferentiation through mechanisms still unclear.
Materials andMethods: Various cell culture techniques allowed the establishment of 4 cell lines out of the non-malignant human bronchial epithelial system BEAS-2B. Cells' characterization involved cytogenetic and flow cytometry tools, metabolic studies with [^{18}F]fluoro-2-deoxyglucose(^{18}FDG) and nuclear magnetic resonance (NMR) spectroscopy, real time PCR and immunocitochemistry. Sphere-formation assay was used to isolate CSC-sand co-cultures and cytokine multiplex arrays to disclose dedifferentiation.
Results: BEAS-2B was malignantly transformed into the RenG2 using low density culture in the presence of hexavalent chromium [Cr(VI)]. Under the same conditions, though inthe absence of Cr(VI), Cont1 was also produced. Two derivative cell lines (DRenG2 and DDRenG2) were attained following sub-cutaneous (*s.c.*) injection of xenograft RenG2 and DRenG2 cells, respectively. Metabolic studies using ^{18}FDG and NMR spectroscopy performed in all cell lines revealed a more glycolytic phenotype for the derivatives (DRenG2 and DDRenG2), compatible with a quiescent phenotype. CSCs' presence hypothesis was strengthened by the identification and characterization of different cellular sub-populations within each cell line, with different karyotype and real time PCR-based signatures. The sphere-formation assay revealed the presence of CSCs only in DRenG2 and DDRenG2 cell systems, suggesting that a dedifferentiation process featured the formation of CSCs during RenG2 derivation in nude mice. The involvement of mice stroma in this process was uncovered by surgical isolation of mouse stromal cells of the *s.c.* compartment and subsequent co-culture with RenG2 cells, which resulted in the emergence of aCSCs sub-population. A cytokine multiplex array analysis using the conditioned medium of the co-cultured cells revealed the paracrine orchestrators of this stromal-induced dedifferentiation process.
Conclusions: The dedifferentiation process observed in the derivation of RenG2 cell line in the mice lumbar region was driven by paracrine signalization released from mice stromal cells. These results, more than highlighting the role of stromal cells in tumor formation, classify the dedifferentiation process as essentially chemical and specie-unspecific, as human cells can respond to mice cells-released molecules.
No conflict of interest.

526 POSTER

Molecular signature and functional features of cancer stem cells isolated from prostate cancer tumors

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Background: Prostate cancer (PCa) is a leading cause of male oncologic death wideworld. Metastasis, recurrence and hormone-drug resistance are the main issues of this disease. Cancer stem cells (CSCs) have been identified in several cancers including PCa and are believed to be responsible for cancer dissemination. For this reason, CSCs are being extensively studied, mainly in cell lines models, as possible therapeutic targets. In previous report we have correlated stem markers with Gleason grade using tissue micro array and have developed a method for isolation, enrichment and culture of CSCs from tumor explants.
Materials and Methods: CSCs were isolated from PCa tumor samples through combined methods of differential cloning capacity, sphere growing induction and Magnetic-Associated Cell Sorting (MACS). Molecular markers were determined by qPCR-array, immunocitochemistry and immunofluorescence. Functional characterization was assessed by migration, drug resistance, proliferation and apoptotic assays. An orthotopic model of PCa was established in NOD/SCID immuno-compromised mice for metastasis evaluation using in vivo imaging methods. Protocols were approved by institutional Ethics Commitees.
Results: Molecular signature of CSCs from tumor explants was CD133+/CD44+/ABCG2+/Integrin$\alpha 2\beta 1$+/Oct3/4+/SOX2+/CD24−. CSCs showed increased migration capacity, decreased proliferation an apoptosis rate and high drug resistance compared with a non-stem PCa cell population. Metastatic capacity included lung, liver and kidney dissemination.
Conclusions: Enriched populations of CSCs from PCa patients show a signature with high expression of stem genes. These genes may represent appropriate diagnostic and prognostic markers as well as new therapeutic targets for PCa. Orthotopic model of human PCa in NOD/CSID mice represent a suitable model to evaluate metastasis and recurrence of PCa.
Funding: Projects Fondecyt 1100183 and U-Moderniza U-MOD-02, VID, U. Chile.
No conflict of interest.

527 POSTER

The binding of translationally controlled tumour protein to HDM2 is inhibited by Nutlin-3

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Background: Translationally Controlled Tumour Protein (TCTP) has a number of key functions including an anti-apoptotic role. Recently, TCTP was shown to interact with the tumour suppressor p53 and the ubiquitin ligase HDM2, inhibiting auto-ubiquitination of the latter, thereby promoting p53 degradation. Nutlin-3, a small molecule known to promote apoptosis and cell cycle arrest by blocking HDM2-p53 binding, has also been shown to inhibit TCTP's effects on HDM2. We investigated the interaction between TCTP and HDM2, mapping their reciprocal binding sites and observing the effect of Nutlin-3 on their interactions.

Material and Methods: Interactions between HDM2 and TCTP and the effects of Nutlin-3 were investigated using pull-down assays with both *in vitro* expressed and recombinant proteins. Peptides derived from putative interaction sites were also used in pull-down experiments. Cellular interactions were assessed in the HCT116 $p53^{-/-}$ and H1299 $p53^{-/-}$ cell lines by immunoprecipitation. Western blotting was used to identify interacting proteins.
Results: Using C-terminal deletion analysis, we mapped TCTP's HDM2 interaction site to within residues 80–133 corresponding to basic domain 2. C-terminal deletion analysis of HDM-2 showed that the N-terminal region alone was sufficient for interaction with TCTP, with residues 44−65 proving key. This region is also crucial in HDM2's interaction with p53. A p53 peptide, corresponding to part of the p53 transactivation domain that interacts with HDM2's N-terminal region, was shown to compete with TCTP for HDM-2 binding. Nutlin-3 produced a dose responsive inhibition of TCTP-HDM2 binding *in vitro* and abrogated endogenous TCTP-HDM2 interaction.
Conclusions: The value of modulating p53−HDM2 interactions as a target for cancer therapeutics is an area of great activity. The discovery that TCTP has a binding site on HDM2 which overlaps with that of p53 and that they compete for binding *in vitro*, adds further complexity to the p53−HDM2 interaction model. We found that Nutlin-3, currently undergoing clinical trials, competes with TCTP for binding to the p53-binding cleft in the N-terminus of HDM2. This finding should influence future studies looking at the effects of Nutlin-3 and related compounds.
No conflict of interest.

528 POSTER

Senescence sensitivity of breast cancer cells is defined by positive feedback loop between CIP2A and E2F1

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Background: Senescence induction contributes to cancer therapy responses and is crucial for p53-mediated tumor suppression. However, whether p53 inactivation actively suppresses senescence induction has been unclear. CIP2A (cancerous inhibitor of protein phosphatase 2A) is an oncoprotein that has been shown to overexpress in several human cancer types. Nevertheless, the *in vivo* relevance of CIP2A in cancer has been obscure.
Materials and Methods: In order to study the role of CIP2A in breast carcinogenesis *in vivo* CIP2A heterozygous genetrap hypomorphic mutant mice were crossed with MMTVneu mice expressing oncogenic HER2. To study the role of CIP2A in either Nutlin-3-, vinorelbine- or p21-induced senescence stable expression of CIP2A in human breast cancer cell lines was introduced with adenoviral delivery. Also, two different cohorts of human breast cancer tumor samples were immunostained for CIP2A in order to investigate the expression levels and the prognostic role for CIP2A in breast cancer.
Results: Here, we show that E2F1 overexpression, due to p53 or p21 inactivation, promotes expression of human oncoprotein CIP2A, which in turn, by inhibiting PP2A (protein phosphatase 2A) activity, increases stabilizing serine 364 phosphorylation of E2F1. Several lines of evidence show that increased activity of E2F1-CIP2A feedback renders breast cancer cells resistant to senescence induction. Importantly, mammary tumorigenesis is impaired in a CIP2A-deficient mouse model, and CIP2A-deficient tumors display markers of senescence induction. Moreover, high CIP2A expression predicts for poor prognosis in a subgroup of patients with breast cancer treated with senescence-inducing chemotherapy.
Conclusions: Together, these results implicate the E2F1-CIP2A feedback loop as a key determinant of breast cancer cell sensitivity to senescence induction. This feedback loop also constitutes a promising prosenescence target for therapy of cancers with an inactivated p53−p21 pathway.
No conflict of interest.

529 POSTER

Rapid and extensive CD40-mediated cytotoxicity in colorectal carcinoma cells by death-receptor cross-talk: Identification of a novel apoptotic pathway involving TRAIL-induced, caspase-10-mediated cell death

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Background: Their ability to induce apoptosis in carcinoma cells renders TNF Receptor (TNFR) superfamily members promising targets for cancer therapy. However, clinical findings have highlighted the need for a better understanding of their underlying mechanisms of action, if these molecules are to be suitable for therapy. We have previously shown that CD40, unlike classical 'death' TNFR members, such as Fas, TNFR and TRAIL-R, does not have a death domain, yet can uniquely induce apoptosis in carcinoma but not normal cells by activation of an intrinsic caspase-9/JNK-mediated apoptotic pathway. CD40 ligation by its cognate ligand in a membrane-presented form (mCD40L) has the ability induce extensive apoptosis in colorectal carcinoma (CRC) cells, however the mechanism of death is unknown.
Materials and Methods: We used CRC lines that naturally express CD40 and cells in which *de novo* CD40 expression was engineered by retroviruses. CD40 was activated by mCD40L via co-culture with growth-arrested, mCD40L-expressing third party cells. Apoptosis was quantified by fluorescence- and luminescence-based assays detecting cell membrane integrity and caspase-3/7 activation. Expression and localisation of CD40 adaptor proteins and intracellular apoptotic mediators was determined by immunoblotting and combined with cell fractionation.
Results: mCD40L caused extensive and extremely rapid apoptosis (<6 hrs) in CRC cells. This is unlike our previous findings in other carcinoma types and suggested of a novel mechanism of action. We show that early after ligation there was rapid induction of TRAF3/6 adaptors (<1.5 hrs), phosphorylation of p38 and JNK (<3 hrs) and Bax/Bak recruitment to mitochondria (<6 hrs). We found induction of intracellular TRAIL, but not FasL, which in turn drives apoptosis by activation of caspase-10, but not caspase-8. The pro-apoptotic cross-talk is not only at the receptor level but also at an intracellular pathway level, as we detected tBid formation (1.5 hrs) and functional studies showed that activation of both caspase-10 and −9 was critical in apoptosis. Pharmacological blockade of p38/JNK abrogated TRAIL induction, Bax up-regulation, caspase activation and death.
Conclusion: We show for the first time that in CRC cells CD40 triggers rapid and dramatic cytotoxicity via a novel, multi-level cross-talk mechanism which involves p38/JNK-mediated TRAIL induction that activates the caspase-10 and −9 axes to cause extensive and rapid CRC cell death.
No conflict of interest.

530 POSTER

Concomitant detection indicates differential expression of miR-21 and PDCD4 in breast lesions

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Background: Programmed cell death 4 (PDCD4) or neoplastic transformation inhibitor, is a protein located in the nuclei of proliferating cells. A sequence motif in the 3'UTR of the PDCD4 mRNA contains a potential microRNA (miR)-21binding site, suggesting that PDCD4 biosynthesis is regulated at the post-transcriptional level by miR-21. Several studies of cultured cells have suggested that PDCD4 is an *in vivo*target of miR-21. If this is the case, PDCD4 and miR-21 must be present in the same cell population at a transitional stage. In breast cancer, PDCD4 is predominantly expressed in the cancer cells in contrast to miR-21, which is predominantly expressed in stromal cells. This differential expression, however, may not be explained by higher miR-21 activity of the latter, since PDCD4 may not be part of the regulatory repertoire of stromal cells. MiR-21, on the other hand, can be seen in some breast cancer cells, mostly from high-gradetumors, allowing an evaluation of the differential expression of PDCD4 andmiR-21.
Material and Methods: To explore this possibility, we developed a multiplex fluorescence assay (DAPI, FITC, Cy3 and Cy5), which combines immunohistochemistry with microRNA in situ hybridization for simultaneous detection of PDCD4, miR-21 and a cell-type specific marker in tissue sections. Seven high-grade in situ carcinoma/early invasive cancers were examined.
Results: In five cases, miR-21 was predominant in stromal cells, whilemiR-21 expression in cancer cells or benign epithelial cells was sparse.

In one case, miR-21 was seen in focal clusters of cancer cells, and in another casemiR-21 was seen exclusively in cancer cells. PDCD4 immunohistochemical staining was prevalent in both malignant and benign epithelial cells, and in the case with miR-21 positive cancer cells these were negative for PDCD4. In the case with focal clusters of miR-21 positive cancer cells, a miR-21 signal was accompanied by weakly stained or PDCD4-negative cells, where as PDCD4 positive cells were often miR-21 negative. Similar differential expression patterns were observed in both benign glands and in CIS foci, though co-expression of PDCD4 and miR-21 was occasionally seen.
Conclusion: We show that multiplex assays allow confirmatory evaluation of expression of microRNAs and their target protein *in vivo*, as here exemplified by PDCD4 and miR-21.
Conflict of interest: *Other substantive relationships: BSN, TRM and KHO are full term employee at the contract research organization (CRO): Bioneer A/S, Denmark*

531 POSTER

ROS-mediated, ASK1/MKK4-dependent apoptosis induced by CD40 ligation: Development and pre-clinical testing of a novel, highly pro-apoptotic, tumour cell-specific combinatorial therapy

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Background: We were the first to show that CD40 ligation by membrane ligand (mCD40L), but not soluble agonist, triggers extensive apoptosis in carcinoma cells, whilst sparing their normal epithelial counterparts. However, the need to deliver the CD40 signal by presentation of membrane-bound agonist poses important therapeutic obstacles. Our aim was to identify the signalling mechanisms that render mCD40L tumour-specific and exploit this knowledge to design novel CD40-based therapies.
Materials and Methods: We used our human uro-epithelial model to culture normal, para-malignant and tumour-derived carcinoma cell lines. CD40 was activated by mCD40L (co-culture with mCD40L expressing third party cells) or soluble agonist (recombinant CD40L or agonistic antibody). Reactive oxygen species (ROS) generation was detected using H2DCFDA and apoptosis quantified using assays detecting membrane integrity and caspase activation. Expression and localisation of intracellular apoptotic mediators was determined by immunoblotting and the functional role of identified proteins confirmed by stable shRNA-mediated knockdown.
Results: CD40 ligation by mCD40L recruited TRAF3 to trigger phosphorylation of ASK1 and MKK4-mediated JNK activation and induced Bax/Bak-driven apoptosis in tumour cells. This was dependent on up-regulation of NADPH oxidase (Nox) and rapid elevation of intracellular ROS levels, as pharmacological inhibition of both Nox and ROS abolished CD40-killing. As mCD40L but not soluble agonist elevated ROS, we tested whether pharmacological interference with the related endogenous antioxidant pathway of Thioredoxin (Trx) could render the soluble agonist pro-apoptotic. We show that Trx blockade dramatically sensitised malignant, but not normal cells, to CD40 ligation by soluble agonists and induced death to a level equivalent to that observed for mCD40L and in a tumour cell-specific fashion.
Conclusion: Unravelling for the first time the molecular nature of the CD40 signalling 'black-box' has permitted the design of a combinatorial approach involving use of soluble CD40 agonist in parallel with sub-cytotoxic doses of Trx pharmacological inhibitor. The inhibitor has conferred the non-apoptotic soluble CD40 agonist the capacity to sufficiently trigger the required pro-apoptotic 'ROS threshold' and induce apoptosis. This novel approach is tumour-specific and as highly pro-apoptotic as mCD40L, thus negating the need for complex mCD40L delivery strategies.
No conflict of interest.

532 POSTER

BP-C1, a new therapeutic compound for the treatment of cancer

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Background: Breast cancer is the most frequent malignancy in women in western countries and despite progress in the treatment options such as surgery, radiation, chemotherapy and hormonal therapy it is still the leading cause of cancer death. BP-C1 is a novel anti-cancer complex of benzene-poly-carboxylic Acids with Cis-diammineplatinum (II) developed by Meabco ltd, Denmark. The aims of the present study are to give a clinical overview and the preclinical mechanism of action data obtained so far.
Methods: The effect of BP-C1 on growth of human breast cancer cells, MCF7 and T47D, was studied. Cells were exposed to different doses of BP-C1,and cell viability, toxicity (LDH release), cell cycle, apoptosis, caspase activation and gene expression were examined. The effects on immune modulating properties were studied *in vitro* and *in vivo*. A Phase I dose escalating study in 15 metastatic breast cancer patients (Stage IV) was conducted to determine treatment routine, Maximum Tolerated (MTD) and Minimum Efficient Dose (MED) of BP-C1.
Results: BP-C1 reduced cell viability by 90%, induced apoptosis by activation of caspases 8 and 9, increased the pro-apoptotic genes and lowered levels of mRNA transcripts of some inhibitory apoptotic genes. Cytokines were significantly increased by BP-C1: IL-1beta, TNF-alpha, GM-CSF, IFN-gamma, and IL-25. IL-6 production was also found. The primary targets for the reagent are monocytes. No toxicity of BP-C1 was seen after IM administration daily during a period of 32 days. BP-C1 can safely be administrated intramuscularly daily during a period of 32 days. Based on the RECIST criteria, 7 patients were classified as responders: 1 complete response, 2 partial responses and 4 stable disease. The cumulative MTD is most probably larger than 1.12 mg/kg/Body Weight [BW] and MED estimated to 0.96 mg/kg/BW.
Seven out of 15 patients were classified as responders. The cumulative MTD is most probably larger than 1.12 mg/kg/BW and MED estimated to 0.96 mg/kg/BW.
Conclusion: BP-C1 induced apoptosis through activation of the extrinsic (death receptors) and the intrinsic (mitochondrion) apoptotic pathways. BP-C1 activated multiple immunological mechanisms of anti-tumour response. These findings have been confirmed in patients and may lead to the development of new therapeutic strategies for treatment of advanced cancers using BP-C1.
No conflict of interest.

533 POSTER

Regulation of breast cancer cell growth and migration by the steroid-converting enzyme 17-beta-HSD 1

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Background: Estradiol (E2), the most potent estrogen, stimulates breast cancer cell growth, whereas the androgen dihydrotestosterone (DHT) has shown an antiproliferative effect. In breast cancer cells, E2 is principally synthesized by human 17beta-hydroxysteroid dehydrogenase type 1 (17-beta-HSD 1), a steroid-converting enzyme that also inactivates DHT. Here, the role of 17-beta-HSD 1 in the regulation of breast cancer cell proliferation and its impact on cell migration are shown.
Material and Methods: RNA interference technique was used in conjunction with a steroidal inhibitor of 17-beta-HSD 1 to establish its direct role in DHT and E2 level modulation in breast cancer cell lines T47D and MCF-7 and the regulation of cell proliferation was evaluate by MTT assay. 17-beta-HSD 1 was further stably transfected in MCF-7 and the effect of the enzyme on MCF-7 cell migration was verified by a wound-healing assay using the generated cells overexpressing 17-beta-HSD 1 and the wild type MCF-7 cells.
Results: 17-beta-HSD 1 expression is negatively correlated to DHT levels in breast cancer cell but positively correlated to E2 levels and cell proliferation. 17-beta-HSD 1 inhibition reduces DHT inactivation, increasing the antiproliferative effect by DHT in T47D cells after 8-day treatment. Thus, 17-beta-HSD 1 up-regulates BCC growth by a dual action on estradiol synthesis and DHT inactivation. Increasing 17-beta-HSD 1 expression lead to an increase by 3.6 times of the mRNA transcript and the protein expression of the metastasis suppressor gene nm23-H1 and the expression of the two enzymes are closely correlated. Intriguingly, 17-beta-HSD 1 expression is positively correlated with the migration of the breast cancer cell line MCF-7, revealing its role as a positive regulator of cell migration, contrary to nm23-H1.
Conclusions: In spite of its positive regulation of the antimetastatic gene *NM23*, 17-beta-HSD 1 increases cell migration and significantly contributes to the proliferation of some breast cancer cells. These findings strongly support the rationale for inhibiting 17-beta-HSD 1 in breast cancer therapy.
No conflict of interest.

534 POSTER

Negative regulation of death receptors expression on cancer cells by epithelial–mesenchymal transition (EMT)

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Background: Death receptors (DR) are involved in the induction of TRAIL or Fas-mediated extrinsic apoptosis. DR agonist antibodies are currently assessed in clinical trials in pancreatic carcinoma. Tumor cells, which undergo epithelial–mesenchymal transition (EMT), acquire increased capacities of proliferation, invasion and have the ability to generate metastases. We have previously shown that Neuropilin-2 (NRP-2) promotes transforming growth factor-β1-mediated EMT and tumor cell proliferation. In the current study, we investigated the influence of NRP2-mediated EMT in immune evasion.
Methods: pCDNA3.1 plasmids were used to induce NRP2 or snail gene expression in HT29 or BxPC3 cells. Bes-PAC cell lines are tumor cells derived from patient's ascites in Besançon university hospital. All cell lines were cultured in DMEM complete medium. DR4, DR5, Fas antibodies were purchased from Diaclone-biotech. Anti-E-cadherin or Vimentin were purchased from RnDsystem.
Results: The sensitivity of pancreatic and colorectal carcinoma to DR agonist antibodies was investigated in vitro. By contrast NRP-2-negative cell lines, NRP-2^+ cancer cells were resistant to apoptosis induced by DR agonists. Then, the expression of DR on pancreatic cancer cells was investigated by western blot and flow cytometry. A negative correlation was observed between DR and NRP2 expression. The transfection of NRP2 in HT29 cell lines induced a complete loss of DR expression. Since NRP-2 mediates EMT, we decided to analyse the precise role of EMT in DR regulation. Then, EMT was induced by gene transfer of snail in epithelial cell lines (BxPC3 and Bespac07). Snail-induced EMT was also correlated to a complete loss of DR expression in these cell lines. Considering that Snail is not expressed in NRP2^+ cells, we decided to investigate the role of p53 and the NF-κB subunit RelA, two transcriptional regulators of DR expression. We first observed that EMT induces in all cell lines tested a loss of both p53 and RelA. However, the restoration of p53 and RelA expression in NRP2^+ cell lines did not restore DR expression.
Conclusion: These results show that EMT represses DR expression in a p53 and RelA independent manner. The negative regulation of death receptors DR4, DR5 and Fas by EMT can be identified as a mechanism of resistance to death receptors based therapies; this should be taken into account to better identify patients eligible for DR agonist therapies.
No conflict of interest.

535 POSTER

Regulation and role of CCAAT/enhancer binding protein during differentiation of intestinal epithelial cells

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Background: The molecular mechanisms of differentiation of intestinal epithelial cells, is poorly understood and disruption of this balance may result in neoplastic transformation and malignant growth. The family of CCAAT/*E*nhancer *B*inding *P*rotein (C/EBP) transcription factors is implicated in cellular growth, differentiation, inflammation and development and control differentiation in several cell types. The involvement of these transcription factors in intestinal differentiation is not known. The aim of this study is to elucidate the transcriptional, translational and post-translational regulation of C/EBP proteins and their role during the course of intestinal epithelial differentiation.
Materials and Methods: The colorectal cancer cell line Caco-2, a well established differentiation model, was used. The expression of C/EBP genes was analyzed using publicly available microarray data. The protein levels and the phosphorylation status of translation initiation factors were checked by Western blot. The activity of C/EBP was determined by luciferase reporter and chromatin immunoprecipitation assays. Cytoplasmic calcium levels were determined fluorometrically by calcium binding with Fura-2AM.
Results: Microarray data analyses of Caco-2 differentiation have shown that C/EBPα and β expression increases during differentiation. The major regulatory mechanism for C/EBP proteins is translational in which several isoforms are produced from alternative translation initiation sites. The ratio of the two isoforms C/EBPβ1 to C/EBPβ3 was found to be decreasing in differentiated Caco-2 cells. This change could be explained by the increase in the active translation initiation factor eIF2α. The activity of C/EBP was shown to increase together with an upregulation of its target genes. The post-translational regulation was investigated by determining SERCA-3 (less affinity to calcium) levels and was shown to decrease. This lead to an increase in the cytoplasmic calcium levels which in turn may cause activation of calcium dependent calmodulin kinase II, hence increase in C/EBP activity.
Conclusions: In this study the involvement of C/EBP proteins in intestinal epithelial differentiation was investigated for the first time. We believe that the findings of this research would reveal important mechanisms underlying the intestinal differentiation-dedifferentiation processes and provide some candidate therapeutic targets for the prevention and treatment of colorectal cancer.
No conflict of interest.

536 POSTER

Modulation of genes expression as an effective tool for enhancing the antitumor effect of death ligands. Novel IFN-gamma − TRAIL/Apo2L fusion protein

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Background: Interferon gamma (IFN-γ), a dimeric soluble cytokine, is an representative of type II interferons family. The molecule is secreted by NK, NKT, Th1, Tc and dendritic cells. IFN-γ ligand binds to two types of IFN-γ receptors and activates the JAK-STAT pathway.
IFN-γ anti-tumor action is mediated through the immunomodulatory function which results from the action of many different classes of IFN-stimulated genes responsible for antigen processing, leukocyte trafficking and tumor cytotoxicity. IFN-γ stimulates antibody-dependent toxicity and potentiates the process of connecting the cells with tumor cells. Additionally, IFN-γ is able to induce an anti-proliferative effects and activates caspases, thereby inducing apoptosis in many cancer cell lines. IFN-γ may cause proapoptotic Bak upregulation, cytochrome C release and Bax translocation. However, despite limited efficacy, existing therapies based on IFN-γ are not satisfying enough to be used in the treatment of cancer diseases.
What was important, in many tumor lines showing resistance to TRAIL-stimulated apoptosis, interferon gamma acted synergistically, contributing to their sensitivity to TRAIL. Additionally, one of IFN-γ effects is an intense stimulation of human monocytes to produce endogenous TRAIL protein.
We developed the novel fusion protein AD-O64.3 consists of artificial dimer of IFN-γ, recombinant variant of TRAIL fragment and sequences recognized by tumor-specific proteases (MMP's, uPa) in between.
Materials and Methods: AD-O64.3 protein was expressed in *E.coli* and purified by IEC. Obtained molecule was characterized biochemically and biophysically using CD spectroscopy, SEC-HPLC, protease cleavage and MTT cell cytotoxicity assays. The proapoptotic effect was tested with using active caspase 3 staining. For *in vivo* potential we examined the efficacy on mice xenograft models of human renal cell carcinoma (ACHN), human colon adenocarcinoma (SW620) and human hapatoma (PLC/PRF/5) cell lines.
Results: Obtained protein has well-defined secondary and quarternary structure and verified mechanism of action. The molecule showed *in vitro* specific cytotoxic effect on various cancer cell lines (IC50 below 0.1 ng/ml). New protein showed very low activity on normal cells. *In vivo* AD-O64.3 showed promising effect displaying significant tumor growth inhibition.
Conclusions: We developed very promising molecule with high pro-apoptotic activity showing synergistic effect with TRAIL/Apo2L.
No conflict of interest.

537 POSTER

The AD-O56.9 − fusion of TRAIL/Apo2L with a membrane permeable peptide as a novel anticancer therapeutic

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Background: The tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL/Apo2L) is a member of the TNF superfamily that initiate apoptosis through the activation of their death receptors. The ability of TRAIL/Apo2L to selectively induce apoptosis of tumor cells but not normal cells makes it an attractive agent for cancer therapy. However, many cancer types have developed resistance mechanisms, such as dysfunctions of proapoptotic proteins.

Here, we report the design of a novel molecule AD-O56.9, which is composed of the soluble domain of TRAIL/Apo2L fused with a cationic alfa-helical (KLAKLAK)2 peptide, that is known to induce cancer cell death by membrane disruption. Because this peptide is not efficiently internalized we fused it with a cell penetrating moiety. Additionally, the TRAIL domain and the (KLAKLAK)2 peptide are linked with a sequence motif recognized by MMPs and uPa proteases, which enables cleavage and release of the proapoptotic peptide.
Materials and Methods: MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide) cell-viability assays was used to assess AD-O56.9-mediated killing of carcinoma cells. Flow-cytometric analysis were used to evaluate the effects of AD-O56.9 on mitochondrial membrane integrity and caspase 3 activation. The expression of Bid was determined by Western Blot analysis. The tumoricidal activity of AD-O56.9 was evaluated in NOD SCID mice bearing different types of cancer xenografts.
Results: AD-O56.9 exhibited cytotoxic effect on various cancer cell lines, including TRAIL-resistant cell lines but showed no toxic effect on normal cells. In relatively sensitive cell line (NCI-H460) and TRAIL-resistant cell line (A549) AD-O56.9 caused strong depolarization of mitochondrial membrane. Importantly, administration of AD-O56.9 caused significant regression of TRAIL sensitive human pancreatic carcinoma MIA PaCa-2 and TRAIL resistant human hepatocellular carcinoma HepG2 grown as xenografts in NOD SCID mice.
Conclusions: Our novel fusion protein AD-O56.9 is able to induce apoptosis in many cancer cell lines, even TRAIL resistant and causes tumor regression in mice bearing human cancer cells.
No conflict of interest.

538 POSTER

TRAIL/Apo2L resistant cancer cells can be sensitized to TRAIL by targeted delivery of peptides derived from BH3 domain of human Bid

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Background: Clinical trials of recombinant human TRAIL (rhTRAIL) and its agonistic monoclonal antibody (MAb) against DR4 and DR5 have established their safety and tolerability, but their clinical utility is limited by the resistance of many cancers to TRAIL-induced apoptosis. Combinatorial therapies of TRAIL/Apo2L in conjunction with other anticancer agents such as chemo or radiotherapy amplify the activities of these agents and widen the therapeutic window by overcoming tumor resistance to apoptosis and driving cancer cells to self-destruction.
Bid, a pro-apoptotic member of the Bcl-2 family, is a mediator of mitochondrial damage induced by caspase-8. Bid induces apoptosis by binding prosurvival Bcl-2 protein and directly neutralizing its function. Bid may also promote apoptosis in a way other than inhibiting Bcl-2 proteins by oligomerization and insertion of Bax and Bak into the outer mitochondrial membrane.
To overcome TRAIL resistance, we created chimeric protein with enhanced proapoptotic and antitumor activity. AD-O57.4 is a fusion protein consisting of a short peptide derived from Bid protein linked to an amino terminus of soluble TRAIL\Apo2L domain. The linking sequence contains additional motif recognized by MMP and uPa proteases that enables cutting-off of the proapoptotic peptide in tumor environment.
Materials and Methods: Cytotoxic activity was examined using a MTT assay. Apoptotic markers and mitochondrial membrane potential change was analyzed using flow cytometry methods. Colocalization of chimeric molecules with cell surface receptors was performed by confocal microscopy. *In vivo* antitumor activity was tested in the xenograft models of human colorectal carcinomas (Colo205, HCT116 and SW620). Safety of AD-O57.4 was confirmed on primary human and cynomolgus hepatocytes.
Results: AD-O57.4 in comparison to TRAIL/Apo2L showed very high cytotoxic activity against most of the analyzed cancer cell lines and it was able to overcome TRAIL resistance in cancer cell lines *in vitro*. Analysis of caspase 3 and 9 activation and expression of Bid protein showed rapid induction of apoptosis by AD-O57.4 in comparison to TRAIL\Apo2L. AD-O57.4 induced mitochondrial depolarization both in sensitive and TRAIL-resistant cell lines. Strong antitumor activity of AD-O57.4 fusion protein was also confirmed in xenograft models. AD-O57.4 causes complete remission in Colo205 and significant regression in HCT116 and SW620 xenograft models.
Conclusion: We demonstrated that AD-O57.4 protein has broad *in vitro* cytotoxic activity against panel of cancer cell lines and *in vivo* antitumor activity in xenograft models. The use of a peptide derived from Bid protein causes a significant increase in TRAIL\Apo2L activity. Our fusion molecule connecting extrinsic and intrinsic apoptotic pathways restores susceptibility to TRAIL/Apo2L induced apoptosis.
No conflict of interest.

539 POSTER

Docosahexaenoic acid-induced reactive oxygen species correlate with apoptotic cell death through MAPK activation in human ovarian cancer cells

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Background: The role of Omega-3 polyunsaturated fatty acids (ω3-PUFAs) in cancer prevention has been demonstrated; however, the exact molecular mechanisms underlying the anticancer activity of ω3-PUFAs in ovarian cancer remain unclear. In the present study, we investigated the effect of docosahexaenoic acid (DHA), a ω3-PUFA, in ovarian cancer cells and showed its cytotoxicity against PA-1 ovarian cancer cells.
Material and Methods: The effects of DHA on cell proliferation and cell cycle were examined by MTT assay and FACS. DHA-induced apoptosis was analysed using the Annexin V staining, TUNEL assay, caspase activity assay, and western blot. Dihydroethidium and MitoSOX were used in PA-1cells for reactive oxygen species (ROS) measurement, and the effect of DHA on mitochondrial function by measuring oxygen consumption rate and tetramethylrhodamine, ethyl ester staining.
Results: DHA treatment inhibited the proliferation of PA-1 cells in a dose-dependent manner and increased caspase-3 activity, the number of AnnexinV-positive cells and TUNEL-positive cells, and the proportion of sub-G1 cells, suggesting that DHA induces apoptotic cell death in ovarian cancer cells. Western blot and immunocytochemistry assays showed that DHA significantly increased the levels of phospho-extracellular signal-regulated kinase (ERK), phospho-c-jun N-terminal kinase (JNK), and phospho-p38 in the cytosol and nucleus. Knockdown of ERK, JNK, and p38 by small interfering RNAs reduced apoptosis induced by DHA, indicating that the pro-apoptotic effect of DHA is mediated by mitogen-activated protein kinase (MAPK) activation in ovarian cancer cells. In addition, MAPK activation was associated with the production of ROS induced by DHA. The ROS scavenger N-acetyl-L-cysteine (NAC) significantly blocked the phosphorylation of ERK, JNK, and p38 triggered by DHA.
Conclusions: Together, these results indicate that DHA induces ROS production and that ROS-dependent MAPK activation plays a role in DHA-induced cell cytotoxicity in human ovarian cancer cells.
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No conflict of interest.

540 POSTER

Apoptosis induction and caspases activation by low voltage electric pulses

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Background: Electric fields have been widely used in a variety of biotechnical applications. Electroporation has been investigated as a novel anticancer therapy, known as electrochemotherapy. However, high-intensity electric fields may also cause undesirable side effects. On the other hand, previous studies reported that a moderate electric field avoided severe cell damage and induced apoptosis. However, few studies have examined apoptosis induced by low-voltage electric pulses (LVEPs).
Material and Methods: *Cell culture:* The B16 (mouse malignant melanoma) cells were cultured in RPMI-1640 medium containing 10% fetal bovine serum at 37ºC under 5% CO_2.
Exposure to LVEPs(Low voltage electric pulses): Cells were re-suspended in RPMI-1640 at a concentration of $2-3\times10^6$ cells/ml. The cell suspensions (400 μl) were transferred to electroporation/fusion chambers with 2-mm gaps. Relatively low-voltage, long-duration (7.5 V/mm, 100–2000 ms) square wave consecutive pulses (1−3 pulses; duty ratio = 0.5) were applied using a function generator.
Assay: A flow cytometry apoptosis detection kit (Annexin V-FITC/7-AAD) was used to identify apoptotic and necrotic cells. Caspase-3, -8 and -9 activities were measured using an activity detection kit with FITC fluorescence by a flow cytometry.
Results: *Induction of apoptosis and cell death:* Apoptosis occurred in $2.8\pm0.3\%$ of the control cells, $3.2\pm0.7\%$ of cells exposed to 100-ms triple pulses, $7.2\pm0.5\%$ of cells exposed to 500-ms triple pulses, $10.5\pm1.6\%$ of cells exposed to 1000-ms pulses, and $7.4\pm0.4\%$ of the cisplatin-treated cells.

Caspase-3, -8 and -9 activity: The relative %-fluorescence intensity of cells exposed to electric pulses increased 142.0±8.3% for caspase-3, 131.4±5.8% for caspase-8, and 141.5±9.4% for caspase-9.
Effects of pan-caspase inhibition on apoptosis: Apoptosis occurred in 2.3±0.6% of the control cells, 3.8±1.4% of the cells incubated with Z-VAD-FMK, 9.1±1.0% of the cells exposed to electric pulses, 5.2±1.3% of the cells exposed to electric pulses with Z-VAD-FMK.
Conclusions: LVEP-induced apoptosis was achieved through caspase-8 and −9 activation and subsequent caspase-3 activation (*i.e.,* both the cell death receptor and mitochondrial pathways). Moreover, long-duration LVEPs caused only mild cell damage, such that the apoptosis ratio (apoptosis/total cell death) in electric pulse-treated cells was similar to that in non-treated control cells. Therefore, LVEP treatment may be a valuable anticancer therapy. Though the mechanism of LVEP-induced apoptosis unclear, it may result from membrane dysfunction that disrupts the transport of Ca^{2+} and extracellular substances, which are potent caspase activators.
No conflict of interest.

541 POSTER

CDC 25A regulating NFAT translocation promotes TGF-β mediated cell proliferation in metastatic breast cancer cells

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Background: Transforming growth factor-β (TGF-β), a multifunctional cytokine triggers metastasis by regulating epithelial to mesenchymal transition (EMT), a concomitantly associated phenomenon. Our main objective was to exhibit the TGF-β mediated cell proliferative mechanism where cell proliferation and EMT are maintained simultaneously.
Materials and Methods: Cell culture: MDA-MB231 and MDA-MB435s cell lines were used.
Methods: MTT and Br-dU incorporation assay, Flowcytometry, Immunofluorescence, Nuclear and Cytoplasmic extract preparation and Immunoblotting, Transfection of si RNA and RT-PCR were applied.
Results: MTT and Br-dU incorporation assay explained TGF-β mediated cell proliferation on MDA-MB231 and MDA-MB435s cells for 48 and 72 h of exposure. Upregulation of Cyclin D1, CyclinE and CDK2 and CDK4 expression both at gene and protein level reflected cell proliferation. Immunoblot results expressed the up regulation of phospho Smad2, NFAT and CDC 25A and RT-PCR results also have the resemblance with immunoblot results. Silencing of NFAT and Smad2 separately, favoured the apoptosis of cells with 48 h exposure of TGF-β. Immunofluorescence showed NFAT translocation from cytoplasm to nucleus with exposure of TGF-β for 48 h. NFAT translocation continued in presence of calcineurin pathway blocker (cyclosporine A) also. Whereas, silencing of CDC 25A expressed the inhibition of TGF-β mediated NFAT translocation and also cell proliferation. Silencing of NFAT and Smad2 separately, illustrated reduced gene expression of CDK2, CDK4 and Cyclin E for both the cases and only Smad2 silencing showed reduced gene expression of CDC 25A.
Conclusions: All of the above observations direct to summarize that TGF-β regulating CDC 25A in a Smad2 dependent way causes the translocation of NFAT. Within the nucleus, NFAT and Smad2 function cooperatively as a transcription factor and regulate the cell proliferative genes Cyclin E, CDK2 and CDK4. This study has another consequence that in absence of calcineurin pathway NFAT translocation is also possible through the CDC 25A activation.
No conflict of interest.

542 POSTER

Omega-3 polyunsaturated fatty acids induces cell death through apoptosis and autophagy in human oral cancer cells

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Background and aims: In the United States, about 40,000 new cases of oral cancer are diagnosed and nearly 8,000 patients die from it each year. Omega-3 polyunsaturated fatty acids (ω3-PUFAs) have been found to have anticancer effects in a variety of cancer cell lines and animal models, but their effect in oral cancer remains unclear. This study was designed to examine the effect of ω3-PUFAs on oral cancer and the molecular mechanism of their action using in vitro and in vivo models.
Material and Methods: SCC4 and SCC9 oral cancer cell lines were treated with ω3-PUFAs, and cell viability, apoptotic parameters as well as autophagic activity were examined. Additionally, to investigate the effect of ω3-PUFAs endogenously, Fat1 stable cells of SCC9 (SCC9-fsc), which express ω3-desaturase and thus contain a higher amount of endogenous ω3-PUFAs, were generated by stably transfection and selection, and the cell growth of the SCC9-fsc was compared with Control vector expressing cells (SCC9-fcc) both in vitro and in vivo.
Results: We found that exposure SCC4 and SCC9 human oral cancer cells to docosahexaenoic acid (DHA, a kind of ω3-PUFA) resulted growth inhibition in a dose- and time-dependent manner. Meanwhile, in addition to the elevated levels of apoptotic markers such as cleaved PARP, subG1 portion and TUNEL-positive nuclei, DHA led to autophagic vesicle formation and an increase in autophagic flux, indicating the involvement of both apoptosis and autophagy in the inhibitory effects of ω3-PUFAs on oral cancer cells. Further experiments revealed that the apoptosis and autophagy induced by DHA were linked to reactive oxygen species (ROS) overproduction and inhibition of Akt/mTOR signalling molecules. Moreover, SCC9-fsc showed retarded proliferation and colony formation capacity and invasion compared to control SCC9-fcc. The tumour size and volume of SCC9-fsc implanted into nude mice were also significantly inhibited with increases in the cell death index.
Conclusions: We propose that ω3-PUFAs induce apoptosis- and autophagy-associated cell death through ROS and Akt/mTOR signalling pathway in oral cancer cells. Thus, utilisation of ω3-PUFAs may represent a promising therapeutic approach for chemoprevention and treatment of human oral cancer.
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No conflict of interest.

543 POSTER

The effects of 2100 MHz UMTS signal of 3G GSM-like radiation on cell viability and nuclear morphology in hepatocellular carcinoma cells

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Background: Widespread increase of mobile telecommunication services has mainly increased the amount of radiofrequency radiation (RFR) in public and residential areas. The carrier frequencies of the 2G were 900 MHz and 1800 MHz frequency band modulated as Global System for Mobile Communication (GSM) whereas 3G frequencies are 2100 MHz frequency band with The Universal Mobile Telecommunication System (UMTS) signal modulation. Even though there is no consensus about possible carcinogenic effect of RFR exposure below present guidelines, there have been concerns that it may alter cellular functions in a way that increases the risks of cancer. Until now few in vivo and in vitro studies have been published by employing UMTS signal and the results are still inconclusive. For this purpose, we aimed to investigate whether exposure to 2100 MHz UMTS signal for cellular phones induces to alter cell viability and the nuclear morphology.
Material and Methods: Quick cell proliferation analyses were done after the HepG2 cells exposed to RFR during 1 hour and 2 and 3 hours. Nuclear morphology was investigated by DAPI staining. Furthermore, supernatant levels of Lactate dehydrogenases (LDH), Glucose (GLU) were detected as biochemical markers of cell viability.
Results: There were slight increase in the cell viability of the RFR-exposed cells in sham-exposed and control groups but these increases were not statistically significant. LDH and glucose levels were correlated with each other and there is no significant difference in RFR-exposed cells with respect to sham-exposed and control cells.
Conclusions: Although our results are consistent with previous published data; we should mention that they are not directly comparable due to the substantial difference in the employed modulation (3G vs. 2G technologies). In addition to this, it has been suggested that biological effects of RF radiation may be related not only to the frequency and the amplitude of the field, but also the type of modulation applied.
No conflict of interest.

544 POSTER

Chemotherapy for adenocarcinomas with neuroendocrine differentiation: A study in two pancreatic cancer cell lines with different somatostatin receptors expression

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Background: Pancreatic cancer, the fourth leading cause of cancer worldwide, is very resistant to surgery, chemotherapy and radiotherapy. Due to pancreatic cancer resistance to chemotherapy, it's important to study the single effects of chemotherapy in this type of cancer in order to improve its effects when allied with other treatment strategies.
Material and Methods: All studies were performed in two human pancreatic duct adenocarcinoma cell lines with different somatostatin receptors (SR) expression: MIA PaCa-2 (SR++) and Panc-1 (SR+). Cells were incubated with different concentrations of 5-FU or docetaxel for different times (24, 48, 72 or 96 h) and cell proliferation was evaluated through MTT assay. Through obtained dose-response curves, half maximal inhibitory concentration (IC50) for 5-FU and docetaxel was achieved. Cells were incubated with drugs IC50 and after 72 h, cell viability/death was analysed by flow cytometry using annexin V and propidium iodide.
Results: IC50 determined for each drug at each time in both cell lines were presented in table 1. After 5-FU IC50 incubation, MIA PaCa-2 and Panc-1 cell death reached 47.7% and 23.17%, respectively. Cell death in both cell lines submitted to 5-FU treatment occurred mainly by apoptosis and necrosis. Docetaxel IC50 induced 62.4% of cell death (mainly by apoptosis) in MIA PaCa-2, whereas Panc-1 cell death (33.5%) occurs either by apoptosis and necrosis.
Discussion: 5-FU and docetaxel inhibit cellular proliferation in a dose dependent-manner. Both cell lines are more sensible to docetaxel than to 5-FU. Docetaxel induces a higher percentage of cell death when compared to 5-FU. Docetaxel must be considered as a serious candidate for the treatment of adenocarcinomas with neuroendocrine differentiation.
No conflict of interest.

Table 1. IC50 (μM) obtained for MIA PaCa-2 and Panc-1 cell lines after incubation with 5-FU and docetaxel after 24, 48, 72 and 96 hours of exposure. R^2 is also indicated.

Drug	Cell line	Time (h)	IC50 (μM)	R2
5-FU	MIA PaCa-2	24	Undetermined	Undetermined
		48	Undetermined	Undetermined
		72	52.945	0.99
		96	10.253	0.99
	Panc-1	24	Undetermined	Undetermined
		48	Undetermined	Undetermined
		72	17.727	0.91
		96	15.763	0.99
Docetaxel	Mia PaCa2	24	0.1260	0.99
		48	0.0010	0.99
		72	0.0008	0.99
		96	0.0016	0.99
	Panc-1	24	0.2350	0.99
		48	0.1210	0.99
		72	0.0360	0.98
		96	0.0350	0.99

545 POSTER

Gossypol: An option in cholangiocarcinoma therapy?

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Background: Cholangiocarcinoma (CC) is the second primary liver tumor most common with limited therapeutic options, with similar incidence and mortality rates. CC is highly resistant to chemotherapy and radiotherapy, which is due in part to resistance to apoptosis which is related to an Bcl2 over-expression. Gossypol, a natural compound extracted from the cotton plant has been shown potential to inhibit the growth of several tumor cell lines. This compound is a potent inhibitor of Bcl2 family of anti-apoptotic proteins. This study aims to test the anti-proliferative effect of gossypol in a human CC cell line, study the type of cell death induced by this compound as well as to check its effect on Bax and Bcl2 expression. We also want to evaluate the effect of gossypol on cell cycle.
Methods: The human CC cell line used was TFK1. The cells were incubated with gossypol in several concentrations. After 24, 48, 72 and 96 hours of incubation, cell proliferation was evaluated by MTT assay. The cell survival factor was evaluated using the clonogenic assay, after 12 days of incubation with gossypol. The type of cell death and the percentage of live cells were assessed by flow cytometry using double staining with Annexin-V and propidium iodide. Bax and Bcl2 expression and cell cycle was also assessed by flow cytometry.
Results: Through the results obtained by the MTT assay, it was found that gossypol inhibits cell proliferation of TFK1 cells on a time and concentration-dependent manner. The clonogenic assay revealed that this compound induces a decreased on cell survival in a concentration-dependent manner, confirming the results obtained by the MTT assay. The results obtained by flow cytometry shown that gossypol induces cell death mainly by apoptosis. These results were confirmed by Bax activation and Bcl2 inhibition and also through a delay in the pre-G1 phase on cell cycle.
Conclusions: Gossypol has an anti-proliferative effect on CC cell line TFK1. This compound can also decrease cell survival. Cell death occurs primarily by apoptosis through Bax activation and a delay in the pre-G1 phase on cell cycle (pre-apoptotic peak). It seems that this compound can reverse the resistance to apoptosis observed in this type of tumor. Thus, gossypol could help to overcome resistance to chemotherapy and radiotherapy in this type of tumor, contributing to the existence of a personalized therapy.
No conflict of interest.

546 POSTER

NQO1 expression correlates with cholangiocarcinoma prognosis

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Cholangiocarcinoma (CCA) is a rare type of liver cancer with a very poor prognosis. The prevalence of CCA is markedly variable with the highest incidence in the northeast Thailand, followed by other parts of Southeast Asia and China. Currently, there is still no reliable biomarker for diagnosis or treatment. NADPH-quinone oxidoreductase 1 (NQO1) is a xenobiotic metabolising enzyme detoxifying chemical stressors and antioxidants, thereby providing cytoprotection in normal tissues. However, NQO1 is over-expressed in some cancers, suggesting roles in carcinogenesis and tumor progression. In this study, we examined NQO1 activity in surgical specimens from CCA patients and found much higher values than in the adjacent normal tissues. Immunohistochemical analysis revealed strong staining in tumour epithelial elements, whereas the non-tumour bile ducts and liver parenchyma were weakly stained. *NQO1* mRNA expression in tumour tissues was widely varied among 43 patients. A significant association was observed between high level of *NQO1* expression and short overall survival time by the Cox proportional hazard ratio of 2.40, $p < 0.05$. By histological classification, non-papillary adenocarcinoma was an independent predictor for poor prognosis with the hazard ratio of 2.79, $p < 0.05$. *NQO1* expression may serve as a prognostic biomarker for the CCA.
No conflict of interest.

547 POSTER

Scalp cooling and protection from chemotherapy-induced alopecia: Using in vitro human keratinocyte models to study the role of temperature and biological mechanisms of cooling-mediated cytoprotection

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Background: Scalp cooling is an efficient method of preventing chemotherapy-induced alopecia (CIA), with a widely reported success for

many anticancer drugs; yet some modalities do not respond well to cooling. It is essential to establish biological models that will allow the study of chemotherapy induced cytotoxicity and the effect of cooling in this context in order to a) provide biological evidence for the role of cooling and b) provide a mechanistic basis for the cell responses. This will permit the improvement of cooling-based CIA preventative strategies.
Materials and Methods: HaCaT cells, which are closely representative of normal human keratinocytes (NHKs), were used to assess cytotoxicity of commonly used chemotherapy compounds. Cells were treated with a range of doxorubicin, docetaxel and the active metabolite of cyclophosphamide, 4-hydroperoxy-cyclophosphamide. Following treatment at normal temperature and cooling conditions, cell viability was determined 48 and 72 hours post-exposure. In further optimisation experiments we tested the importance of cell density on responses. We also adapted HaCaT cells to culture conditions designed for NHKs in order to render them even more representative of normal cells (we named this newly adapted cell line HaCaTa). Using flow cytometry, immunofluorescence microscopy and immunoblotting we have investigated intracellular signalling pathways to assess the effect of cooling on cell responses.
Results: Cooling efficiently protected HaCaT cells from toxicity against most drugs tested for a wide range of concentrations, including doses representative of maximal plasma levels clinically reported. Importantly, our in vitro findings on the ability of cooling conditions to rescue from drug induced cytotoxicity are in direct agreement with clinical observations. HaCaTa cells showed phenotypic and proliferation characteristics that were more typical of NHK cells, and we will present our findings using these cells, as well as data on the role of cooling in modulating intracellular mediators (proliferation and apoptosis-related) following drug treatment.
Conclusions: Our in vitro models show clear biological relevance by reflecting clinical observations. Once fully-optimised, our reductive yet robust models will allow us to characterise the signalling pathways triggered by chemotherapy drugs in keratinocytes and how cooling influences the signalling circuitry in cells to modify cell responses.
No conflict of interest.

548 POSTER

Studying chemotherapy-induced alopecia in vitro: Cellular models accurately mimic the cytoprotective role of cooling against chemotherapy-induced cytotoxicity

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Background: Chemotherapy-induced alopecia (CIA) is the most common and distressing side effect of cancer chemotherapy and is associated with hair loss in an estimated 65% of females. Head cooling represents the only available treatment against CIA and advanced medical devices such as the Paxman scalp cooling system offer a promising solution. For some chemotherapeutic modalities over 90% efficiency in protecting from CIA has been reported, yet other therapeutic regimens do not respond well to cooling and CIA is not efficiently prevented. It is thus necessary to establish biological models that will allow the study of chemotherapy induced cytotoxicity and provide an understanding of the role of cooling.
Materials and Methods: Normal Human epidermal Keratinocytes (NHK), cultured in conditions that allow them to adopt a rapidly proliferating basal phenotype, were used to assess the cytotoxicity of commonly used chemotherapy compounds, such as taxanes and anthracyclines. NHK cells were exposed to a wide concentration range of docetaxel, doxorubicin and the active metabolite of cyclophosphamide, 4-hydroperoxy-cyclophosphamide (4-HC), and combinations thereof. To assess the effect of cooling on cytotoxicity cells were treated with the drugs at normal temperature and cooling conditions and cell viability was determined 72 hours after exposure. In addition, the role of cooling on drug uptake was assessed by high-performance liquid chromatography (HPLC).
Results: We show that cooling is extremely efficient at protecting NHK cells from drug-induced toxicity against all individual drugs. Notably, cooling showed maximal capacity to protect from cytotoxicity caused by drug concentrations representative of maximal plasma drug levels clinically reported. In contrast to results with individual compounds, combination of these drugs (also referred to as TAC regimen) caused cytotoxicity that was not rescued by cooling. Strikingly, our in vitro findings are in agreement with available clinical observations. Data will also be presented from our studies on the effect of cooling on cellular drug uptake.
Conclusions: We provide for the first time evidence that, despite their reductive nature, our in vitro models are robust and biologically relevant and will help us understand the role of cooling in rescuing from keratinocyte cytotoxicity. This will permit the design of scalp cooling-based protocols with improved efficiency.
No conflict of interest.

549 POSTER

Enhanced proliferation by NGF-NTRK1 signaling makes AsPC-1 cell more sensitive to 2-DG induced apoptosis

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Background: Rapid proliferating cancer cells rely on increased consumption of glucose for cell survival. Glucose analog 2-deoxy-D-glucose (2-DG) inhibits glycolysis and demonstrates anti-cancer ability against pancreatic cancers. Activation of NGF-NTRK1 signaling results in enhanced proliferation in pancreatic cancer cells, it is unknown whether inhibition of glycolysis inhibits their growth.
Methods: The cell viability of AsPC-1 and NTRK1-AsPC-1 transfected cells was analyzed by MTT assay following 2-DG treatment. LY294002 was used to inhibit PI3Kinase. Cell apoptosis was determined by detecting the cleavage of pro-caspase 3. Phosphorylation of Akt was used to monitor the activation of p38 pathway.
Result: In response to NGF, ectopic overexpression of NTRK1 in AsPC-1 cells resulted in increased cell proliferation and was not abolished by LY294002 mediated suppression of PI3Kinase. In comparison to the isogenic AsPC-1 cells,150nM 2-DG induced more apoptosis in the cells transfected with NTRK1, which was attenuated by addition of glucose. Moreover, blocking PI3K-Akt pathway by LY294002 effectively abolished the apoptosis induced by 2-DG.
Conclusion: 2-DG induced cell apoptosis is more effective in pancreatic cancer cells with a high expression of NTRK1 through PI3Kinase pathway.
No conflict of interest.

550 POSTER

New options in primary liver tumors: The role of quercetin

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Background: Hepatocellular carcinoma (HCC) is the most common primary liver malignancy followed by cholangiocarcinoma (CC). The mortality is high and the therapeutic options are limited. It is urgent to find new therapeutic targets and complementary therapies. Glucose transporter-1 (GLUT-1) expression is increased in primary liver tumors (PLT's) and promotes tumorigenesis. Flavonoids, including quercetin, have shown potential as GLUT-1 function inhibition and can be useful as therapeutic weapons against these highly aggressive tumors. The aim of this study is to evaluate the potential anticancer effect of quercetin on two HCC cell lines which differ on p53 expression and one CC cell line, evaluate its effect on ^{18}F-FDG uptake and in GLUT-1 expression.
Materials and Methods: Two different HCC cell lines (HepG2 (wp53) and HuH7 (mp53)) and a CC cell line (TFK-1) were used. In order to assess the effect of quercetin, the cells were incubated in the presence of different concentrations of this compound for different periods of time, and after cell proliferation was evaluated by the MTT assay in order to calculate half maximal inhibitory concentration (IC_{50}). The type of cell death was assessed by flow cytometry using the double staining with annexin-V/propidium iodide. Bax, Bcl-2 and GLUT-1 expression was also assessed by flow cytometry. For uptake studies, ^{18}F-FDG was incubated with a cell suspension pre-incubated with quercetin and control cells. At different times, samples were collected to eppendorf tubes, centrifuged and radioactivity of pellets and supernatants was measured with a well-type gamma counter for uptake calculation.
Results: Quercetin inhibits cell proliferation in all cell lines in a time-dependent manner. This compound does not inhibit GLUT-1 expression, however is able to decrease the ^{18}F-FDG uptake in all cell lines. Flow cytometry results have shown that quercetin has a cytotoxic effect only at high concentrations. When cell death occurs, is mainly by apoptosis and this is accompanied by Bax activation.
Conclusions: This study showed that quercetin has a considerable anti-proliferative effect in all cell lines used. This compound probably modifies the function but not the expression of GLUT-1, since it inhibits ^{18}F-FDG (a glucose analogue that is transported into the cell by GLUT-1 and GLUT-3) uptake. In this context quercetin may represent a new therapeutic option in PLT's.
No conflict of interest.

551 POSTER

Hepatocellular carcinoma and chemotherapy: The role of GLUT-1 antagonists

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Background: Hepatocellular carcinoma (HCC) is the third cause of cancer dead on the world. Therapeutic options are limited, and chemotherapy is in most cases mainly palliative, which is due, in part, to the resistance that HCC presents to the chemotherapy drugs. Thus urge investigate new therapeutic targets as well as new molecules for the combat to this type of tumor. The glucose transporter 1 (GLUT-1) has been suggested as a new target for this cancer. Gossypol and quercetin have been described as competitive inhibitors of GLUT-1. Thus, the objective of this experimental work was to test the combined effect of quercetin and gossypol with a drug frequently used in conventional chemotherapy, the doxorubicin.
Material and Methods: Three human HCC cell lines which differ in p53 expression: HepG2 (wp53), HuH7 (mp53) and Hep3B2.1−7 (p53 null) were used. The cells were incubated with constant concentrations of quercetin or gossypol. The concentrations of these compounds used, alone, do not inhibit more than 5% of cell proliferation. Immediately after the addition of antagonists, or after 24 hours, the cells were incubated with increasing concentrations of doxorubicin. 48 h after the addition of gossypol or quercetin, the proliferation was evaluated using the MTT assay.
Results: Taking into account the results obtained by us previously, the values of IC50 with doxorubicin are 0.68 μM for HepG2, 0.24 μM for HUH7 and 0.83 μM for Hep3B2.1−7 cell line, it was found that the IC50 decreased with the addition of gossypol or quercetin. Comparing the additive effect of the drugs used, a better effect was observed when added simultaneous than when are added with a difference of 24 hours.
Conclusion: The results obtained with the combination therapy were greater when both compounds were added simultaneously. Hep3B2.1−7 was the cell line where better results were obtained, which is a very promising result, since this cell line does not express p53, which gives a more aggressive phenotype. These results also indicate that GLUT-1 is a promising therapeutic target, once the results of the combination of GLUT-1 antagonists and doxorubicin, was much more expressive than doxorubicin alone. Thus, quercetin and gossypol enhances the effect of doxorubicin, which can be a weapon in the combat of chemotherapy resistance in HCC.
No conflict of interest.

552 POSTER

Comparative study of antioxidant activity and antiproliferative action of rutin and its derivatives in human tumor cell lines

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Background: Rutin (quercetin-3-O-rutinoside) is a diglycoside of quercetin which has several pharmacological functions such as antioxidative, cytoprotective, vasoprotective, antiproliferative, antithrombotic and cardioprotective activities. Bioavailability and biological properties of various flavonoids glycosides can be improved after the hydrolysis enzymatic of specific glycosyl groups. In the present study, the antiproliferative action of rutin, quercetin (aglycone form of rutin) and quercetin-3-glucoside, a monoglycosyltated derivative obtained by enzymatic hydrolyses of rutin, was evaluated in ten human tumor cell lines and correlated to their antioxidant activity.
Material and Methods: Quercetin-3-glucoside was obtained by hydrolysis of rutin performed by α-L-rhamnosidase previously heated at 70ºC for 30 min. The antioxidant capacity of compounds was investigated regarding radical scavenging activity by DPPH and xanthine oxidase inhibition activity. Antiproliferative *in vitro* activity was studied in ten human cancer cell lines, including melanoma, breast, renal, ovarian, prostate, colon, leukemia and lung cancer.
Results: Quercetin-3-glucoside and quercetin demonstrated high radical scavenging activity evaluated by DPPH assay, however quercetin-3-glucoside and rutin were weak as xanthine oxidase inhibitor. *In vitro* inhibitory activity against human tumor cell showed that quercetin-3-glucoside exerted a more powerful antiproliferative effect than quercetin and rutin on various cancer cell lines, showing higher activity for glioma, ovarian and breast adenocarcinoma.
Conclusions: The data suggest that the 3-O-glucosylation improves the quercetin antiproliferative potential, whereas the binding of a rhamnose to the aglycone greatly depresses it. The results indicate that quercetin-3-glucoside can be a promissory functional derivative obtained by rutin hydrolyses. Further *in vivo* evaluations are needed.
No conflict of interest.

553 POSTER

MEIG1, a new player in the system responsible for maintaining genome integrity

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Background: *Meig1* is a highly conserved gene first identified in mouse pachytene spermatocytes undergoing meiotic recombination. In these cells the MEIG1 protein enters the nucleus and forms foci along the meiotic chromosomes, reminiscent of foci obtain by proteins known to be involved in the DNA damage response. Meig1 knockout (KO) male mice are infertile. These mice exhibit significantly fragmented DNA in the few epididymal sperm cells that could be obtained, and increased apoptosis of post recombination spermatogenic cells. Given these findings we hypothesized that MEIG1 might play a role in the system responsible for maintaining genome integrity.
Materials and Methods: Immunocytochemistry of meiotic chromosomes and γH2AX signaling were used to analyze DNA integrity of post recombination chromosomes in KO versus WT spermatocytes, as well as in KO and WT MEFs exposed to etoposide treatment (50μM). Real-Time PCR was used to monitor expression of Meig1 in U2OS cells (human osteosarcoma cells) after exposure to genotoxic treatment [UV-radiation (254 nm, 50mJ/cm^2) and etoposide (50μM)]. Tumors from KO mice were analyzed histologically.
Results: Analysis of γH2AX signaling in meiotic chromosomes of late pachytene spermatocytes showed that in KO mice they were highly 'decorated' with γH2AX foci, compared to WT chromosomes. Moreover, analysis of post-recombination meiotic chromosomes revealed the existence of numerous chromosomal fragments in KO meiotic preparations whereas no such fragments could be seen in preparations from WT spermatocytes. Regarding somatic cells, KO MEFs exposed to etoposide treatment exhibited significantly slower disappearance of the γH2AX foci compare to WT MEFs, suggesting delayed or aberrant repair. In U2OS cell *Meig1* expression was significantly up-regulated soon after exposure to etoposide, whereas following UV radiation Meig1 up-regulation was delayed concomitant to the appearance of double strand breaks. Interestingly, most Meig1 KO mice (more than 30 mice to date), and about one third of the Meig1 $^{+/-}$ heterozygotes developed huge and aggressive tumors between 6−18 months of age, whereas none of the age-matched wild-type (WT) mice developed tumors. These tumors were identified as being mainly malignant adeno-carcinomas and lymphomas.
Conclusions: MEIG1 seems to be involved in maintaining chromatin integrity not only in spermatogenic cells but in somatic cells as well, rendering it as a new player in the general DNA damage response, especially the response to DSB. Meig1 has tumor suppressive properties.
No conflict of interest.

554 POSTER

PIM-2 is an essential component of the UV damage response that acts upstream to E2F-1 and ATM

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Background: PIM-2, a member of the PIM serine/threonine kinase family, is known for its pro-survival activity. Increased expression of PIM-2 was reported in several tumors, emphasizing PIM-2's involvement in human tumor formation. However, the roll of PIM-2 in the context of DNA damage has not been determinate yet. The aim of this study was to assess the potential involvement of PIM-2 in the cell's response to UV radiation and the activation of the DNA damage response.
Materials and Methods: A Tet-ON inducible system was established for expression of a HA-tagged 34kDa isoforme of PIM-2, in U2OS osteosarcoma cells. PIM-2 over-expressing cells, and control cells, were exposed to UVC radiation (254nm, 4−50mJ/cm^2), and various DNA damage mediators were monitored by real time PCR and Western Blot analysis.DNA legions (CPDs) were detected by ELISA and immunocytochemical staining. Apoptosis was determined by the anaxin/PI method or by determining the sub-G1 phase in FACS analysis. Silencing of Pim-2 or E2F1 was performed using shRNA or siRNA.
Results: U2OS cells that were exposed to UV-radiation reacted in a significant increase in endogenous PIM-2 levels. Silencing PIM-2 in U2OS cells rendered these cells much more sensitive to UV radiation whereas PIM-2 over-expressing cells showed decreased sensitivity and increased

survival following UV radiation, exhibiting increased kinetics of repair of DNA lesions compared to control cells. These protective effects of PIM-2 were mediated by increased levels of E2F-1, and activation of ATM. The protective effects of PIM-2 were much less dramatic upon silencing of E2F-1 and completely abrogated upon inhibition of ATM.
Conclusion: PIM-2 is an essential component of the UV damage response that acts upstream to E2F-1 and ATM. The increased E2F-1 levels and activation of ATM, possibly render the cells more ready for the coming UV-induced DNA damage.
No conflict of interest.

555 POSTER

Proof of concept in breast cancer and identification of sensitivity biomarkers of a new DNA repair inhibitor (Dbait)

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Background: Numerous therapies are available for the treatment of Breast Cancer (BC): surgery, radiation therapy, chemotherapy, hormone therapy, and most recently, targeted therapy. The limit of targeted therapy is that they are usually directed at specific targets in the body (extracellular receptors, kinases and enzymes) and therefore apply for limited number of patients. For exemple, PARP inhibitors that act as synthetic lethal with BRCA deficiency have shown promising results, but seem however less efficient in patient with active homologous recombination repair. We have recently developed a new strategy (DNA repair bait, Dbait in short) that inhibits three central repair pathways (Homologous Recombination, Non Homologous End Joining and Single Strand Break Repair). Dbait(DT01) is the 1st drug candidate of this family of DNA repair inhibitor already in a phase 1 trial in local metastatic melanoma. This study demonstrates the efficiency of Dbait in BC treatment and identify new biomarkers that predict tumor sensitivity to its administration.
Materials and Methods: Twelve BC cell lines were characterized for DNA repair gene expression and activation of the DNA damage response DDR (pH2AX and PAR detection) by western blot analysis of the proteins and classified according to their BRCA status. Clonal survival to Dbait (the DT01 in vitro variant) was analyzed 10 days after treatment. Four xenografted models derived from cell lines or patient samples were assayed for sensitivity to DT01. DT01 (5 mg) was subcutaneously administered every day for a week (5 sessions) or four days per week for three weeks (12 sessions of 2 mg). In parallel, the PARP inhibitor ABT-888 was orally administered at the dose of 25 mg/day/kg during one week to compare efficiencies. Tumor growth and survival of untreated and treated animals were monitored. Tumor biopsies were analyzed for micronuclei formation.
Results: This study provides the evidences that: i) Dbait induces death *in vitro* in BC cells independently of BRCA defect; ii) DT01 controls tumor growth and increase survival in all tested models; iii) DT01 alone cured 30% $BRCA^{-/-}$ tumors; iv) DT01 was more efficient that ABT-888 in vitro and in vivo. Micronuclei biomarkers predict the sensitivity to Dbait and are detected in many patient biopsies.
Conclusion: DT01 is a promising investigational medicinal product to treat Breast Cancer. Its association with radiotherapy is under investigation.
Conflict of interest: *Ownership: M. Dutreix and JS. Sun are co-founder of the society DNA-Therapeutics. Other substantive relationships: F. Devun is a employee of DNA-Therapeutics*

556 POSTER

Knockdown of the caveolin-1 gene abrogates radiation-induced Akt nuclear translocation in triple negative breast cancer cells

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Background: Triple negative breast cancer (TNBC), an aggressive subtype of breast cancer, often lacks effective targeted therapy and is insensitive to chemo-or radiotherapy. We had previously detected that epidermal growth factor receptor (EGFR) nuclear translocation after ionizing radiation (XRT) was associated with radioresistance in TNBC cells and caveolin-1 was critical for this process. Akt is one of the downstream molecules of EGFR signaling cascade and Akt activation often indicates poor clinical outcome and resistance to therapy in cancer patients. Thus, we hypothesize that Akt would localize to nucleus after activated by XRT to confer radioresistance and aim to explore whether downregulate caveolin-1 could impair the radiation-induced Akt nuclear translocation in TNBC cells.
Material and Methods: Akt activation and the cytoplasmic-to-nucleus trafficking of Akt at various time points (0−2 h) following irradiation were examined in two established TNBC cell lines (Hs578t and MDA-MB-231) through western blot and confocal assay. Further, we applied small interfering RNA (siRNA) targeting caveolin-1 to downregulate its protein expression and then examined level changes of nuclear Akt. Immunofluorescence (IF) was done to observe the expression of p-DNA-PKcs (T2609) which indicates DNA repair capacity as well as γ-H2AX which is a marker of DNA damage.
Results: Our results showed that in two TNBC cell lines, radiation-treated cells exhibited an increase in nuclear Akt level while the expression of caveolin-1 in cytoplasmic and nucleus fractions did not changed. Phosphorylation of Akt on Ser-473 also increased after XRT in both cytoplasmic and nucleus, suggesting that phosphorylation at this site of Akt might be necessary for radiation-induced Akt nuclear accumulation. Downregulation of caveolin-1 by siRNA was able to block Akt nuclear import regardless of Akt phosphorylation status. Impairment of Akt localized to the nucleus further inhibited DNA repair via decreasing the expression of p-DNA-PKcs (T2609) and promoted DNA damage by enhancement of γ-H2AX foci formation to 24 h post-XRT thus eventually increased radio-sensitivity.
Conclusions: These data support the hypothesis that irradiation-induced nuclear Akt accumulation is related to radioresistance. Moreover, caveolin-1 played a prominent role in regulating Akt transportation and proved to be a promising target to exert radiosensitizing effect in TNBC cells.
No conflict of interest.

557 POSTER

Correlation between BRCA1/2 mutation and treatment side effects in breast cancer patients

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Introduction: *BRCA1/2*are the tumor suppressor genes which are responsible for DNA damage repairs, cell cycle regulation, transcriptional control, ubiquitination and regulation of apoptosis. The presence of *BRCA* gene mutation and low expressions of BRCA proteins is associated with greater sensitivity of tumor cells to ionizing radiation and cytostatics damaging cells' DNA. This study was conducted to evaluate the influence of *BRCA1/2* mutation on toxicity of anthracycline based chemotherapy and radiotherapy.
Methods: This retrospective study was conducted on 370 patients treated with anthracycline-based chemotherapy for breast cancer in years 2006–2012. All patients were examined for the presence of *BRCA1* and *BRCA2* mutations. Medical records were reviewed to document the characteristics of each cancer and the treatments received.
Results: In analyzed group 275 (75%) received adjuvant chemotherapy and 95 (25%) neoadjuvant treatment. In 48 (13%) of patients *BRCA1/2*mutation was detected: in 44 (12%) early breast cancer and in 4 (1%) advanced breast cancer patients. Overall toxicity grade 3−4 was observed more often in non − carriers (10% vs. 17%), $p = 0.045$. Nausea and vomiting in grade 3−4 was detected only in non carriers (5%). Gastrointestinal toxicity in all grades (1−4 according to CTCAE) together also occurred more often in patients without the presence of BRCA1/2 mutations (20% vs. 7%), $p = 0.05$. In contrary, hematological side effects such as neutropenia were observed more frequently in patients withBRCA1/2 mutation (32% vs. 10%) $p = 0.0008$. No significant differences were observed between this two groups according to other side effects. Acute radiotherapy toxicity was reported in 6% patients with BRCA1/2 mutations and 9% without mutations, $p = 0.766$.
Conclusion: Anthracycline-based chemotherapy was generally well tolerated by BRCA1/2 associated breast cancer patients. The acute side effects were sporadic. BRCA1/2 mutation carriers seem to be more at risk of neutropenia and non carriers more at risk of gastrointestinal toxicity. There was no evidence of increased radiation sensitivity in BRCA patients compared with patients without mutations.
No conflict of interest.

558 POSTER

Age-related prognostic value of global expression of histone modifications and histone modifying enzymes in colorectal cancer

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Background: Epigenetic processes, including DNA methylation and histone modifications, are frequently deregulated in cancer. Histone modifications, in addition to DNA methylation, are key regulators of gene expression. In search for new biomarkers to improve the current staging system for colorectal cancer, we studied global expression of histone

modifications and their corresponding enzymes in colorectal cancer. We hypothesized that global expression of histone modifications reflect the aggressiveness of the tumor and can therefore predict clinical outcome.
Materials and Methods: Histone modifications H3K9Ac and H3K27me3 and histone modifying enzymes BMI1, EZH2 and LSD1 were immunohistochemically stained on tissue microarrays (TMA) of colorectal cancer patients (n = 249). The TMA included three tumor tissue cores per patient, and the average percentage of positive tumor cells per patient were used for survival analyses. Patients were divided into groups based on median expression of individual markers. Uni- and multivariate survival analysis was used to analyze the association between the individual markers and clinical outcome. Kaplan–Meier curves were generated in order to visualize survival differences between the expression groups.
Results: In survival analyses for all of markers reported in this study, we identified an interaction between the expression of the studied markers and age at surgery. Hazard ratios increased significantly with age at surgery. For all markers, higher expression correlated to better survival in younger patients, whereas lower expression correlated to better survival in older patients. A similar pattern was observed for recurrence free survival.
Conclusions: Based on current knowledge that global DNA methylation decreases with age, we assumed a similar decrease in expression of histone modifications and enzymes with age. In older patients, higher expression of histone modifications was considered aberrant and was therefore expected to be associated with worse prognosis, as indeed shown in this study. For younger patients, we expected and showed the opposite effect, with lower expression considered aberrant and correlating to worse prognosis. In conclusion, global expression of histone modifications can predict clinical outcome in colorectal cancer patients in an age-dependent way.
*Note: A. Benard and I.J. Goossens-Beumer contributed equally to this study.
No conflict of interest.

559 POSTER

Significance of the histone demethylase jumonji domain containing 2B in human lung carcinogenesis and the prognosis of patients with resected lung adenocarcinoma

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Background: Histone methyltransferases and demethylases are known to regulate transcription; however, the pathologic role of dysfunction of these molecules in human cancer remains to be elucidated. We herein examined the significance of jumonji domain containing 2B, JMJD2B, in the pathogenesis of lung cancer cells and clinical lung cancer patients.
Materials and Methods: The protein expression in lung cancer samples was examined using immunohistochemistry with an antibody that specifically detects JMJD2B. Cell growth and the cell cycle in lung cancer cell lines were analyzed following siRNA treatment using an MTT assay and the BrdU labeling. A microarray analysis was performed to investigate downstream genes of *JMJD2B*, while chromatin immunoprecipitation was conducted to analyze transcriptional regulation by *JMJD2B*. A total of 78 patients with resected lung adenocarcinoma were examined using immunohistochemistry, and the significance of the JMJD2B expression for the DFI and OS after surgical operation was evaluated.
Results: Immunohistochemistry revealed an elevated protein expression in the lung cancer tissues. The siRNA-mediated reduction of the expression of *JMJD2B* in the lung cancer cell lines significantly suppressed the proliferation of cancer cells, while suppression of the *JMJD2B* expression led to a decreased population of cancer cells in the S phase with a concomitant increase in the number of cells in the G1 phase. A microarray analysis conducted after the knockdown of *JMJD2B* revealed that *JMJD2B* regulates multiple pathways that contribute to carcinogenesis, including the cell-cycle pathway. Chromatin immunoprecipitation showed that, of the downstream genes, *cyclin-dependent kinase 6* (*CDK6*), which is essential for G1−S transition, is directly regulated by *JMJD2B* via demethylation of histone H3-K9 in its promoter region. The expression levels of *JMJD2B* and *CDK6* were significantly correlated with each other in the various types of cancer cell lines. Furthermore, in a total of 78 resected lung adenocarcinomas, immunopositivity for JMJD2B was observed in 50 cases, and, intriguingly, the OS of these patients after surgery was inferior to that of the patients without any JMJD2B expression.
Conclusions: In conclusion, this study revealed a novel mechanism for human lung carcinogenesis and demonstrated that JMJD2B is a feasible molecular target for anticancer therapy. Furthermore, JMJD2B may be a novel prognostic factor for resected lung adenocarcinoma.
No conflict of interest.

560 POSTER

Functional characterization of EZH2 rs3757441 polymorphism in colorectal cancer (CRC) samples

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Background: The enhancer of zeste-homolog 2 (*EZH2*) is a cancer stem cell-related gene involved in cancer development through gene silencing by methylation of lysine 27 of histone 3 (H3K27). The *EZH2* allelic variant rs3757441 CC was shown to be associated with poor prognosis in metastatic CRC patients, but molecular and pathological characterization of the single nucleotide polymorphism (SNP) is lacking.
Material and Methods: A total of 119 formalin-fixed paraffin-embedded tissues of primary colorectal tumours were collected and used for DNA extraction, molecular and pathological analyses. *EZH2* rs3757441 SNP variants were identified by real-time PCR from colonic healthy tissue. EZH2 and H3K27 expression were evaluated by immunohystochemistry (IHC), while *KRAS* codon 12−13 and *BRAF* V600E mutational status were assessed by pyrosequencing. Statistical analysis was performed by Fisher exact test, chi-square test, T test and ANOVA.
Results: Characteristics of the specimens are summarized in Table 1. The rs3757441 CC genotype significantly correlates with both EZH2 (100 vs. 46%, p = 0.02) and H3K27 (100 vs. 38%, p = 0.01) increased expression (defined as 3+ at IHC) compared with CT and TT genotypes. We observed a significant correlation between the expression of EZH2 and H3K27 (p = 0.04), but the expression of EZH2 and H3K27 is not associated with tumour stage, site, mucinous histology or *KRAS* and *BRAF* mutational status. Poorly differentiated (grade 3) tumours display higher H3K27 expression (p = 0.05) and higher percentage of H3K27-positive cells (p = 0.06).
Conclusions: *EZH2* rs3757441 CC genotype is associated with stronger EZH2 and H3K27 immunoreactivity in primary CRC samples. Higher tumour grade shows a trend toward higher H3K27 expression and percentage of H3K27-positive cells, which may contribute to more aggressive behaviour. *EZH2* is a candidate therapeutic target in CRC and rs3757441 SNP may be a promising biomarker.
No conflict of interest.

Table 1. Characteristics of 119 specimens

Feature	n	(%)
Stage, I/II/III/IV	5/41/52/21	4/34/44/18
Grade, 2/3	76/43	64/36
Site, right colon/left colon/rectum	52/45/22	44/38/18
Mucinous histology, yes/no	37/82	31/69
KRAS, wild-type/mutant	67/52	56/44
BRAF, wild-type/mutant	108/11	91/9
EZH2 rs3757441 genotype, CC/CT/TT	5/51/63	4/43/53
EZH2 IHC staining intensity, 3+/2+/1+/neg	55/33/14/17	46/28/12/14
H3K27 IHC staining intensity, 3+/2+/1+/neg	48/40/17/14	40/34/14/12

561 POSTER

Sensitization of TRAIL in combination with sub-toxic dose 5-FU induces apoptosis and inhibits cell proliferation in cholangiocarcinoma

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Background: Cholangiocarcinoma (CCA) although is a rare type of primary liver cancer, the incidence and mortality rates have been reported to increase worldwide in the past decade. Surgical resection is only a potentially curative approach for the CCA patients. However, a vast majority of the CCA cases are unresectable and commonly represented in the advanced stages. Previous clinical studies have reported the relatively low responsiveness of CCA to chemotherapy with a partial response approximately 10−20%. Our recent study has shown that death receptor-induced apoptosis through TRAIL signaling is rarely silenced by epigenetic aberration in term of DNA methylation. The result suggests the advantage for optional cancer therapy using recombinant TRAIL or TRAIL receptor

agonistic monoclonal antibodies to induce cancer cell death in CCA. In the present study, we aimed to investigate the therapeutic effect of recombinant human TRAIL (rhTRAIL) in CCA cell lines (M213, M214 and KKU-100) compared with the immortal biliary cell line MMNK1.
Methods: Sulforhodamine B (SRB) assay was used to determine cell proliferation. Apoptosis was determined by assaying activities of caspases 8, 9 and 3/7. Expression of apoptotic related genes (DcR1, DcR2, DR4, DR5, and CASP8) and p53 was detected by reverse transcription polymerase chain reaction (RT-PCR).
Results: rhTRAIL is a potential agent which significantly inhibits cell proliferation and mediates apoptosis by inducing caspase activities (caspases 8, 9 and −3/7) in CCA cells. The combined treatment of 5-FU at sub-toxic dose (8 μM) and 10 ng/mL rhTRAIL was significantly inhibited cell growth in all cell lines tested compared to untreated control, 5-FU, or rhTRAIL while those combinations showed less effect on MMNK1 with cell survival >60%. mRNA of TRAIL related genes was expressed in CCA cell lines and not related to responsiveness of cells to 5-FU and/or rhTRAIL treatments.
Conclusions: The combination of rhTRAIL and 5-FU at sub-toxic concentrations could inhibit cell growth and induce apoptosis in CCA with lower cytotoxicity in immortal biliary cell.
No conflict of interest.

562 POSTER

The relationship between microsatellite instability and diabetes mellitus in colorectal cancer patients

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Background: Mutations in DNA mismatch repair genes result in a failure to repair errors in repetitive sequences, leading to microsatellite instability (MSI) of the tumors. MSI can occur in tumors of many organs, but it is mainly the hallmark of colorectal cancer. Colorectal cancers (CRCs) with high-frequency microsatellite instability (MSI-H) are known to show differences in their clinical and pathological features compared to microsatellite stable (MSS) cancers. In addition, previous studies revealed that type 2 diabetes mellitus (T2DM) is a risk factor of malignant tumor including colorectal cancer. In this study, we prospectively investigated the relationship between T2DM and MSI positive colorectal cancer in Japanese individuals.
Material and Methods: We consecutively selected 415 colorectal cancer patients who underwent surgical resection at the Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital from January 2008 to December 2010 after obtaining informed consent. Patients with inflammatory bowel disease, familial adenomatous polyposis or hereditary non-polyposis colon cancer (Lynch syndrome) were excluded. Microsatellite status was assessed using standard markers which are BAT25, BAT26, D2S123, D5S346, and D17S250.
Results: 22 cases (5.3%), 28 cases (6.7%) and 365 cases (88.0%) of tumors showed MSI-H, low-frequency microsatellite instability (MSI-L) and MSS, respectively. Of the 415 colorectal cancers, 90 (21.7%) were T2DM. One patient (4.5%) was T2DM of the 22 MSI-H patients, 82 (22.5%) were T2DM of the 365 MSS patients. Thus, the rate of T2DM in MSI-H patients is significantly less than that in MSS patients ($\chi 2$ test: $p = 0.497$).
Conclusion: We conclude that the rate of T2DM in MSI-H patients is significantly less than that in MSS patients.
No conflict of interest.

563 POSTER

Endoxifen and hTra2-beta1 regulate estrogen receptor a alternative splicing pattern in breast cancer cells

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Background: Endoxifen is the major metabolite of tamoxifen and acts as a selective estrogen receptor modulator (SERM) by blocking estrogen receptor alpha (ERα) transcriptional activity. Alternatively spliced ERα mRNA variants are present in normal and malignant breast tissues. These alternative ERα variants possess the potential for increased estrogen activities. Human Tra2-beta1 is a splicing factor regulating splicing processes in a sequence-specific and concentration-dependent manner. hTra2-beta1 intracellular localization may vary during cancer progression or is changed by exogenic stimuli, e.g. therapeutic drugs. Here we analyzed the potential impacts of endoxifen and hTra2-beta1 on ERα expression pattern. In addition, we examined the effect of endoxifen on hTra2-beta's alternative splicing.
Material and Methods: Three ERα-positive and one ERα-negative breast cancer cell line were subjected to parallel functional experiments. Cell lines underwent estrogen stimulation following different treatment. Cells were either kept continuously cultivated under estrogen stimulation, or treated with endoxifen. Transient knock-down of hTra2-beta1 was operated by transfection with shRNA plasmids. PCR, RT-PCR, immunocytochemistry and Western blot were applied for expression analysis on mRNA and protein level.
Results: Endoxifen induced a significant reduction of ERα protein expression in ERα positive breast cancer cells. As a feedback effect, the ERα mRNA expression levels markedly increased. Endoxifen treatment triggered a shift in ERα splicing toward the ERα Δ7 variant. hTra2-beta knock-down created a similar impact on ERα alternative splicing. In addition, a novel isoform of hTra2-beta1 occurred under endoxifen treatment. Interestingly, endoxifen also triggers an intracellular translocation of hTra2-beta1 characterized by decreased nuclear protein expression and increased accumulation in cytoplasm.
Conclusion: We hypothesize that endoxifen exerts a regulatory impact on hTra2-beta1 alternative mRNA splicing pattern and intracellular protein localization. hTra2-beta1 is most likely involved in ERα-dependent regulation of breast cancer by triggering aberrant ERα alternative splicing. The presence of different ERα mRNA and protein variants exerts different functions in controlling ERα signaling pathways. ERα Δ7 might be of auspicious clinical significance to potentially serve as a prognostic indicator for evaluation of human breast cancer endocrine therapy efficacy.
No conflict of interest.

564 POSTER

Dioxin receptor (AhR) binding to Alu elements X14S, X36S and X45S modulates the expression of stemness-relevant genes Oct4 and Nanog

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Background: Eukaryotic genomes are organized into expression domains whose activity depends on local chromatin structure. To accomplish that, functional gene clusters are defined by the binding of transcription factors to conserved regulatory sequences. Transposable elements seem to regulate gene expression by modulating genome organization and stability. Such transposons functions are likely associated to their ability to bind specific transcription factors.
Material and Methods: Ntera 2D1 cells of wild type phenotype (WT) and Ntera-2 infected via retrovirus with a short hairpin to induce the knockdown of AhR (shAhR) were used in the study. Chromatin immunoprecipitacion (ChIP) were performed to check protein bindings. We used retinoic acid (RA) treatment during 24−48 hours to promote differentiation.
Results: In the human genome, we have identified three Alu elements containing a conserved AhR binding site. These Alu(s) (hereafter X14S, X36S and X45S) are present in most stemness-relevant genes including Oct4, Nanog, Shh, Sox2 and Notch1. In the undifferentiated embryonic carcinoma Ntera 2D1 cell line, treatment with retinoic acid (RA) induces differentiation by decreasing Oct4 and Nanog expression levels. Remarkably, RA-induced differentiation promotes a parallel increase in AhR protein levels. Silencing of AhR by RNA interference (siRNA of shRNA) blocks the decrease in Oct4 and Nanog induced by RA thus maintaining an undifferentiated state. Chromatin immunoprecipitation (ChIP) experiments were performed to confirm AhR binding to the X14S, X36S and X45S Alu elements present in the promoter of such target genes. Binding of CTCF, PARP-1, Pol II and Pol III to these Alu(s) was also reported. In addition, enhancer blocking assays (EBAs) will be used to address the insulator activity of these Alu elements, and also will be confirmed in vivo in zebrafish.
Conclusions: We suggest that X14S, X36S and X45S Alu elements can represent evolutionary conserved genome-wide insulators and modulators activated by the transcription factor AhR to control developmental, oncogenic or toxicological-dependent processes.
No conflict of interest.

565 POSTER

Dioxin receptor expression inhibits basal and transforming growth factor beta-induced epithelial-to-mesenchymal transition

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Background: Recent studies have emphasized the role of the dioxin receptor (AhR) in maintaining cell morphology, adhesion and migration.

These novel AhR functions depend on the cell phenotype and while AhR expression maintains mesenchymal fibroblasts migration it inhibits keratinocytes motility. These observations prompted us to investigate whether AhR modulates the epithelial-to-mesenchymal transition (EMT).
Material and Methods: We have used primary *AhR*+/+ and *AhR*−/− keratinocytes and NMuMG cells engineered to knock-down AhR levels (sh-AhR) or to express a constitutively active receptor (CA-AhR) by retroviral transduction. To analyze the role of AhR in EMT, the following experimental procedures were performed: transient transfection and RNA interference, clonogenic and migration experiments, immunofluorescence, immunoprecipitation and immunoblotting assays as well as Real-time PCR analyses.
Results: Both *AhR*−/− keratinocytes and sh-AhR NMuMG cells had increased migration, reduced levels of epithelial markers E-cadherin and beta-catenin and increased expression of mesenchymal markers Snail, Slug/Snai2, vimentin, fibronectin and alfa- smooth muscle actin. Consistently, *AhR*+/+ and CA-AhR NMuMG cells had reduced migration and enhanced expression of epithelial markers. AhR activation by the agonist FICZ inhibited NMuMG migration whereas the antagonist alfa-naphthoflavone induced migration as did AhR knock-down. Exogenous TGF beta exacerbated the pro-migratory mesenchymal phenotype in both AhR-expressing and AhR-depleted cells, although the effects on the latter were more pronounced. Rescuing AhR expression in sh- AhR cells reduced Snail and Slug/Snai2 levels and cell migration and restored E-cadherin levels. Interference of AhR in human HaCaT cells further supported its role in EMT. Interestingly, co-immunoprecipitation and immunofluorescence assays showed that AhR associates in common protein complexes with E-cadherin and beta-catenin, suggesting the implication of AhR in cell-cell adhesion. Thus, basal or TGF beta-induced AhR down-modulation could be relevant in the acquisition of a motile
Conclusion: AhR has an intrinsic role in EMT and cross talks with TGFbeta.
No conflict of interest.

566 POSTER

Implication of transposons in differentiation process in NTERA 2D1 cell line

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Background: Transposons are mobile elements of the genome which are implicated in gene expression regulation. Cell differentiation is an important process regulated by these elements. The B1X35S is a transposon found in mouse which expression is mainly regulated by the aryl hydrocarbon receptor (AhR), having a role RNA polymerase III and PARP1. Human cells contain XS Alus, another family of transposons comparable with B1X35S. There are many genes implicated in cell differentiation that contain XS Alus.
Material and Methods: To understand the role of Alus elements in the expression of gene related with cell differentiation, we have used NTERA 2D1 cells of wild type phenotype (Wt line) and transfected with a short hairpin to induce the knockdown of AhR (Sh line).
Results: The treatment of Wt line cells with retinoic acid to differentiate NTERA cells to neuronal cells, induces an increase of the AhR level and a downregulation of Oct4 and Nanog expression, genes of undifferentiated state maintenance. On the contrary, the same treatment in Sh line cells only produces a low increase of AhR expression and a similar expression level of the undifferentiated state genes. In addition, we checked the protein levels of undifferentiated state marker Oct4 and several neuronal differentiation markers (TAU, NSE, GAP43 and βIIITubulin) and the results are in agreement with the gene expression data showing a more differentiated state in the Wt line than in the hairpin Sh line. To analyze the role of RNA polymerase III and PARP1, we measured the Nanog and Oct4 expression in the Wt line cells treated with WYE, an RNA polymerase III inhibitor through mTOR, or with 3-aminobenzamide (3AB), a PARP1 inhibitor. We observed a recovery of the expression of both genes after the decreased induced by the retinoic acid treatment. The same treatment using Sh line cells retrieves an increase of the expression of both genes with WYE treatment and a similar expression with the 3AB treatment than control non-treated cells.
Conclusion: All together, these results suggest an implication of AhR, RNA polymerase III and PARP-1 in the cell differentiation process regulating the expression of Alus elements which may be downregulating genes of undifferentiated state maintenance.
No conflict of interest.

567 POSTER

SNAIL interacts with syndecan promoters in prostate cancer cell lines

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Background: Biopsy Studies from prostate cancer (PCa) patients show that expression pattern of syndecan 1 and 2 (SDC1 and SDC2) is associated with malignancy prognosis of biochemical recurrence. On the other hand, it has been shown an increased expression of SNAIL in biopsies from more aggressive PCa which is associated with a decreased expression of SDC. The same is observed in PCa cell lines with high tumorigenic capacity such as PC3 regarding cells with low tumorigenic potential as LNCaP. The aim of the preset work was to evaluate the specific interaction of SNAIL with gene promoter regions of SDC1 and SCD2 in PCa cell lines LNCaP and PC3.
Material and Methods: Commercial PCa cell lines of low (LNCaP, ATTC, Cat. CRL-1740) and high (PC3, ATCC, Cat. CRL-1435) tumorigenic capacities were used. Interaction of SNAIL with E-box sites of SDC1 and SDC2 promoters were assessed by chromatin immunoprecipitation (ChIP). Only E-box located −1100 bp downstream from transcription origin in both promoters were considered. To evaluate specific binding sites of promoter regions (ChIP positive) electrophoretic mobility shift assay (EMSA) were applies using fusion protein and nuclear extracts.
Results: ChIP results show interaction of SNAIL with two regions of SDC1 promoter in PC3 cells. In addition, an increase in the percentage of histone H3 input was observed in PC3 cells compared with LNCaP, suggesting an increase in chromatin compaction and the corresponding transcriptional repression of this region. No evidence for SNAIL binding to SDC2 promoter was found, suggesting no functional interaction of SNAIL with SDC promoters in none of cell lines studied. EMSA results suggest that SNAIL binding to DNA may be dependent on other factors due to no mobility retardation was found in presence of recombinant protein. When super-shift assay was performed to discriminate between two SNAIL members (SNAIL1 and SLUG) no shift difference was observed.
Conclusion: SNAIL interacts with SDC1 but not with SCD2 E-box promoter regions. SNAIL may be regulating SDC1 expression in PCa, suggesting a role in malignant progression.
Funding: Fondecyt Grant 1110269 (HC)
No conflict of interest.

568 POSTER

Role of AhR in murine spermatogenesis through regulation of the SINE B1-X35S retrotransposon

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Background: The dioxin receptor (AhR) is a transcription factor highly conserved in murine genome. Recent studies have shown that AhR has an important role in cell and organ homeostasis. We have also reported that AhR cooperates with the EMT regulator factor Slug in the activation of the novel murine B1-X35S retrotransposon, which has an insulator/boundary activity able to repress gene expression. The alterations in processing of retrotransposon-derived transcripts are considered a very relevant mechanism in disease progression, particularly in cancer. In mammals, methylation is the main transposable elements (TEs) silencing mechanism. This DNA methylation is temporarily lost in male germ cells, being the piRNA pathway the main defense against transposons. Those piRNAs are produced in a dense perinuclear cloud-like region called Nuage, where they associate with MILI and MIWI (murine orthologs of PIWI proteins) to form an active piRNA-induced silencing complex.
Material and Methods: AhR wild type (WT) and AhR knockout (KO) mice were used. Mouse testis were taken at different stages of spermatogenesis in order to obtain paraffin sections for immunohistochemistry experiments. Total RNA preparation was made to perform Northern Blot assays.
Results: We have seen that mice AhR KO show a deregulation in the B1X35S/piRNAs balance. Thus, these animals displayed a higher B1X35S mRNA expression compared to wild type ones. Furthermore, we determined small RNA expression by radioactive SDS-PAGE and found that piRNAs were increased in AhR KO, and individual RNA bands that were detected by Northern Blot assays were absent in AhR WT. We have also found differences in MILI, MIWI and MVH (another Nuage component) expression levels by both qPCR and WB assays. Moreover, we observed relocation towards the more differentiated areas of the seminiferous tubules in all of three proteins in the KO phenotype earlier. Molecular beacons *in situ* and *in situ* hybridization techniques will be used to address possible co-

localization between these proteins and transcripts derived from B1X35S and piRNAs.
Conclusions: Our results suggest a higher expression level of MILI and MIWI proteins in the AhR KO phenotype, as well as an early internalization towards the light of the seminiferous tubules of MVH, MILI and MIWI. RNA analysis by radioactive SDS-PAGE revealed that piRNAs were increased in AhR KO. These mice showed slightly reduced testis size and structural differences compared to the WT ones.
No conflict of interest.

569 POSTER

Insights into the regulation of GRIM-19 expression in renal cell carcinoma

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Background: GRIM-19 (Gene associated with Retinoid Interferon-induced Mortality − 19) is a novel tumor suppressor gene involved in interferon-β (IFN-β) and retinoic acid (RA)-induced cell death and is also a subunit of mitochondrial respiratory chain(MRC) complex I. It has been proposed that GRIM-19 plays a critical role in the etiopathogenesis of thyroid and kidney tumors. In thyroid, mutations in GRIM-19 gene were found to be exclusively associated with mitochondrion-rich tumors of thyroid (oncocytomas), suggesting that these alterations could be the reason for mitochondria accumulation, as a compensatory mechanism. On the other hand, renal oncocytomas did not harbor GRIM-19 mutations (unpublished data). However, we found GRIM-19 loss of expression or downregulation, but no mutations, in the majority of the renal cell carcinomas (RCC) studied. The data suggest that other mechanism(s), such as GRIM-19 transcription regulation or promoter methylation, may be involved in GRIM-19 loss of expression or downregulation in RCC.
The main purpose of this study was to clarify the mechanism behind GRIM-19 loss of expression or downregulation in RCC, particularly in clear cell RCC (ccRCC), which is the most common RCC histotype and the one that shows stronger downregulation of GRIM-19.
Material and Methods: Two ccRCC derived cell lines (Caki-2 and 786-O) showing different levels of GRIM-19 protein expression were tested. GRIM-19 gene mutations were evaluated by PCR and Sequencing and GRIM-19 mRNA expression by Real-time PCR. GRIM-19 promoter methylation was evaluated by bisulfite sequencing. In order to test how promoter methylation status impacts GRIM-19 expression, we treated the two cell lines with the DNA demethylating agent, 5-aza-2′-deoxycytidine (5Aza-dC).
Results: The 786-O cell line had lower expression of GRIM-19 protein than the Caki-2 cell line. No mutations in GRIM-19 gene were found in both cell lines. GRIM-19 mRNA levels correlate with the protein expression levels. Furthermore, we evaluated GRIM-19 promoter methylation status by studying in detail the methylation profile of the CpG islands. Surprisingly, the GRIM-19 promoter in the Caki-2 cell line appears to be more methylated than in the 786-O cell line. Upon treatment with a 5Aza-dC, we found a significant decrease in the promoter methylation status of Caki-2 cell line, while the 786-O cell line did not showed significant alterations. Additionally, protein expression analysis, after 5Aza-dC treatment, did not affect GRIM-19 expression in 786-O cell line and lead to a marked reduction (approximately 50%) in GRIM-19 expression in Caki-2 cells. We further observed that the 5Aza-dC treatment resulted in an increase in STAT3 mRNA levels.
Conclusions: GRIM-19 downregulation in ccRCC cell lines is not due to gene mutations. Caki-2 and 786-O cell lines have different expression of GRIM-19 protein and also show differences concerning the methylation status of the putative GRIM-19 gene promoter region. Our results suggest that GRIM-19 expression can be regulated by changes in promoter methylation. Further analyses are necessary to prove that the binding of transcription factors to GRIM-19 promoter (e.g. STAT3) is dependent on its methylation status and play a role in the regulation of GRIM-19 protein expression.
With this study we provided, for the first time, evidence that GRIM-19 expression might be under regulation of a repressive mechanism, through the action of transcription factors.
No conflict of interest.

570 POSTER

Genome-wide investigation of FK866-induced effects in Jurkat cells

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Acute lymphoblastic leukemia is a relatively uncommon form of cancer (17.3 per million in United States, of which T-ALL comprises about 25%) that usually affects infants, children and young adults. In T cell leukemia cell lines, apoptosis occurs when endogenous NAD synthesis is limited using FK866. This is a specific inhibitor of nicotinamide phosphoribosyltransferase (NAMPT), a key enzyme in the regulation of NAD biosynthesis from the natural precursor nicotinamide, that on lymphocyte activation becomes up-regulated to compensate for the increased metabolic demands.
By using Jurkat cells as a model of acute T-cell leukemia, we evaluated the effect of FK866 by AnnexinV/7AAD FACS analysis revealing a decrease in the number of cycling cells after treatment. The calculated IC_{50} at 48 hours was 5.5 nM. A significant, dose-dependent reduction of NAD-levels in treated samples confirmed the efficacy and specificity of the drug. To determine gene-expression changes caused by FK866-induced NAD depletion in leukemic T cells, we performed microarray analysis of RNA samples after sucrose gradient fractionation of Jurkat lysates (sub-polysomes, polysomes, total). Among the identified DEGs we analyzed polysomal/subpolysomal distribution in treated or untreated cells to characterize the multi-level gene-expression regulation effects of the drug. Up-regulated DEGs in the polysomal RNA from treated samples code for proteins involved in chromatin modification, nucleotide and RNA bioprocessing and metabolism.
The identified differentially expressed genes, in the early phase of cell response to FK866, and the genes accounting for a specific post-transcriptional regulation may help the identification of pathways involved in pharmacoresistance.
No conflict of interest.

571 POSTER

Peculiarities of molecular chaperone Hsp60 expression in thyroid cancer

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Background: Heat shock proteins (HSPs) are the most ancient defence system of all living organisms. HSPs function as molecular chaperones in regulation of cellular homeostasis and maintenance of cell survival. They are involved in numerous diseases, including cancer, revealing changes of their expression. A wide range of tumour cells have been shown to express Hsp60 atypical levels and localisation. For example, high expression of Hsp60 on the cell surface in breast cancer was associated with poor prognosis and resistance to chemotherapy. Hsp60 expression in thyroid cancer has not been studied extensively. Understanding its role in thyroid carcinogenesis has important implications regarding tumour behaviour and potential prognostic implications. The aim of our study was to evaluate the possible changes in Hsp60 expression and localization in thyroid tissue and content of anti-Hsp60 autoantibodies in patients' sera in normal state and upon pathology.
Material and Methods: Sera of 49 patients (12 nodular hyperplasia of thyroid gland, 12 autoimmune thyroiditis, 18 follicular adenoma, 6 papillary and 1 follicular carcinoma) and 12 healthy donors were used for determination of anti-Hsp60 antibodies by ELISA. We used surgical material obtained from 50 patients with thyroid gland pathology for immunohistochemical analysis. By histology, 23 malignant tumours (21 papillary thyroid carcinoma, 1 follicular thyroid carcinoma, 1 anaplastic thyroid carcinoma), 18 benign tumours − follicular thyroid adenoma, 4 Hashimoto's thyroiditis and 5 nodular hyperplasia were diagnosed. As a control, autopsy material of 11 thyroid tissue samples without morphological signs of thyroid pathology was used.
Results: More than 50% of non-malignant pathologies and 100% of malignant tumours were characterised by increased level of anti-Hsp60 antibodies. The highest titers of anti-Hsp60 antibodies were in group of malignant tumours (by 353%). The highest frequency of elevated Hsp60 expression has been found in cancer tissues (39%). The significant difference ($p < 0.05$) of staining index for Hsp60 has been observed only for thyroid cancer group as compared with control. There was no correlation between anti-Hsp60 antibodies and Hsp60 content in thyroid gland tissue at thyroid cancer (Spirman test, $r = 0.012$, $p = 0.94$).

Conclusion: We have determined increased level of anti-Hsp60 antibodies in sera of patients with thyroid gland pathology. The highest titers of anti-Hsp60 antibodies have been revealed in sera of patients with thyroid cancer. The increase of Hsp60 expression and changes in cellular localisation in thyroid cancer tissue have been detected and it was associated with morphological signs of pathology − lymphoid infiltration and sclerotic changes of tissue.
No conflict of interest.

572 POSTER

The effect of conditioned media of mesenchymal stem cells on proliferation and apoptosis of breast cancer cell line

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Background: Breast cancer remains the most prevalent malignancy among women of all races in the world. Induction of apoptosis and proliferation inhibition are widely recognized approaches to control cancer progression and reduced cancer risk. Recent studies reported that bone marrow (BM) derived from mesenchymal stem cells (MSC) migrate to sites of inflammation, tumor and injury in response to signals of cellular damage. In this study, the effects of conditioned medium (CM) of MSCs on proliferation and apoptosis of breast cancer cell lines was investigated through expression analysis of STK15 and surviving genes.
Material and Methods: MCF-7 cells were seeded into 6 well in CM of pre-cultured mesenchymal stem cells comparing the control group. Sub confluent cultures were isolated and expression level of STK15 and Survivin genes were analyzed by Q-RT-PCR.
Results: MSCs-CM have altered the expression of anti-apoptotic and prolifrative genes. After indirect coculture, in comparison with the control group, the expression of survivin and STK15 were upregulated 1.3 times.
Conclusions: It is mentioned in previous studies that mesenchymal stem cells can migrate into the tumor microenviroment and they are among the ideal candidate of cancer targeting and therapy. Overexpression of Survivin and STK15 as anti-apoptotic and proliferative genes may point to the negative effect of mesenchymal stem cells on cancer cells. Further research is needed to clarify the interaction of these cells and cancer cells.
No conflict of interest.

573 POSTER

Rutin induces cyclooxygenase (COX)-2 expression and matrix metalloproteinase (MMP)-9 expression via PI3K/Akt and JNK pathway in A549 human lung cancer cell

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Background: Rutin is a flavonoid with a wide range of biological activities and is found in many plants such as citrus fruits and vegetables. It is known to possess the anti-cancer and anti-inflammatory properties, although the underlying mechanisms have not been fully elucidated. In this study, we investigated the effect of rutin on COX-2 expression and MMPs expression of A549 cells.
Material and Methods: A549 human lung cancer cell was incubated for 24 h with rutin in the absence or presence of specific PI3K/Akt and JNKinase inhibitors, LY294002 or SP600125. Expression of COX-2 was performed by Western blot analysis and PGE_2 production was determined by PGE_2 assay. Expression of MMP-9 was detected by gelatin zymography.
Results: We found that rutin increases COX-2 expression and prostaglandin E_2 (PGE_2) production in a dose-dependent manner as determined by Western blot analysis and PGE_2 assay, and induces MMP-9 expression in a dose- and time-dependent manner as detected by Western blot analysis and Zymography. Rutin also stimulated the activation of PI3K/Akt and JNKinase pathways. In the presence of LY294002 or SP600125, specific inhibitor for PI3K/Akt or JNK, respectively, could significantly inhibit the COX-2 expression and PGE_2 production, and MMP-9 expression.
Conclusion: These data suggest that the activation of PI3K/Akt and JNKinase is required for rutin-caused COX-2 expression and MMP-9 expression in A549 cells.
No conflict of interest.

574 POSTER

Salinomycin inhibits cell proliferation and causes cyclooxygenase (COX)-2 expression via the mitogen-activated protein (MAP) Kinase pathway, JNK and ERK, in HT1080 human fibrosarcoma cells

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Background: Salinomycin is a monocarboxylic polyether antibiotic belonging to the group of inophores isolated from Streptomyces albus. It has recently been used to inhibit various cancer stem cells and is known to regulate various cancer cell responses including growth, proliferation, migration and apoptosis. However, the effect of salinomycin on HT1080 human fibrosarcoma cells has not yet been fully. Therefore, we investigated the effect and the regulatory mechanisms of salinomycin in HT1080 human fibrosarcoma cells.
Material and Methods: HT1080 human fibrosarcoma cells were treated for 24 h with salinomycin in the absence or presence of specific JNK and ERK inhibitors, SP600125 or PD98059. Cell proliferation was performed by MTT assay. Expression of COX-2 was detected by Western blot analysis and PGE_2 production was determined by PGE_2 assay.
Results: We found that salinomycin inhibits the cell viability and proliferation in dose- and time- dependent manner as detected by MTT assay and it significantly increases COX-2 expression and PGE_2 production as determined by Western blot analysis and PGE_2 assay. Salinomycin also increased the phosphorylation states of MAP kinases, the JNK and ERK, but not of p38. Using SP600125 or PD98059, specific JNK and ERK inhibitors, we found that JNK and ERK significantly are recovered cell viability and proliferation, and are prevented COX-2 expression and PGE_2 production.
Conclusion: These results suggest that salinomycin inhibits proliferation and increases COX-2 expression via MAP kinases, the JNK and ERK, in HT1080 human fibrosarcoma cells.
No conflict of interest.

575 POSTER

Whole exome sequence of BON-1 and QGP-1, two human pancreatic neuroendocrine tumor cell lines, reveals loss of heterozygosity and homozygotic mutations in the TP53 and MUC genes

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Background: The human BON-1 and QGP-1 cell lines are two often used models in pancreatic neuroendocrine tumor (PNET) research. Data on mutations in these cell lines is lacking.
Methods: The identity of the BON-1 and QGP-1 cell lines was confirmed using short tandem repeat profiling. The exome of both cell lines was sequenced using the HiSeq 1000 next generation sequencing platform (Illumina). Exonic sequences were enriched using Illumina's Truseq Exome Enrichment Kit. Paired-end reads were aligned to the human reference genome using the Burrows-Wheeler aligner. Single Nucleotide Variants (SNVs) and indels were called using the Genome Analysis ToolKit. Found mutations were validated using Sanger sequencing.
Results: The average region coverage for QGP-1 and BON-1 was 425x and 266x respectively. After filtering, possible protein-altering indels and SNVs were called (Table 1). We identified 55 frameshift-indels and 969 SNVs in the BON-1 cell line. Of these SNVs, 951 were non-synonymous, 17 stopgain and 1 stoploss. The QGP-1 sequences revealed 53 frameshift-indels and 651 SNVs of which 638 were non-synonymous and 13 stopgain. Heterozygosity of filtered SNVs was 65% in BON-1 and 75% in QGP-1, indicating loss of heterozygosity (LOH) in these rare polymorphisms. Homozygous (HoZ) mutations in *TP53* with a possible loss of function (LOF) were identified in both cell lines. Different *MUC* genes, implicated in cell signaling, lubrication and chemical barriers and frequently expressed in PNET tissue samples, showed HoZ protein-altering SNVs in the BON-1 and QGP-1 cell line. No mutations were found in known NET-associated genes.

Table 1. Number of single nucleotide variansts (SNVs) and insertion-deletions (indels) per filter step.

Filter steps	BON-1		QGP-1	
	SNVs	Indels	SNVs	Indels
Predicted mutations	63209	6424	56948	5888
Quality and coding DNA	46871	4618	41643	4243
Novel mutations	5509	4616	2936	4241
Protein-altering mutations	969	55	651	53

Quality and coding DNA: total reading depth $\geqslant$10, mapping quality $\geqslant$50, Fisher-Scaled Strand Bias $\leqslant$20, allelic ratio $\geqslant$0.3, snpEff annotation = coding;
Novel mutations: only SNVs and indels not in NCBI dbSNP130 database;
Protein-altering mutations: stopgain, stoploss, non-synonymous SNVs and frameshift indels.

Conclusion: LOH is associated with aggressive tumor behaviour and is observed in both cell lines. The LOF mutations identified in *TP53* may explain how QGP-1 and BON-1 escape apoptosis. Variations found in the *MUC* genes may play a role in PNET carcinogenesis.
No conflict of interest.

576 POSTER

Roles of genetic polymorphisms in ERP29, a tumor suppressor, and in IKBKAP, a DNA transcription factor, in mRNA levels, microRNA targets and protein structure

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Background: Our previous genome-wide association study identified single nucleotide polymorphisms (SNPs) located in 3′ un-translated region (3′UTR) of tumor suppressor *ERP29* (c.*293A>G, rs7114) and in coding sequence (CDS) of DNA transcription factor *IKBKAP* (c.3214T>A, rs3204145) associated with higher risk for base of tongue carcinoma. The overexpression of ERP29 was inversely correlated to breast cancer cells progression and with increased radio resistance in nasopharyngeal carcinoma. Recently, the IKBKAP was related to hypoxia-inducible factor 2-alpha network, an angiogenic factor, in melanoma cell line. However, the roles of the referred SNPs in the gene expression are still unknown.
Objectives: We aimed to investigate whether the SNPs in *ERP29* (rs7114) and *IKBKAP* (rs3204145) alter the mRNA levels, microRNA targets and protein structure.
Materials and Methods: The mRNA levels of *ERP29* and *IKBKAP* were quantified by real-time PCR using total RNA from peripheral blood leukocytes of 31 healthy individuals with distinct genotypes (wild-type, heterozygous, and variant homozygous). The reference housekeeping beta-actin gene was amplified in same plate of all samples. The gene expression was calculated by comparative DDCt threshold cycle method. Bioinformatics analysis of microRNA targets and protein structure were performed by *mirsnpscore* (bigr.medisin.ntnu.no/mirsnpscore) and SIFT (sift.jcvi.org) algorithms, respectively. The comparison of groups was performed by analysis of variance model.
Results: The mRNA levels (mean (standard deviation)) of *ERP29* (AA: 0.7 (0.3), AG: 1.2 (1.0) and GG: 0.9 (0.9) arbitrary units (AUs), $P = 0.45$) and *IKBKAP* (TT: 2.1 (1.8), TA: 2.6 (3.3) and AA: 1.4 (1.5) AUs, $P = 0.65$) were similar in individuals with distinct genotypes. We found that a microRNA, the *miR-362212-3p*, shared binding site complementary with 3′UTR of 'G' variant allele of *ERP29* while the 'A' allele disrupt this target site. We also found that amino acid substitution (p.Cys1072Ser) determined by c.3214T>A SNP in *IKBKAP* predicted a damage protein (SIFT score 0.02).
Conclusions: Our data present preliminary evidence that *ERP29* (rs7114) and *IKBKAP* (rs3204145) SNPs do not alter the expression of the respective proteins, but their variants alleles alter microRNA targets of *ERP29* and structure of the protein encoded by *IKBKAP*, respectively. Functional analyzes of the variant proteins in cancer cells should be conducted to confirm their roles in carcinogenesis.
No conflict of interest.

577 POSTER

Copy number profiling of primary colorectal cancer in a South African cohort by Affymetrix® Cytogenetics Whole-genome 2.7M microarrays

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Background: Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in Europe. This particular disease is one of the top five cancers in South Africa. Furthermore, CRC patients in South Africa generally present with advanced stages of disease (i.e. TNM stage II − IV). A deeper understanding of this disease is still required, as it has been reported that there is a 20−40% likelihood of recurrent disease in stage II, and approximately 40% in stage III disease. High-throughput genomic techniques are one way to facilitate an understanding of the molecular changes underpinning the pathophysiology of this disease.
Materials and Methods: DNA was isolated from 20 paired CRC tumour and normal mucosa samples. The isolates were then subjected to high-throughput copy number profiling. These assays were performed using the Affymetrix® Cytogenetics Whole-genome 2.7M microarray platform. The resultant datasets were analysed using Affymetrix® Chromosome Analysis Suite to detect chromosomal segments with altered copy number profiles. The results were then further analysed using R: a software environment for statistical computing and graphics. In particular, the distribution of copy number alterations (CNAs) across the genome was assessed, as well as the copy number profile of the genes associated with each chromosomal segment reported to have CNAs. The Gene Ontology enRIchment anaLysis and visuaLizAtion tool (GOrilla), Reduce and Visualize Gene Ontology (REViGO), and Gene Annotations co-occurrence discovery (GeneCodis3) web-service tools were used to assess the biological relevance of the list of genes with CNAs. This study is approved by the Human Research Ethics Committee (HREC) of the Faculty of Health Sciences at the University of Cape Town (HREC ref. no. 434/2010).
Results and Conclusions: Through analysis of the distribution of CNAs across the genome we have identified potentially novel regions of the genome with CNAs. By investigating the genes associated with these regions we are able to rationalise the biological functions and pathways potentially affected by such copy number changes. These data, when assessed alongside Affymetrix® GeneChip® Human Gene 1.0 ST gene expression datasets generated on the same samples, provide in some cases a putative explanation of the etiology of altered gene expression profiles, and the consequent change in biological processes associated with disease. The results of this study will provide further insight into the molecular underpinnings driving the pathology of CRC.
No conflict of interest.

578 POSTER

Genome instability in metachronous esophageal cancer

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Background: The development of novel therapeutic drugs and regimens to treat cancer has led to improvements in long-term survival but this success has been accompanied by the emergent problem of second primary therapy-induced cancers. Indeed, patients who received regional radiotherapy for Hodgkin's disease (HD) or breast cancer might develop a solid metachronous tumor many years later. Esophageal cancer is one of these malignancies that can arise in patients who have suffered of HD or breast cancer. Despite extensive epidemiological studies, little information is available regarding the genetic changes involved in the pathogenesis of these solid therapy-related neoplasias.
Material and Methods: We analyzed 18 samples from metachronous esophageal cancer patients: 12 squamous cell carcinoma (SCC) and 6 adenocarcinoma (ADC) raised in HD and breast cancers long-survivors.

As control, 19 samples (15 SCC and 4 ADC) from sporadic esophageal cancer were included in the study. The median time of appearance of the metachronous tumor was 22.5 years (range 5−40 years). Genetic instability was evaluated as the occurrence of LOH (Loss of Heterozygosity) and MSI (Microsatellite Instability) in several chromosomal regions. Three indices: FAL (Fractional Allelic Loss), FRL (Fractional Regional Loss) and MA (Microsatellites Alterations) were determined to calculate overall frequencies of LOH and MSI. Fisher's exact test was used to compare the frequencies; p value <0.05 was considered as significant.
Results: Using microsatellites markers located in chromosomal regions reported as frequently deleted in sporadic esophageal cancer (i.e. 3p24; 5p12; 5q11; 8p23; 9p21; 13q13; 17q21), and nearby genes that may contribute to carcinogenesis, we assessed LOH and MSI frequencies in both metachronous and primary esophageal cancers. No significant difference was found in LOH and MSI frequencies, with metachronous esophageal cancer exhibiting the same genomic alterations reported for the sporadic one, even when SCC and ADC were considered separately.
Conclusions: This finding may suggest that the cancerogenic pathway of primary and metachronous esophageal cancers are quite similar. The etiology of esophageal cancer is putatively related to environmental agents exposure and lifestyle (i.e. alcohol and tobacco). In this context, radiation, chemotherapeutic drugs and patients lifestyle may induce analogous damages and recapitulate the natural history of esophageal carcinogenesis.
No conflict of interest.

579 POSTER

NPM/NCL gene structure and B23/C23 expression in metastatic cutaneous melanoma

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Background: Cutaneous melanoma (CM) is characterised by an uncontrolled, clonal, cellular proliferation, as a result of numerous genetic and epigenetic aberrations. Genetic testing of CM is important for prognostication, when results are integrated with histological and clinical data. Nucleolin/C23 and nucleophosmin/B23 are major nucleolar argyrophilic proteins (AP) involved in carcinogenesis. There are none data on C23/B23 encoded genes *NCL*/*NPM* in CM although altered AP expression seems to associate with CM progression.
Material and Methods: DNA samples from 23 CM patient (CMP) metastatic nodes were analyzed by PCR for *NCL* and *NPM* gene structure followed by PAG electrophoresis of PCR products and DNA sequencing. Alterations in *NCL*/*NPM* encoded regions (23 CM samples) + *V600E BRAF* mutation (7 CMP) and 2 human CM xenografts (X) were studied. B23/C23 expression in X was estimated by specific immunohistochemical staining, quantity (density) and dispersion of positive dots per cell (>300 cells for sample) using MatLab 7.0 program.
Results: Genetic alterations in *NCL*/*NPM* gene structure in 23 CMPs and 1/2 X were grouped in several types: (1) two simultaneous nucleotide substitutions *IVS5−31G*/*A* + *IVS6+ −42G*/*A* in *NPM* gene in 13/23 (56%) CMPs and 1/2X; (2) nucleotide substitution *IVS8−63A*/*G* in *NPM* in 9/23 (39%) CMPs + two substitutions from the group (1); (3) 1 nucleotide substitution *IVS2 + 31G*/*A* in *NCL* gene; (4) germinal deletion p.D255delGAT (c.763–765delGAT − was also found in CMP blood cells) + common polymorphism p.E149E in *NCL* gene + intron structure variant in 1 CMP with 4 CM relapses. Somatic mutations *V600E BRAF* (70% in all CM cases) and *K600E BRAF* + AGT/AAA *BRAF* were revealed in 3/7 and 1/7 CMPs with 2−5 relapses, consequently. Somatic mutation *V600E BRAF* in 2CMPs with numerous metastasis was accompany by substitutions in *NPM* gene from the group (1) + group (2), except *IVS6−39A*/*G*. AP dots number and AP density was higher in X exponent growth than in slow growth phase ($p < 0.05$). AP irregular distribution in nucleoplasma was found in the majority of tumor cells during X exponent growth and more regular − in X with slow growth.
Conclusion: Some certain types of *NCL*/*NPM* gene alterations were found in 17/23 CMPs, and somatic *BRAF* mutations − in 4/7 CMPs. These genetic alterations and irregular distribution of B23/C23 with high density in nucleoplasma seems to be linked with numerous metastasis and tumor progression in CMPs.
No conflict of interest.

580 POSTER

MicroRNA-146a controls melanoma via a novel pathway

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MicroRNAs (miRs) are small endogenous non-coding RNAs able to post-transcriptionally downregulate the expression of target genes via sequence-specific interactions with the 3′ untranslated regions (UTRs) of cognate mRNAs. They act as fundamental regulators of a variety of biological processes, including tumour establishment and progression. As malignant melanoma is the most aggressive form of skin cancer, accounting for only 4% of cases but for as many as 74% of all skin cancer deaths at its metastatic stage, it is crucial to disclose its underlying molecular mechanisms. By taking advantage of a melanoma progression model, we identified a novel pathway controlled by miR-146a, whose expression enhances primary tumour growth while it impairs metastatization. MiR-146a's role in melanoma has been investigated by performing *in vitro* studies like proliferation assays, soft agar anchorage-independent growth, transwell migrations and invasions as well as *in vivo* injections of miR-146a-modulated cells into the flank or the tail vein of nude mice. Relevant miR-146a-modulated genes were investigated using bioinformatics and biological analyses, like quantitative real-time PCR (qRT-PCR), western-blot (WB) and luciferase assays. *In vitro* and *in vivo* phenocopy and rescue experiments were performed as well. Stable overexpression of miR-146a enhances cell growth *in vitro* as well as primary tumour growth *in vivo*, while it impairs cell movement *in vitro* and metastatic colonization *in vivo*. On the other hand, miR downmodulation by 'microRNA sponges' completely reverts these phenotypes. Such effects are exerted through repression of multiple genes; two of the targets, Numb and Lunatic Fringe (LFNG), have been described as negative regulators of Notch in breast cancer. Interestingly, both resulted strongly repressed in miR-146a-enriched cells. Numb modulation in melanoma cells reproduces miR-146a-mediated growth phenotypes. Therefore, we have found that miR-146a overexpression leads to increased Notch levels and transcriptional activity, as confirmed by enforced Hairy and Enhancer of Split 1 and 5 (HES-1 and HES-5) and N-cadherin expression. Furthermore, cyclin D1 upregulation was observed, maybe contributing to cell proliferation. Taken together, these findings suggest that miR-146a exerts a pleiotropic role in cancer. MiR-146a-dependent Numb targeting and consequent Notch signaling alteration could partly account for these phenotypes.
No conflict of interest.

581 POSTER

Loss of epigenetic control of proto-oncogenic eEF1A2 as a potential way to cancer progression

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Background: The eukaryotic translation elongation factor 1A2 (eEF1A2) is a known proto-oncogene. The overexpression of eEF1A2 has been observed in pancreatic, lung, ovarian and breast cancers. In the majority of ovarian cancer samples the overexpression of the gene was not related to the genetic or epigenetic modifications in the EEF1A2 locus. Thus, deregulation of the eEF1A2 expression can occur on the posttranscriptional level. We proposed that the eEF1A2 expression in cancer tissues is controlled by microRNAs.
Materials and Methods: Dual-luciferase assay was applied to detect the influence of miRNAs on EEF1A2 expression. For proliferation assay, human cells were transfected with miRNA precursors. After 72 h of incubation, the cells were stained and their number in each well was calculated using the Operetta® High Content Imaging System (Perkin Elmer). Changes in the eEF1A2 mRNA and miRNAs levels were quantified by qPCR.
Results: We found that eEF1A2 is a direct target of two oncosuppressor microRNAs hsa-mir-663 and hsa-mir-744. Both miRNAs were able to downregulate the expression of luciferase gene attached to the 3′UTR of EEF1A2 up to 20% and 50% respectively. Next, we examined the effect of hsa-mir-663 and hsa-mir-744 on the cellular eEF1A2 expression in MCF7 cell line. In this case, overexpression of hsa-mir-663 and hsa-mir-

744 reduced the EEF1A2 mRNA level by 44% and 68% and decreased the eEF1A2 protein level by 20 and 40% respectively.
Overexpression of both hsa-mir-663 and hsa-mir-744 inhibited the proliferation of MCF7 cell line. Treatment of MCF7 cell line with eEF1A2 siRNA showed similar inhibitory effect of the MCF7 proliferation. Hsa-mir-663 is well-known oncosuppressor and it was shown to be upregulated during resveratrol treatment of THP-1 and SW-480 cells. Resveratrol also inhibited eEF1A2 expression by blocking Akt in serum- or insulin-stimulated PA-1 cells. We observed upregulation of mir-663 and mir-744 with corresponding downregulation of eEF1A2 in resveratrol treated MCF7 cells, suggesting that resveratrol may influence the eEF1A2 expression through miRNA dependent pathway.
Conclusion: Obtained data are in favor of a novel explanation for the abnormal occurrence of the eEF1A2 isoform in tumor tissues, indicating that it may be caused by the loss of microRNA-mediated post-transcriptional control of the eEF1A2 expression.
No conflict of interest.

582 POSTER

The role of miR-196a and HOXB9 in head and neck squamous cell carcinoma

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Background: HOX genes are involved in embryogenesis and organogenesis in vertebrates. In total there are 39 HOX genes separated into 4 clusters (A-D) and 13 paralogous groups. HOX gene clusters contain conserved miRNA families including miR-196, with HOXB9 having a close spatial relationship with miR-196a-1 on chromosome 17q21. Our preliminary microarray data suggested marked up-regulation of miR-196a and HOXB9 in HNSCC.
Methods: The levels of miR-196a and HOXB9 in RNA extracted from normal (NOK), immortalised normal (iNOK), oral pre-malignant (OPM) keratinocytes and HNSCC-derived cell lines were assessed by quantitative-RTPCR (qRTPCR). Laser capture microdissection (LCM) followed by qRTPCR and immunohistochemistry were used to measure miR-196a and HOXB9 expression, respectively, on FFPE tissue samples. Anti-miR-196a and HOXB9 siRNA were transfected into OPM and HNSCC cells followed by functional assays for adhesion, proliferation, invasion and migration. Nested PCR was used to test the presence of a novel HOXB9 and miR-196a-1 primary transcript. Microarray analysis of anti-miR-196a and pre-miR-196a transfected cells was conducted using Agilent Sureprint G3 array and analysed by Qlucore Omics Explorer and gene expression changes validated by qRTPCR.
Results: 600–4000 and 400–40000 fold up-regulation of miR-196a and HOXB9 respectively was observed in OPM and HNSCC cells relative to NOK's. FFPE cancer tissue samples showed significant up-regulation compared to normal tissue for miR-196a and HOXB9 ($p < 0.05$). Transfection of anti-miR-196a resulted in reduced adhesion, invasion and migration ($p < 0.001$) and no change in proliferation of HNSCC cells. HOXB9 siRNA transfected cells showed no significant change in adhesion but migration, invasion and proliferation were decreased ($p < 0.05$). Nested PCR showed the presence of common primary transcript consisting of HOXB9 and miR-196a-1. Microarray analysis and qRTPCR validation showed HOXC8, MAMDC2 and RFC3 to be putative targets of miR-196a.
Conclusions: Our data shows that miR-196a and HOXB9 are over-expressed in HNSCC. miR-196a and HOXB9 promote functional effects in HNSCC and changes in expression of known and novel miR-196a target genes. The identification of a novel primary transcript suggests coordinated expression of HOXB9 and miR-196a-1; elucidation of factors responsible for regulating levels of this transcript may therefore represent important therapeutic targets.
No conflict of interest.

583 POSTER

miRNAs in resistance to lapatinib in HER2-positive breast cancer

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Background: Despite significant progress in HER2-directed therapy, only a subset of patients derives optimal benefit from treatment, whereas other patients have refractory disease or develop resistance. Recent studies have shown that microRNAs are potentially linked with drug resistance, however, their role in resistance to HER2-directed therapy is currently unknown.
Material and Methods: Taqman Low Density miRNA Human A and B Arrays were used to identify a panel of miRNAs differentially expressed between a lapatinib-sensitive and paired lapatinib-resistant HER2 positive breast cancer cell line (BT-474). A selection of miRNAs were chosen for further investigation based on biological relevance of putative targets. BT-474 cell lines were transfected with mirVana mimics or inhibitors and IC50 determined by AlamarBlue to determine if there was altered sensitivity to lapatinib. Cellular proliferation (AlamarBlue) and apoptosis (CaspaseGlo 3/7) was measured at 6, 10 and 24 hrs, D2, D3, D5 and D7. Putative targets of miRNAs were determined by *in silico* analysis of miRWalk predicted targets and gene expression array data (Illumina HT-12 Expression BeadChip). Targets were validated by qPCR, Western blotting and luciferase reporter assay.
Results: Sixteen miRNAs were up-regulated and 14 down-regulated in the BT474 lapatinib-resistant cell line (<2.0 fold difference) relative to the BT-474 lapatinib-sensitive cell line, which was confirmed by qPCR. Transfection of the BT-474 lapatinib-sensitive cell line with 1nM miR-127-3p, miR-409-3p or miR-495 mirVana mimic altered the sensitivity to Lapatinib and proportion of cells undergoing apoptosis at 24 hrs. *In silico* analysis identified 7, 63 and 207 mRNAs down-regulated in the BT-474 lapatinib-resistant cell line that were putative targets of miR-127-3p, miR-409-3p and miR-495, respectively. Preliminary data suggests that transfection of the BT-474 cell line with miR-495 mimic may modulate multiple components of the RAC/RHO GTPase signalling system, downstream of ErbB2.
Conclusion: These data provide the first evidence indicating miRNAs may confer resistance to lapatinib in HER2 positive breast cancer. In addition, the putative regulation of multiple components of the Rac/Rho GTPase signalling pathway downstream of ErbB2 by miR-495 suggests novel pathways involved in resistance to Lapatinib.
No conflict of interest.

585 POSTER

The role of HOXD10 in head & neck and lung cancers

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Background: Genetic alterations in non-small cell lung cancer (NSCLC) and head & neck squamous cell carcinoma (HNSCC) are variable and correlate with the cancer site and stage. Microarray analysis comparing HNSCC with normal mucosa revealed changes in HOX gene expression, particularly HOXD10. HOXD10 expression is altered in many cancers and interacts with important molecules such as miR-7 and miR-10b in breast cancer and IGFBP3 in gastric cancer. We hypothesise that the variation of HOXD10 expression in NSCLC and HNSCC development produces differential effects, with high expression giving cancer cells proliferative advantage over normal cells while low expression might support the metastasized cells to survive.
Materials and Methods: Expression of HOXD10 and associated molecules was assessed by qPCR and Western Blotting (WB). HOXD10 protein in tissues was detected by immunohistochemistry (IHC). Cloned-HOXD10 and shRNA/siRNA were transfected into low- and high-HOXD10 expressing cells, respectively. The resultant phenotype was assessed by MTS assay, fibronectin adhesion assay, and modified transwell migration assay. Novel HOXD10 putative targets and differentially activated pathways were identified using Agilent microarray. Dual luciferase reporter assay was used to detect direct targets of HOXD10.
Results: HOXD10 RNA and protein level showed low expression in normal cells; low/variable in precancerous cells; high in most primary tumours; but very low in cancer cells derived from lymph node metastases. Manipulating HOXD10 expression affected cell proliferation, adhesion to fibronectin, and migration. Microarray and DLR experiments have revealed putative and direct targets of HOXD10, respectively, in HNSCC cells that might explain some of these effects seen.
Conclusion: The results suggest that high HOXD10 expression allows primary tumours to grow and spread while its loss at the advanced front allow cancer cells to be less adhesive and have more metastasis potential. The large number of molecules identified to be direct or putative targets of HOXD10 suggests a range of effects and might explain its stage-dependent role.
No conflict of interest.

586 POSTER

Methylation status of selected microRNAs in imatinib-sensitive and imatinib-resistant chronic myeloid leukaemia (K562) cell lines

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Background: Several microRNAs (miRs) are involved in carcinogenesis and can be either oncogenic (oncomir) when tumour suppressor genes are targeted or tumour suppressive when their targets are oncogenes. Several miRs, including 124−1, 124−3, 126, 145, 150, 17−92, 200c, 203, 34a and let7a3 are known to be deregulated in haematological malignancies and implicated in disease progression and/or drug resistance.
Material and Methods: We analyzed promoter methylation in the above referred miRs in the human chronic myeloid leukaemia (CML) cell line (K562), sensitive and resistant to the front-line standard treatment, Imatinib, using methylation-specific PCR. Expression was determined with quantitative Real-Time PCR using microRNA PCR primer sets (Exiqon).
Results: Our data revealed that in both resistant and sensitive K562 cells miRs 150, 17−92 and 145 aren't methylated, 124−3 is hypermethylated, miR 34a is heterozygously methylated (more methylated than unmethylated) and let7a3 is hemizygously methylated. MiR 126 gave opposite results depending on the CpG island studied. A distinct methylation profile between sensitive and resistant K562 cells was found for miRs 203, 124−1 and 200c. MiRs 124−1 and 200c aren't methylated in sensitive cells but are hemizygously methylated in resistant cells. MiR 203 is hemizygously methylated in sensitive cells and almost totally unmethylated in resistant cells. Preliminary results of miR expression revealed that miRs 124 and 200c are in fact more expressed in sensitive cells than in resistant cells. However, we could not detect miR 203 expression in either K562 cells.
Conclusion: Our results don't confirm previous reports which showed hypermethylation of miR 203 in CML, a tumour suppressor miR that controls the expression levels of the BCR-ABL1 translocation protein. We show that methylation of miRs 124−1 and 200c may be acquired during disease progression and after chronic treatment followed by resistance development. Therefore, studies modulating the expression levels of these miRs are warranted to ascertain if they are indeed critical targets for increasing CML sensitivity to clinical therapies.
No conflict of interest.

587 POSTER

Shifts in microRNA expression impair DNA methylation and chromatin remodeling in cancer cells

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Background: Epigenetic instability, deregulation of chromatin remodeling as well as impaired balance between DNA methylation and demethylation is typical of many cancer cells. Also, tumor growth is tightly associated with regular shifts in microRNA (miRNA) expression pattern. Usually, expression of miRNAs miR-16, miR-122, miR-31, miR-143, miR-145 and miR-320 is down-regulated in cancer cells whereas expression of miRNAs miR-18a/b, miR-19, miR-21, miR-29a, miR-155, miR-181, miR-206, miR-210 and miR-221/222 is up-regulated. This investigation aims to identify in what way these shifts in miRNA expression contribute to the abnormalities in DNA methylation and chromatin remodeling in cancer cells.
Material and Methods: miRNA targets within gene transcripts were predicted in silico using TargetScan software.
Results: MiRNAs miR-17-5p, miR-26 and miR-205 can silence KAT2B gene encoding histone acetyltransferase PCAF. MiRNAs miR-145, miR-206 and miR-15a/16 target transcript of gene encoding acetyltransferase Elp3. miR-204 and miR-26 suppress ATF2 gene. MiRNA miR-22 silences KAT6A/B and KAT5 genes encoding acetyltransferases MOZ, MORF and TIP60. Also, miR-320 and miR-122 can suppress KAT6B gene. MiRNA miR-143 targets transcript of MYST2 gene coding acetyltransferase HBO1. MiRNA miR-26 can silence genes encoding CREBBP and EP300 factors. Also, miR-22 and miR-17-5p target transcript of EP300 gene. At least one of miRNAs miR-204, miR-145, miR-320, miR-26, miR-17-5p, miR-125a-3p, miR-22 or miR-31 can suppress KDM1A/B, KDM2/B, KDM3A, KDM4A/B/C and KDM5A/C/D genes encoding histone demethylases. MiRNAs miR-31, miR-22, miR-122 and miR-320 can silence ARID1A/B, SMARCC2, SMARCD1/2 and ACTL6A genes coding components of SWI/SNF chromatin remodeling complex. Transcripts of HDAC1/2/4/6/7/8/9 as well as SIRT1/3/5/7 genes encoding histone deacetylases carry targets for at least one of up-regulated miRNAs miR-155, miR-23a/b, miR-375, miR-21, miR-29, miR-206, miR-19, miR-221/222, miR-181 or miR-18. Also, these miRNAs can silence ASH1L, DOT1L, EHMT1/2, EZH1, MLL, MLL2/3/5, NSD1, PRDM2, SET, SETBP1, SETD1A/B, SETD2/3/5/6/7/8, SETDB1/2, SMYD1/2/4/5, SUV39H1/2 and SUV420H1/2 genes encoding histone methyltransferases. MiRNAs miR-29, miR-221/222, miR-206, miR-21 and miR-375 suppress genes encoding de novo DNA methyltransferases DNMT3A, DNMT3B and DNMT3L.
Conclusions: MiRNAs, hyperexpression of which is essential for abnormal proliferation and surviving of cancer cells, silence also genes encoding histone deacetylases, histone methyltransferases and de novo DNA methyltransferases. Down-regulation of other miRNAs allows overexpression of genes encoding histone acetyltransferases, histone demethylases as well as components of chromatin remodeling complexes. This causes increase of overall level of chromatin acetylation and expression and, therefore, makes possible the reactivation of silent oncogenes and transposons, which can rapidly lead to DNA damage and genome destabilization. Such shifts may underlie the initial stage of carcinogenesis.
No conflict of interest.

588 POSTER

Intra-tumor heterogeneity in STAT3 activity is linked to CIP2A expression

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Background: Constitutive STAT3 activity plays a critical role in development and progression of many types of cancer. Head and neck squamous cell carcinoma (HNSCC) in particular is highly dependent on STAT3 activation, to the extent that it has been described as oncogene addiction. This makes STAT3 an appealing drug target, however, more detailed understanding of STAT3 regulation is needed. There is considerable intra-tumor heterogeneity in STAT3 activity, STAT3 has functions in tumor microenvironment, and in some cases STAT3 functions to limit tumor growth. We identified a potential novel mechanism for regulation of STAT3 activity in human cancers.
Materials and Methods: STAT3 phosphorylation levels were analyzed by western blotting in CIP2A depleted human cancer cell lines and CIP2A knockout MEFs. CIP2A depleted cancer cells were treated with STAT3 inhibitor S31–201 and cell viability was measured in a colony formation assay. Tissue microarray (TMA) of human HNSCC samples was stained for total STAT3, pY705 STAT3, pS727 STAT3, and CIP2A.
Results: CIP2A depletion increases STAT3 Y705 and S727 phosphorylation and sensitizes cancer cells to S31–201. Phosphoproteomics and microarray analysis of CIP2A depleted cells identified a potential molecular mechanism by which CIP2A regulates STAT3 activity. In HNSCC TMA CIP2A expression positively correlated with cytoplasmic to nuclear ratio of total STAT3 ($p = 0.0271$) and pS727 ($p = 0.0005$). Nuclear pY705 showed some correlation with CIP2A ($p = 0.0193$), however, in heterogeneous samples CIP2A and pY705 were often observed in different cell populations. Cells expressing high levels of CIP2A were generally poorly differentiated, whereas nuclear STAT3 was observed in the well differentiated cell populations.
Conclusions: Our results suggest that CIP2A is a novel negative regulator of STAT3 activity and determinant of the heterogeneity in STAT3 activity in HNSCC. Furthermore, strong CIP2A staining and predominantly cytoplasmic STAT3 staining were associated with poorly differentiated phenotype. Recent studies on HNSCC, lung, breast, and salivary gland carcinoma have associated high nuclear pY705 with better prognosis and reported reduced levels in advanced stage cancers. In our model, CIP2A is a driver of STAT3 independent phenotype. This is supported by our finding that following CIP2A depletion cells revert to a more STAT3 addicted state, in which STAT3 is highly phosphorylated and cells are more sensitive to STAT3 inhibitor.
No conflict of interest.

589 POSTER

Genetic variants in CHI3L1 influencing YKL-40 levels: Resequencing 900 individuals and genotyping 9000 individuals from the general population

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Background: Despite its important role in many serious diseases, including cancer, the genetic background for plasma YKL-40 still has not been systematically catalogued. Therefore, we aimed at identifying genetic variants in *CHI3L1* influencing plasma YKL-40 levels in the general population.
Material and Methods: We resequenced the promoter, all 10 exons and exon-flanking intron segments of *CHI3L1* in 904 individuals from the Danish general population ($n = 8\,899$) with extreme plasma YKL-40 levels, adjusted for age. To potentially identify clinically important genetic variants with

elevated plasma YKL-40 levels, we included twice as many individuals with the highest plasma YKL-40 levels (n = 603) compared to the lowest plasma YKL-40 levels (n = 301). Next, we mapped linkage disequilibrium for all variants with a minor allele frequency (MAF)>0.005. Finally, all participants were genotyped for 8 variants that had divergent MAFs in the two extreme plasma YKL-40 groups and were not in strong linkage disequilibrium (except 2 promoter SNPs).
Results: We identified 59 genetic variants in *CHI3L1*. Fifteen of the genetic variants were associated with plasma YKL-40 levels. Three promoter SNPs, 1 non-synonymous SNP, and 4 intronic SNPs tagging C*HI3L1* were associated with plasma YKL-40 levels at or below genome wide association significance levels (unadjusted p for trend: from $4x10^{-8}$ to $6x10^{-243}$; age adjusted percentiles p for trend: from $3x10^{-12}$ to $2x10^{-304}$).
Conclusion: In a systematic search to identify genetic variants influencing plasma YKL-40 levels, we identified 8 SNPs associated with plasma YKL-40 levels in the general population.
No conflict of interest.

590 POSTER

Novel alternatively spliced isoform of synuclein gamma

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Introduction: Since Synuclein γ (SNCG) is found highly expressed in advanced breast cancer it was initially described as breast-cancer specific gene (BCSG1). Clinical studies demonstrate the correlation of high SNCG expression with advanced stages, metastasis and poor prognosis in breast and ovarian carcinomas, i.e. reduced relapse-free and overall survival periods. In vitro analyses revealed a SNCG-dependent stimulation of ligand-dependent transcriptional activity of estrogen receptor alpha. Thus, SNCG might be an auspicious prognostic marker and therapeutic target for the treatment of estrogen-dependent cancers. So far, four mRNA isoforms of SNCG were described, but only isoforms 1 and 2 code for active proteins. For the first time, we analyzed expression levels of SNCG mRNA isoforms in regard to hypoxia or extracellular acidosis, as typical epiphenomena of solid tumors, in vitro in endometrial cancer cells.
Material and Methods: Four different endometrial cancer cell lines with varying receptor status and one SNCG-positive breast cancer cell line (reference) were cultured under hypoxic, acidic or regular (control) conditions. RNA and protein isolation was followed by PCR, RT-PCR, Western blot and immunohistochemical analysis.
Results: In comparison to the reference breast cancer cell line, endometrial cancer cell lines displayed a general significantly reduced expression of SNCG isoform 1, 2, 3 and 4. In contrast, a novel, shortened mRNA variant of isoform 2 was identified in endometrial cancer cells. Hypoxia and acidosis triggered a marked up-regulation of the novel *isoform 2 short*, while the expression of constitutive isoform 2 did not significantly change under altered conditions. Immunohistochemistry and Western blot revealed a hypoxia- and acidosis- dependent increase in SNCG protein expression.
Conclusion: We hypothesize, that the novel SNCG *isoform 2 short* bears a specific oncogenic potential in endometrial cancer cells, since it could be detected in elevated levels under hypoxic and acidic conditions, as typical epiphenomena of solid tumors. Furthermore we postulate that this novel isoform is capable to code for a biologically active protein isoform. Since up to date no isoform-specific antibody is available for explicit SNCG isoform characterization, a definite verification is subject to current further analysis.
No conflict of interest.

591 POSTER

CIP2A stabilizes MYC in cancer cells and during in vivo tissue regeneration

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Background: The MYC oncogene contributes to the genesis of many human cancers. Post-translational regulation of MYC stability correlates with tumorigenesis and Cancerous inhibitor of PP2A (CIP2A) has been shown to be an important mediator of MYC stability in cancer cells. However, the physiological relevance of post-translational regulation of MYC stability in normal tissues has remained very poorly understood.
Material and Methods: The importance of MYC serine 62 phosphorylation during intestinal regeneration were addressed in AhCre $Myc^{fl/fl}$ mice with mice carrying a Lox-stop-Lox c-myc or Lox-stop-Lox c-myc^{T58A} allele to generate $Myc^{fl/fl}$ $Rosa^{Myc/+}$ and $Myc^{fl/fl}$ $Rosa^{MycT58A/+}$ mice respectively. $CIP2A^{HOZ}$ mice and their wild-type controls were used to determine if increased CIP2A expression functionally contributes to MYC-dependent intestinal regeneration, crypt regeneration following irradiation. Cell autonomous function for CIP2A in regulating MYC serine 62 phosphorylation and activity was demonstrated in CIP2A-deficient MEFs. The subcellular distribution of CIP2A and MYC was examined by cell fractionation and differential detergent fractionation (DDF).
Results: Here, we found that DNA-damage-induced intestinal regeneration was significantly perturbed upon deletion of CIP2A. In regenerating intestine, deletion of CIP2A corresponded with a reduction in serine 62 phosphorylated MYC and failed induction of MYC target genes. Cell autonomous function for CIP2A in regulating MYC serine 62 phosphorylation and activity was demonstrated in CIP2A-deficient MEFs. Furthermore, we found that serine 62 phosphorylated subpopulation of MYC at nuclear lamina is exclusively sensitive to CIP2A-mediated regulation.
Conclusions: Together these results demonstrate that post-translational regulation of CIP2A-sensitive sub-population at nuclear lamina is a critical determinant of MYC's biological activity in proliferation induction, and may help to develop CIP2A-based MYC targeting therapy for cancer.
No conflict of interest.

592 POSTER

Functional characterization of NIMA (never in mitosis gene a)-related kinase 2 in hepatocellular carcinoma

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Background: The centrosomal kinase NIMA (never in mitosis gene a)-related kinase 2 (Nek2), which regulates the separation of centrosome, has been reported to be overexpressed in various cancers. Nevertheless, the expression profile of Nek2 in HCC has not been investigated and its role in HCC remains unknown. Previously our team has demonstrated the involvement of centrosomal protein TAX1BP2 in hepatocarcinogensis, prompting us to examine the functional role of Nek2 in HCC.
Material and Methods: Nek2 mRNA and protein expressions were examined in paired clinical HCC samples by RT-PCR and immunohistochemistry respectively, and the clinical significance was evaluated. Nek2 knockdown stable clones were established in HCC cell line PLC and metastatic 97L cell line by lentiviral transduction. The stable clones were then subjected to various functional assays. The effects of Nek2 on cell proliferation, migration and invasion were investigated.
Results: Overexpression of Nek2 was found in 80% (39/49) of tumours as compared to their non-tumour counterparts (P<0.0001). Nek2 expression was significantly associated with the absence of tumour encapsulation (P = 0.013), higher tumour stage (P = 0.003) and presence of venous invasion (P = 0.012). Immunohistochemistry revealed Nek2 localization at nucleus and cytoplasm, suggesting that Nek2 might have functions other than controlling centrosome separation. Nek2 expression was detected in all HCC cell lines. Diminution of Nek2 dramatically impeded the proliferation rate of HCC cells (P<0.0001) and profoundly suppressed the cell motility (P<0.0001) as well as invasiveness (P = 0.0232).
Conclusions: Our data has shown for the first time the oncogenic role of Nek2 in HCC. We believe that Nek2 expression encouraged aggressive tumour behaviour by promoting cell proliferation and invasiveness.
No conflict of interest.

593 POSTER

Glutathione and glutathione-S-transferase in the forecast of cancer therapy in patients with non-Hodgkin's lymphoma (NHL)

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NHL is often characterized by unpredictable clinical course, i.e. patients with the same disease stage, morphology, and treatments for this disease can be dramatically different. As a consequence, one can remain latent for many years, and others, on the contrary, rapidly progressing incurable with the spread of the disease. One possible reason for the unexpected course of the disease may be the multidrug resistance of tumor cells to chemotherapeutic drugs.
Resistance of malignant cells to chemotherapeutic drugs is a major cause of recurrence of disease and death of most patients. One of the major

causes of cellular drug resistance is over expression of the transport-gene family of multi-drug resistance, as well as the expression of specific proteins responsible for the 'neutralization' of chemotherapeutic drugs in cancer cells. These proteins include Pgp170, multidrug resistance-associated protein − MRP, LRP, glutathione transferase.
The task of the study: Evaluation of clinical perspectives of the determination of glutathione and activity of glutathione-S-transferase in the medicinal treatment of patients with NHL.
Materials and Methods: Investigation of the content of glutathione (GSH) and activity of glutathione 5-transferase (GT) in malignant tumors and in 37 NHL patients erythrocytes, who received chemotherapy according to standard procedure.
Results: It is shown that the level of GSH (0.65±0.03 mmol/g) and the activity of GT (1.85±0.05 mmol/min/g) is higher in NHL. At the same time, it was found that initially in tumors treated effectively levels of GSH and the activity of GT is lower than in progressing disease. An inverse correlation between biochemical parameters and the effectiveness of treatment ($r = -0.81$, $p = 0.003$ and $r = -0.88$, $p = 0.005$).
In patients with NHL initial GSH levels varied within wide limits (from 0.4 to 2.03 mmol/ml in erythrocytes). Retrospective analysis showed that the in case of effective treatment the initial GSH levels did not exceed 0.8 mmol/ml (at a rate of 1.19±0.17). In contrast, patients with a high content of GSH (from 0.95 to 2.03, i.e. above 0.8 mmol/mL) showed disease progression. The inverse correlation was also observed when comparing the activity of GT and the effectiveness of treatment ($r = -0.76$, $p = 0.002$). Effective treatment is accompanied by a gradual increase in the content of GSH and a decrease in the activity of GT, which may be one of the causes of resistance to the drug in the treatment process.
Conclusions: There was an inverse correlation between the level of GSH, the activity of GT and the effectiveness of treatment. Established unidirectional changes in tumors and erythrocytes gives grounds to recommend the evaluation of these parameters in NHL patients for prognostic assessment of tumor sensitivity to medication.
No conflict of interest.

594 POSTER

GDNF confers chemoresistance through specific GFR isoforms in human glioma cell line

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Background: Malignant gliomas, the most common brain tumours in adults, are characterised by their highly aggressive nature and poor prognosis. High grade glioma develop resistance to the standard first line drug, Temozolomide (TMZ) rapidly and at high frequencies. Although the TMZ resistance was found to be associated with DNA repair pathways, the underlying mechanism of chemoresistance is largely unclear and the prognosis remains unsatisfactory. While the emerging view is that autocrine and paracrine signals can influence tumour biology, there is a lack of knowledge in the role of the growth factor signalling in TMZ resistance. We attempted to investigate the role of Glial derived Neurotrophic Factor (GDNF), a ubiquitous compound in the brain, overexpressed and released by glioblastoma in TMZ resistance.
Material and Methods: From U251MG and LN229 cell lines, glioma cell lines possessing acquired resistance to TMZ were developed. Initiating treatment at 2.5 μM, cells were cultured in the presence of incremental TMZ concentrations: 2.5, 5, 10, 20, 40, 80, 160 and finally 320 μM. During the selection of resistant clones, cells were allowed to adapt to TMZ for 30 days before exposure to the next dose. The expression of GDNF receptor complex and GDNF signalling pathway were monitored. The function of GFR receptor in TMZ resistance was examined through siRNA knockdown studies.
Results: We found that GDNF conferred chemoresistance in both LN229 and U251MG parental cell lines. We further showed that knockdown of GFR isoform 1b and RET9 but not NCAM reversed drug resistance induced by GDNF. Interestingly, expression of GFR receptor isoforms altered when cells acquired resistance to higher dose of TMZ where upregulation of RET9 but not NCAM was observed.
Conclusions: This study provides the first evidence that specific GFR isoforms are involved in chemoresistance. The identification of GDNF signalling conduit may shed new insight into the molecular mechanisms of TMZ chemoresistance and may provide novel targets for glioma prognosis or therapeutics.
No conflict of interest.

595 POSTER

The role of erlotinib − induced autophagy in non-small cell lung carcinoma

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Background and Aim of Study: Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer deaths. Tyrosine kinase inhibitor (TKI) like erlotinib is commonly used as a treatment regimen since epidermal growth factor receptor (EGFR) is frequently deregulated in NSCLC. Autophagy is a regulated cellular catabolic process in response to deprivation of nutrients or growth factors. This study aims to investigate whether autophagy confers acquired resistance to erlotinib treatment in NSCLC.
Methods: Two NSCLC cell lines (HCC827 and HCC4006) with EGFR mutations (exon 19 deletions) were selected. Proliferation (MTT) assay and annexin-V binding assay were performed to determine cell proliferation and cell death upon erlotinib treatment. Autophagy induction was monitored by ATG-5/ATG12 conjugation, p62 degradation and conversion of LC3I to LC3II using Western blot. Increase in acidic vesicular organelle (AVO) formation was determined by acridine orange staining. Autophagy inhibitor (chloroquine) and RNA interference were used to study the effect of erlotinib-induced autophagy.
Results: MTT confirmed that both cell lines were sensitive to erlotinib (IC_{50} <0.5 μM). Erlotinib treatment increased LC3II expression, ATG-5/ATG12 conjugation, formation of AVO and p62 degradation, compatible with induction of autophagy. Combination of 10uM chloroquine (autophagy inhibitor) with 0.2uM erlotinib increased apoptotic events compared to erlotinib or chloroquine alone (HCC827: 52.3±2.8% vs 21.2±4.2% vs 13.0±2.5%, $p < 0.01$; HCC4006: 49.3±4.8% vs 9.4±2.4% vs 9.0±1.8%, $p < 0.01$; chloroquine + erlotinib vs erlotinib vs chloroquine respectively). Atg5 and beclin 1 knockdown with siRNA resulted in significant autophagy inhibition. Apoptotic cell death in erlotinib combined with ATG-silencing (51.8±1.9%) or beclin-silencing (53.4±2.0%) was increased comparing with erlotinib alone (22.8±3.8%, $p < 0.01$), ATG-silencing alone (7.3±4.4%, $p < 0.01$) or beclin-silencing alone (10.3±4.6%, $p < 0.01$) in HCC827 cells. Similarly, in HCC4006, apoptotic cell death was significantly enhanced in erlotinib combined with ATG-silencing (53.1±3.4%) or beclin-silencing (61.9±5.1%), comparing with erlotinib alone (27.4±8.6%, $p < 0.01$), ATG-silencing alone (6±2.7%, $p < 0.01$) or beclin-silencing alone (11.5±4.3%, $p < 0.01$).
Conclusions: Erlotinib can induce both apoptosis and autophagy in EGFR mutated (exon 19 del) NSCLC cell lines. Inhibition of autophagy with chloroquine or siRNA can enhance erlotinib-induced cell death. Autophagy may serve as a protective mechanism for NSCLC upon treatment with erlotinib.
No conflict of interest.

596 POSTER

Effects of vitamin D binding protein-derived macrophage activating factor on human neuroblastoma cells and predicted molecular interaction with the vitamin D receptor

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Background: Vitamin D binding protein-derived Macrophage Activating Factor (GcMAF) proved effective in a variety of experimental and human carcinomas. In this study we evaluated its effects on human neuroblastoma cells and we studied the predicted molecular interactions with the vitamin D receptor (VDR).
Materials and Methods: Human neuroblastoma cells (cell line SH-SY5Y, ATCC) were treated with increasing concentration (0.4−40 ng/ml) of purified GcMAF (Immuno Biotech) for 24−48−72 h. Cell viability and proliferation were assessed by MTT assay (Sigma-Aldrich). cAMP levels were measured by competitive EIA assay (Abnova) after 15 min challenge with GcMAF. Cells were observed by light microscopy (Optika, Nikon) at 24−48−72 h.
Results: GcMAF decreased human neuroblastoma cell viability and induced morphological alterations that were interpreted as induction of apoptosis. These data are consistent with the hypothesis that GcMAF exerts a direct effect on cancer cells in addition to its immunostimulating properties. GcMAF stimulated the rapid formation of cAMP that could be responsible for the induction of apoptosis. We also determined the predicted molecular interactions between GcMAF and VDR that could be

responsible for the observed non-genomic effects. GcMAF and VDR share 20% identity of amino acid (aa) sequence in the tract coded for by exons 1, 2, 3, 4, 5, i.e. aa 1–197. A higher degree of identity (40%) was observed in the tract coded for by exons 6, 7, 8, i.e. aa 217–330. The first 23 aa of the NH-terminus of GcMAF and the last 23 aa of VDR are highly hydrophobic and could represent a site of interaction for the two proteins.
Conclusions: The proposed mode of interaction between GcMAF and VDR could explain the observed association between VDR gene polymorphisms and the responsiveness of human monocytes to GcMAF. This interaction is likely to occur at the level of the plasma membrane thanks to the hydrophobic interactions between the two proteins and it could be facilitated by the presence of vitamin D binding to both proteins, with GcMAF on the outer side of the membrane and VDR on the inner side. In addition, since it had been previously observed that GcMAF induced the formation of cAMP also in normal human monocytes, it could be concluded that the cAMP signalling pathway is involved in the early event of GcMAF-stimulated cell responses independently of the cell type, possibly through interaction with VDR as part of the non-genomic responses to vitamin D-axis components.
No conflict of interest.

597 POSTER

Isoproterenol increases the expression of histone deacetylase 6 via EPAC- and Erk-dependent pathway to stimulate migration of H1299 human lung cancer cells

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Background: Isoproterenol, a beta adrenergic receptor agonist, stimulates cAMP production and regulates various cellular metabolism and gene expression. Histone deacetylases (HDACs) remove acetyl groups from histones and non-histone proteins to regulate gene expression epigenetically and other cellular functions. HDAC6 deacetylates and regulates many non-histone substrate proteins such as α-tubulin, Hsp90, cortactin, and ku70. α-Tubulin is the first identified substrate of HDAC6, and affects microtubule dynamics to regulate cell migration. This study investigates the effect of isoproterenol on the expression of HDAC6 in lung cancer cells.
Material and Methods: Lung cancer cells including H1299 cells were treated with isoproterenol, forskolin, H89, 6-Bnz-cAMP, and 8-pCPT-2'-O-Me-cAMP to activate or inhibit cAMP signaling pathway. PD98059 and PD0325901 were used to inhibit Erk pathway. Stimulatory heterotrimeric GTP-binding protein Q227L (GαsQL), EPAC shRNA, and constitutively active MEK1 (CA-MEK1) were transiently transfected with $CaCl_2$ or lipofectamine 2000®. HDAC6 protein and mRNA expression was analyzed by western blot and real time PCR. Transwell chamber was used for cell migration assay.
Results: The expression of HDAC6 mRNA and protein was increased by treatment with isoproterenol treatment in H1299 lung cancer cells. The expression of constitutively active Gαs proteins (GαsQL) and forskolin treatment also increased HDAC6 levels. Isoproterenol treatment decreased the acetylation level of α-tubulin, and stimulated cell migration. Isoproterenol-stimulated cell migration was blocked by knockdown of HDAC6 with shRNA. Treatment with H89, a selective inhibitor of PKA, or 6-Bnz-cAMP-sodium, a selective activator of PKA, did not affect HDAC6 expression levels. However, treatment with 8-pCPT-2'-O-Me-cAMP, a selective activator of EPAC, or expression of EPAC shRNA affected HDAC6 expression. Isoproterenol inhibited MAPK and Akt signaling pathways in H1299 cells. Inhibition of Erk1 by treatment with PD98059 and PD0325901 increased HDAC6 levels, and expression of constitutively active CA-MEK1 decreased isoproterenol-induced HDAC6 expression.
Conclusion: It is concluded that isoproterenol stimulates migration of H1299 lung cancer cells by increasing HDAC6 expression via EPAC- and Erk-dependent pathway.
No conflict of interest.

598 POSTER

Augmentation of histone deacetylase 8 expression by cyclic AMP signaling system in H1299 human lung cancer cells

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Background: Histone deacetyalses (HDACs) are enzymes that catalyze the removal of acetyl groups from histones to regulate gene expression epigenetically. HDAC8 belongs to class I HDAC together with HDAC1, 2 and 3 isoforms. Cyclic AMP (cAMP) signaling pathway is activated by cAMP, which is formed by adenylate cyclases activated by various extracellular signals including hormones and neurotransmitters. cAMP signaling system regulates various cellular functions such as gene expression, proliferation and apoptosis. HDAC8 has been reported to be phosphorylated by cAMP-dependent protein kinase A (PKA), which results in negative regulation of HDAC8 activity and hyperacetylation of histone H3 and H4. Moreover, HDAC8 is known to be correlated with the activity of cAMP response element binding (CREB) protein. Thus this study investigated how cAMP signaling system modulates the activity of HDAC8 to regulate gene expression epigenetically.
Material and Methods: cAMP signaling system was activated by expression of a constitutively active mutant Gαs protein (GαsQL) and by treatment with isoproterenol, a β-adrenergic receptor agonist, in H1299 human lung cancer cells. Expression of HDAC8 mRNA and protein was determined by quantitative RT-PCR and western blotting. Changes in the phosphorylation of signaling molecules were analyzed by western blotting using specific antibodies.
Results: HDAC8 expression was increased by expression of GαsQL and treatment with isoproterenol or prostaglandin E2. Treatment with forskolin also increased HDAC8 protein expression, but not mRNA levels. Both activators of PKA and Epac also increased HDAC8 expression. Inhibition of Epac2 blocked the increase in HDAC8 expression induced by treatment with isoproterenol, but the inhibition of PKA or Epac1 did not block the isoproterenol effect. Isoproterenol increased Rap1 activity, and activation of Rap1 led to an increase in HDAC8 expression. Isoproterenol decreased Akt activity. Moreover, inhibition of PI3K or Akt activity led to an increased in HDAC8 expression.
Conclusions: cAMP signaling system augments HDAC8 expression in H1299 human lung cancer cells, which involves Epac2-Rap1 or PI3K/Akt pathways.
No conflict of interest.

599 POSTER

Dolastatin, along with celecoxib, stimulates apoptosis by a mechanism involving oxidative stress, membrane potential change and PI3-K/AKT pathway down regulation

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Background: Phosphoinositide 3-kinase (PI3-K) is an important regulator of oncogenesis and apoptosis in various types of cancers including colon. A combinatorial strategy of using Cyclooxygenase-2 inhibitor, celecoxib and dolastatin, a linear peptide from marine mollusk of Indian Ocean origin has been shown the anti-neoplastic effects in colon cancer in a rat model.
Methods: The signal transduction pathway of PI3-K/AKT and the downstream signalling proteins had been studied in an early stage of colon carcinogenesis (DMH induced) by gene and protein expression, apoptotic studies by colonocyte apoptotic bleb assay, intracellular calcium level by fluorescence spectrometry, mitochondrial membrane potential by Rhodamine 123 flow cytometry and Reactive oxygen species measurement. Molecular docking analysis was employed to study the interaction of oncogenic proteins and the ligand, celecoxib and dolastatin.
Results: Apoptotic cell index was lowered with DMH while both the drugs increased it and inhibiting PI3-K and AKT expression. Docking studies revealed both the proteins targeted by the drugs via ATP binding site. An increased expression of GSK-3β, pro-apoptotic protein Bad, transcription factor Egr-1, tumour suppressor protein PTEN while a downregulation of G1-associated cell cycle protein, Cyclin D1 and increased intracellular calcium as well as reactive oxygen species were observed. Also, the number of cells having higher mitochondrial membrane potential was lowered.
Conclusion: Celecoxib and dolastatin inhibited the tumour development through regulation of PI3-K/AKT pathway which can act as a novel target for these drugs.
No conflict of interest.

600 POSTER

Overexpression of RUKI/CIN85 promotes the enrichment of human breast adenocarcinoma MCF-7 cells and rat pheochromocytoma PC12 cells by cancer stem-like cell population

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Background: There is increasing evidence that a variety of human cancers are maintained by a subset of cells, cancer stem cells (CSCs), which sustain tumor growth, underlie its malignant behavior, and possibly initiate distant metastases. There are data that certain adaptor proteins may be involved in the development and maintenance of CSCs phenotype. The aim of this study was to investigate the possible role of adaptor protein Ruk_I/CIN85 in the acquisition of CSCs characteristics.

Material and Methods: All experiments were carried out on wild type human breast adenocarcinoma MCF-7 cells and rat pheochromocytoma PC12 cells as well as cells with stable overexpression of Ruk_I/CIN85. Such features of CSCs as the ability to form spheroids on low-adhesive plastic in growth factor-supplemented medium, expression of certain markers, the resistance to cytotoxic agents action were studied.
Results: When subjected to a sphere forming conditions MCF-7 and PC12 cells with Ruk_I/CIN85 overexpression effectively developed spheroids. The ability to form effectively secondary spheroids evidence for their self-renewal property. CSCs are known to be characterized by tissue specific markers. The increased expression of CD44 surface marker as well as the increased number of $CD44^+/CD24^-$ cells in Ruk_I/CIN85 overexpressing breast adenocarcinoma MCF-7 cells was revealed. High expression level of inhibitor of differentiation 1 (ID1) and low level of MATH2/NEUROD6 transcription factor was found in pheochromocytoma PC12 cells with Ruk_I/CIN85 overexpression. Another feature of CSCs is their increased resistance to cytotoxic agent action. A measure of metabolic activity of cells treated with doxorubicin (in case of MCF-7 cells) and hydrogen peroxide (in case of PC12 cells) revealed that cells with overexpression of Ruk_I/CIN85 were more resistant to studied agents than control cells.
Conclusions: The data obtained indicate the potential role of adaptor protein Ruk_I/CIN85 in the development of CSCs-like phenotype in breast adenocarcinoma MCF-7 cells and rat pheochromocytoma PC12 cells.
No conflict of interest.

601 POSTER

Nanoscopic hyperthermia by modulated electric field

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Background: There are numerous studies showing effects of hyperthermia in oncology, however controversial results block its wide distribution. Our objective is to show the controlled energy-liberation in nanoscopic range that solves the central problem of hyperthermia.
Method: Nano-heating, modulated electro-hyperthermia, (mEHT) is developed, which selects and heats up the membrane of the malignant cells. The nano-range energy-liberation could be precisely controlled. The nano-selection is based on the metabolic, adherents and organizing differences of the malignant cells. The technology is impedance controlled capacitive coupling; no plane-wave radiation dominates as in other capacitive (radiative) solutions. The method mEHT uses impedance matching at 13.56 MHz carrier frequency, with time-fractal modulation. The efficacy is measured immunohistochemically by mRNA and protein levels too. The surface power-density of the signal is limited by the toxic (blistering) limit 0.5 W/cm^2. The cell-killing mechanisms are proven in experiments, as well as in preclinical and clinical applications.
Results: The main medical advantages of the method are its personalized targeting together with the effective selection and distortion of the malignant cells. Selectivity and strong synergy of the temperature and the applied electric field is proven, which dominantly kills the malignant cells on apoptotic way. The macro- and micro-morphology, the β-catenin nuclear relocalization, the activated early and late apoptotic pathways as well as the DNA defragmentation by time show apoptosis. E-cadherin-β-catenin complex is reconstructed by the mEHT treatment. This coupling can suppress the dissemination and the metastatic activity. Numerous clinical studies are available with altogether more than 3700 cancer patients involved. The results show higher first-year survival than the Eurocare database, despite the only high-line treatment by the mEHT method. Some studies show monotherapy applications as a promising way of the refractory diseases. The safety of mEHT is specially presented on such a sensitive organ as the brain.
Conclusion: mEHT shows its definite advantages in local cell-killing and in blocking of the metastatic processes too. It is a feasible method for the reliable and controllable basic of the modern hyperthermia demands in clinical oncology.
No conflict of interest.

602 POSTER

Galectin-3 accelerates M2 macrophage infiltration and angiogenesis in tumors

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Background: It is widely accepted that aggressive invasion of tumor associating macrophage (TAM) resembling M2 macrophage correlates with cancer malignancy affecting cancer cell invasion, metastasis, and angiogenesis. Many chemokines that induce migration of macrophages have been isolated in the inflammatory response; however, further precise analysis of macrophage migration in tumor microenvironment is required. Here, we analyzed the function of galectin-3 (Gal3) for chemotaxis of macrophage. By using Gal3−/− mice as a host of tumor xenograft model, we induced concentration gradient of Gal3 spreading from tumor to normal organ.
Methods and Results: In this model, we found that infiltration of macrophage is enhanced in tumor developed in Gal3−/− mice compared with that in Gal3+/+ mice, resulting in enhanced tumor angiogenesis and tumor growth in Gal3−/− mice. Especially, we found that macrophages showing M2 macrophage phenotype dominantly infiltrate in Gal3−/− mice and they express low level of Gal3. When Gal3 was knocked down in macrophages by siRNA, chemotaxis of macrophages by Gal3 was enhanced. These suggested that cells like M2 macrophage originally have possibility to migrate toward Gal3 and infiltrate upon high level expression of Gal3 in tumor resulting in acceleration of angiogenesis and tumor growth. Therefore, Gal3 is one of targets for development of new strategy to inhibit tumor growth.
Conclusion: Our present model using Gal3−/− mice as a tumor host recapitulates the tumor condition in which expression of Gal3 in the tumor increases. It has been reported that Gal3 directly induces endothelial tube formation. Therefore, higher levels of Gal3 induce angiogenesis directly affecting endothelial cells (ECs) within the tumor; however, macrophage recruitment by Gal3 may also be involved in the acceleration of tumor angiogenesis. In summary, knowledge of Gal3 expression may help in the assessment of cancer patient status. Indeed, one line of evidence suggests that Gal3 expression levels are related to the degree of biological aggressiveness in human colorectal tumors. Therefore, suppression of the function or expression of Gal3 may be a promising approach for cancer therapy.
No conflict of interest.

603 POSTER

Effect of E-cadherin silencing on vascularization of experimental brain metastases

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It is thought that angiogenesis is required for the maintenance of primary or metastatic tumor growth. Increasing amount of data suggest that instead of angiogenesis host vessel incorporation plays an important role in the vascularization of metastases in highly capillarized organs (e.g. brain, liver, lung). Our previous research results showed that experimental brain metastases acquire their own blood supply by incorporation of the host vessels. There was a correlation between the differentiation status, the growth pattern and the vascular structure of the five different tumor lines used. Our aim was to investigate the effect of the differentiation status on the vascularization using two variants of the same tumor cell line (human HT-25 colorectal carcinoma): wild type HT-25, E-cadherin silenced HT-25. Human HT-25 colorectal carcinoma cell line and E-cadherin silenced ($E\text{-}cad^-$) HT-25 cell line was used in the experiments. To permanently knock-down the expression of the E-cadherin gene, shRNA Plasmid (SA Biosciences) was used. In order to achieve appropriate tumor size (1−2 mm) required for the angiogenic switch, the tumor cells were injected directly into the brain of male SCID mice. Immunofluorescent labeling of vessels and tumor cells was performed on frozen sections. Intratumoral vessel density and vessel diameter was determined on micrographs.
The growth pattern of the variants differed significantly. The wild type HT25 tumor cell line showed differentiated “pushing-type” tumor growth with coherent cells and smooth tumor-parenchyma interface. The $E\text{-}cad^-$ cell line is less differentiated. There were round scattered tumor cells on the edge of the tumors of $E\text{-}cad^-$ cells. Compared to wild type HT-25 the vessel density was significantly higher, vessel diameter was significantly lower in the tumors of $E\text{-}cad^-$ cells.
Our results show that regardless of the origin, the differentiation status of the tumor determines the growth pattern and the vascular structure of the tumor.
No conflict of interest.

604 POSTER

Histone demethylases expressed under hypoxia and nutrient starvation regulate tumor growth by modulating tumor angiogenesis and metabolism

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Anti-angiogenic strategies can be effective for cancer therapy, but like all therapies resistance poses a major clinical challenge. Hypoxia and nutrient

starvation select for aggressive qualities that may render tumors resistant to anti-angiogenic attack. Here we show that hypoxia and nutrient starvation cooperate to drive tumor aggressiveness. In cancer cells rendered resistant to long-term hypoxia and nutrient starvation, we documented a stimulation of AKT phosphorylation, cell morphological changes, cell migration, invasion and anchorage independent growth in culture. These qualities associated in vivo with increased angiogenesis and infiltration of macrophages into tumor tissues. We identified KDM3A and KDM7A were upregulated in vitro under conditions of hypoxia and nutrient starvation and in vivo before activation of the angiogenic switch or the pre-refractory phase of antiangiogenic therapy. Inhibition of KDM3A or stable expression of KDM7A suppressed tumor growth by downregulating angiogenesis and tumor associated macrophage infiltration. Notably, KDM3A inhibition enhanced the anti-tumor effects of the anti-VEGF compound bevacizumab and the VEGFR/KDR inhibitor sunitinib. In addition, we found that KDM7A regulated expression of several kinases involved in phospholipid metabolism using ChIP-sequencing and microarray. Metabolic analysis revealed that 50–100 folds accumulation of a phosphorylated metabolite within the pathaway, suggesting phospholipid metabolism can play an important role in cancer cells under nutrient starvation. Our results form the foundation of a strategy to attack hypoxia- and nutrient starvation-resistant cancer cells as an approach to leverage anti-angiogenic treatments and limit resistance to them.
No conflict of interest.

605 POSTER

Inhibition PDGF pathway by dual antiangiogenic and proapoptotic fusion molecule is a new preclinical strategy in treat cancer

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Background: For almost two decades tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has been under extensively development as a potential therapeutic due to its ability to induce apoptosis in cancer cells while remaining neutral to normal cells.
Tumor growth is tightly related to new blood vessel formation and tissue remodeling. Platelet derived growth factor (PDGF) is important for vascular development in physiological and pathological processes. Blockade of PDGF pathway has been shown to inhibit pathologic angiogenesis and tumor growth.
According to this knowledge, we proposed a novel protein with dualistic proapoptotic and antiangiogenic activity.
Our new molecule consists of a recombinant TRAIL variant linked with an effector peptide sequence and an activation motif recognized by tumor-specific proteases (MMP's, uPa) between. The effector peptide is formed by 19-amino acid fragment of human PDGF which binds the PDGF receptors competitively to the natural ligand while being itself devoid of activity. As a consequence, angiogenic activity of PDGF is blocked, stimulation of new blood vessels formation doesn't occur and finally tumor growth is inhibited.
Materials and Methods: AD-O54.9 protein was expressed in *E.coli* and purified by IEC chromatography. Our protein was characterized biochemically and biophysically using CD spectroscopy, HPLC-SEC, protease cleavage and MTT cell cytotoxicity assays. Its antiangiogenic activity was evaluated by HUVEC tube formation assay and mice ring aortic assay. The proapoptotic effect was tested using active caspase 3 staining. For *in vivo* potential we examined the efficacy of fusion protein on mice xenograft models of human colorectal adenocarcinoma (Colo205) and human multidrug resistant uterine sarcoma (MES-SA/Dx5) cell lines.
Results: Obtained molecule has well-defined secondary and quaternary structure and verified mechanism of activation. AD-O54.9 showed *in vitro* specific cytotoxic effect on various established and primary cancer cell lines at IC50 below 0.01 ng/ml. We demonstrated that AD-O54.9 is a very potent apoptosis activator and inhibitor of angiogenesis. The fusion protein showed superior effect displaying significant tumor volume regression compared with TRAIL and a standard anticancer chemotherapeutic agent.
Conclusions: The obtained results confirm that we developed very promising molecule with a high potential of anticancer activity that could be considered as a novel therapeutic agent.
No conflict of interest.

606 POSTER

Preclinical evaluation of anticancer potential of AD-O51.4 − novel fusion molecule with dual antiangiogenic and anticancer potential

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Background: Tumor growth and development is tightly related to new vessels formation and tissue remodeling. Vascular endothelial growth factor (VEGF) is important for vascular development in physiological and pathological processes. Blockade of VEGF pathway has been shown to inhibit both pathological angiogenesis and tumor growth.
Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL/Apo2L) has been under intense scientific evaluation because of its remarkable ability to induce apoptosis in cancer cells while omitting normal cells. However, its activity was too low to become the effective single therapy agent.
Here we present a novel fusion protein based TRAIL/Apo2L. The proposed new fusion protein consists of the recombinant variant of TRAIL fragment, which is linked to the repeated antiangiogenic effector peptide sequence and a motif recognized by tumor-specific proteases (MMP's, uPa) in between.
The AD-O51.4 is able to bind and sequester the VEGF receptors on malignant and endothelial cells but it is devoid of angiogenic activity. As a consequence, the peptide blocks the binding of VEGF ligand, preventing formation of new vessels. We postulate that due to the presence of VEGF receptors on cancer cells, they can be targeted by our VEGF receptor-blocking peptide making them susceptible for TRAIL-induced apoptosis.
Methods: Cytotoxic activity was examined using a MTT assay. Cell death and apoptosis markers were analyzed using flow cytometry methods. Direct antiangiogenic activity was confirmed with the ring aortic assay and HUVEC spheroid assay. Safety of the compound was confirmed by direct incubation with primary human and cynomolgus hepatocytes. *In vivo* antitumor activity was analyzed in the xenograft model of human: colorectal (Colo205), liver (HepG2), lung (NCI-H460) and pancreatic (MIA-PaCa-2) cancers.
Results: Almost 90 % of tested cell lines − primary or established − were sensitive to AD-O51.4 protein with extremely low IC50 values, showing no toxic effects towards normal cells.
Hepatotoxicity results revealed a lack of toxic effects at concentrations significantly exceeding the effective doses.
Strong antitumor activity of AD-O51.4 was confirmed in xenograft model of human colorectal adenocarcinoma Colo205 where our protein caused complete tumor remission in comparison to several of tyrosine kinases inhibitors and Bevacizumab, with similar effects on human pancreatic carcinoma MIA PaCa-2 and human hepatocellular carcinoma HepG2, as well as an orthotropic model of human lung carcinoma NCI-H460-luc2.
Conclusion: We demonstrated that AD-O51.4 protein reveals high, tumor specific cytotoxic activity against a number of cancer cell lines and superior *in vivo* activity in subcutaneous and orthotropic xenograft models. We postulate that the combination of two effectors in one protein molecule may be a novel and effective way of anticancer compounds development.
No conflict of interest.

607 POSTER

Impact of RGMb on BMP-7 promoted angiogenesis

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Background: Angiogenesis is an essential process required for normal physiological events and its imbalance is common in disease states such as cancer. Angiogenesis is vital for tumours to develop, progress and metastasise. The current study explores the potential of the Repulsive Guidance Molecule B (RGMb) to impact the regulation of angiogenic traits in response to Bone Morphogenetic Protein 7 (BMP-7) in the human endothelial HECV cell line.
Material and Methods: The expression of RGMb was targeted in HECV endothelial cells through the transfection of these cells with a plasmid containing a hammerhead ribozyme transgene specific to RGMb. Cells transfected with the ribozyme transgene were terms $HECV^{RGMbKO}$ and were used in comparison to control HECV cells transfected with a closed pEF6 plasmid ($HECV^{pEF6}$). Once established these cells were used to examine the impact of RGMb on angiogenic traits such as cell migration and tubule formation following treatment with or without 40ng/ml BMP-7 using *in vitro* Matrigel tubule formation assays and scratch/wounding migration assays.
Results: Treatment of control $HECV^{pEF6}$ cells with 40ng/ml BMP-7 brought about a notable increase in cellular migration, particularly in the end stages of the experiment (60 min, $p = 0.03$; 75 min, $p = 0.14$; 90 min, $p = 0.09$ vs.

untreated control HECV^{pEF6} cells). Additionally, treatment with 40ng/ml BMP-7 could significantly enhance the tubule formation levels in HECV^{pEF6} cells in comparison to untreated HECV^{pEF6} cells ($p = 0.005$). In contrast to this treatment of HECV^{RGMbKO} cells with 40ng/ml BMP-7 did not bring about the same promotional effects on cell migration and tubule formation. Levels of migration (60 min, $p = 0.71$; 75 min, $p = 0.73$; 90 min, $p = 0.75$ vs. untreated HECV^{RGMbKO}) and tubule formation ($p = 0.986$ vs. untreated HECV^{RGMbKO}) remained similar to the untreated HECV^{RGMbKO} cells.
Conclusions: Suppression of RGMb in HECV endothelial cells appears to negatively influence their ability to respond to the promotional impact of BMP-7 on angiogenic traits *in vitro*. RGMb may play a role in regulating tumour angiogenesis in response to BMP-7.
No conflict of interest.

608 POSTER

The expression of CTGF, THBS1, PLAU and PLAUR genes in U87 glioma cells with signaling enzyme ERN1 loss of function: effect of glucose and glutamine deprivation

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Background: The endoplasmic reticulum stress response-signalling pathway mediated by ERN1 is linked to the processes of neovascularisation, tumour growth and cell death, and the complete blockade of this signal transduction pathway has anti-tumour effects preferentially via suppression of angiogenesis and proliferation processes. Ischemic conditions are known to induce the endoplasmic reticulum stress and are responsible for the regulation of numerous growth factors which controls cell proliferation and angiogenesis in tumours via specific adaptive changes in the cell, and that is why it is important to study the role of key regulatory factor (CTGF, THBS1, PLAU, PLAUR) gene expressions in ERN1 signalling pathways in relation to ischemia and tumour progression.
Materials and Methods: We used the human glioma cell line U87 as well as modified variant of these cells with complete (protein kinase and endoribonuclease) suppression of ERN1 enzyme function. For glucose or glutamine deprivation conditions cells were exposure with DMEM without glucose or glutamine for 16 hrs. The expression of genes in glioma cells was measured by qPCR.
Results: It was shown that blockade of ERN1 gene function in U87 glioma cell line significantly increases the expression of *CTGF* (connective tissue growth factor) and *THBS1* (thrombospondin 1) genes, but decreases the level of *PLAU* (urokinase-type plasminogen activator) and *PLAUR* (PLAU receptor) gene expressions. The changes in the expression profile of these genes are correlated with a reduction of tumor angiogenesis and growth in vivo from glioma cells with ERN1 loss of function. Moreover, the increase of *CTGF* and *THBS1* gene expression and the decrease of *PLAUR* genes expression were observed in control glioma cells under glucose or glutamine deprivation conditions; however, in glioma cells with ERN1 loss of function, more significant effect of glucose deprivation conditions on the expression level of PLAU mRNA, as well as a reversible effect on CTGF mRNA expression was shown. At the same time, the expression of *PLAUR* gene was resistant to glutamine deprivation condition in control glioma cells but decreased in glioma cells with ERN1 loss of function.
Conclusion: Results of this investigation clearly demonstrated the crucial role of CTGF, THBS1, PLAU and PLAUR in tumour progression and will be important for developing a new understanding concerning molecular mechanisms of malignant tumour growth in relation to the ERN1 signaling and defines the best targets for potential anti-tumour therapies.
No conflict of interest.

609 POSTER

Tumor vessel maturation by apelin/APJ system improves the efficiency of immunotherapy

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Background: Previously, we reported that apelin is regulator of blood vessel maturation and receptor APJ is specifically expressed in endothelial cells during angiogenesis. Based on these results, we expected that apelin is useful factor for anti-angiogenic therapy in cancer. Recently, ascular normalization has been reported as a new strategy for regulating tumor growth. Therefore we investigated how apelin mediated vessels maturation affects tumor growth.
Material and Methods: The mouse Apelin gene was cloned into the pCAGSIH expression vector. Colon26 cells and PC3 cells were stably transfected and clones of cells showing stable transfection were obtained. The stably transfected colon26 clones, PC3 clones or LLC cells were inoculated subcutaneously into 6- to 8-week-old BALB/c mice, nude mice or C57BL/6 mice, respectively, and tumors were dissected at 12−15 days after implantation. DCs were administered by intravenous injection 4 days after tumor implantation. Tumors sections were stained using an An anti-CD31 monoclonal antibody.
Results: Here we show the expression of APJ in blood vessels in the colon26 and LLC derived tumor and reduction of tumor growth by overexpression of apelin in those tumor cells. By the histological analysis, we confirmed that, tumor vascular maturation was induced by apelin stimulation. This apelin induced vascular maturation enhances the efficacy of cancer dendritic cell-based immunotherapy and significantly suppresses the tumor growth by promoting the infiltration of iNKT cells to the central region of the tumor and thereby robustly inducing apoptosis of tumor cells.
Conclusions: These findings provide a new target for tumor vascular specific maturation which is expected to improve the efficacy of conventional cancer therapies.
No conflict of interest.

610 POSTER

Angiogenic inhibitors induce mature blood vessels surrounding the tumor parenchyma

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Background: Recently reports suggest that cancer cell invasion is induced from the edge of the tumor into peripheral areas after angiogenesis inhibitor treatment. Therefore, it is important to analyze the status of blood vessels at the tumor rim after anti-angiogenesis therapy. In the present study, we investigated that mature blood vessels in which ECs are covered with MCs are present in the outside of tumor parenchyma.
Material and Methods: We treated HT29 (human colorectal adenocarcinoma) and colo320DM (human sigmoid colon cancer) tumor-bearing mice with bevacizumab from Day 14 after tumor inoculation. To measure hypoxia and macromolecule infiltration in tumor tissues, Hyp-oxyProbe-1 (60 mg/kg, i.v.; Hypoxyprobe) or 0.5 mg of FITC-conjugated dextran (MW: 40,000) was injected 2 h before tissues were harvested. Tumor sections were stained using an anti-CD31 monoclonal antibody.
Results: We found that mature blood vessels were destroyed after treatment with angiogenesis inhibitors, but maturation of blood vessels were enhanced. Furthermore, we evaluated whether the increased numbers of blood vessels covered by MCs in the outside of tumor parenchyma resulted in any functional changes. Therefore, administration of angiogenesis inhibitor not only normalizes blood vessels in the tumor parenchyma, but also in the outside of tumor parenchyma.
Conclusions: These findings provide the importance of destroying maturing blood vessels outside of tumor parenchyma to prevent cancer cell invasion.
No conflict of interest.

611 POSTER

Effect of nitric oxide synthase inhibitors on angiogenesis

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Background: Angiogenesis is the process of generating new blood vessels from preexisting vessels and is considered essential in many pathological conditions. It was shown that nitric oxide (NO) production is closely related with the vessel proliferation, tumor growth and tumor aggressiveness. The purpose of the present study was to evaluate the effect of three NOS inhibitors (aminoguanidine, 7-Nitroindazole, N-Nitro L-Arginine [L-NAME]) on angiogenesis.
Material and Methods: Both *in vivo* (chorioallantoic membrane [CAM] assay, rat model of skin wound healing) and *in vitro* (cell viability assay-XTT method, endothelial cell tube formation assay) models were used for evaluation.
Results: In CAM assay, NOS inhibitors decreased angiogenesis in a concentration-dependent manner. Compared with the control group, NOS inhibitors significantly decreased vessel proliferation ($p < 0.001$). In rat model of skin wound healing study, wound closures and histopathological

examinations showed that NOS inhibitor groups had worse healing compared to control group and this was statistically significant ($p < 0.05$). The histopathological examination of NOS group revealed poor angiogenesis with respect to the control group. In 'endothelial cell tube formation assay' tube length/area ratio was less in NOS inhibitors group compared to the control group, proving the anti-angiogenic effect of NOS inhibitors in this model ($p < 0.05$). There was no effect of NOS inhibitors on human umbilical vein endothelial cells (HUVEC) in XTT assay. These results suggested that NOS inhibitors might have anti-angiogenic effects on other NO mediated steps beyond endothelial proliferation. The effect of L-NAME was more prominent in all models. These results provide evidence that NOS inhibitors decrease angiogenesis *in vitro* and *in vivo*.
Conclusions: According to these results; it can be considered that NOS inhibitors might have a desirable effect on patients with diseases based on angiogenesis such as cancer.
No conflict of interest.

612 POSTER

Effect of piperlongumine on angiogenesis in chick chorioallontoic membrane model

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Background: Angiogenesis is the process of generating new blood vessels from pre-existing vessels and is considered essential in many pathological conditions including cancer. The discovery of angiogenesis inhibitors raises the question of whether such molecules might therapeutically suppress or restrain cancer's growth. Piperlongumine, is a biologically active alkaloid/amide from peppers, as from Piper longum L. − Piperaceae. The reported pharmacological activities of piperlongumine include cytotoxic, genotoxic, antiplatelet aggregation, antinociceptive, antibacterial, antifungal, leishmanicidal, trypanocidal, and schistosomicidal activities. So the purpose of the present study was to evaluate the effect of a small molecule piperlongumine on angiogenesis in chick chorioallontoic membrane (CAM) model in vivo.
Material and Methods: Angiogenesis was evaluated using the CAM assay. Atak-S fertilized chicken eggs were used and incubated at 37°C and 85−90% relative humidity throughout the experiment. Experiments were done to determine the mode of action of piperlongumine on vascular development in the sixth day and eighth day on CAM. On day eight CAMs were screened and taken pictures by using a computer-aided stereomicroscope and images were processed with the software 'Leica Application Suite V4 Automated Image Analysis'.
Results: In this model, piperlongumine decreased angiogenesis in a concentration-dependent manner. The effects of piperlongumine over 5μM found more prominent. Compared with the control group, piperlongumine have significantly decreased vessel formation.
Conclusions: These results provide evidence that a natural compound, piperlongumine, inhibits angiogenesis *in vivo* and it may be used in treatment of the diseases; those pathologic bases are about angiogenesis such as cancer.
No conflict of interest.

613 POSTER

Anti-angiogenic treatments decrease PD-1 expression on tumor-infiltrating CD8+ T lymphocytes in colorectal cancer

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Background: The concept of cancer immunosurveillance suggests that the immune system can recognize and destroy tumor cells. However, tumors can develop immunosuppressive mechanisms to escape the immune system. Among the immunosuppressive mechanisms, T lymphocytes can express inhibitory molecules such as Program Death-1 (PD-1) protein which impair their activation. PD-1 activation by its ligands PD-L1 and PD-L2 blocks T cell proliferation, cytolytic activity, cytokine production, and decreases survival. Multi-target anti-angiogenic tyrosine kinase inhibitors (TKI) that are routinely used as first- or second-line treatment of cancer patients, have been shown to modulate immunosuppressive mechanisms especially regulatory T cells. However, the role of specific VEGF/VEGFR blockade on PD-1 expression by T lymphocytes has not been studied.
Materiel and methods: PD-1 expression has been analyzed on tumor-infiltrating $CD8^+$ T cells in a mouse model of colorectal cancer (CT26). Tumor-bearing mice were treated by different anti-angiogenic molecules targeting VEGF/VEGFR axis.
Results: Tumor-infiltrating $CD8^+$ T lymphocytes express high levels of PD-1 in the CT26 tumor model. PD-1 expression on tumor-infiltrating $CD8^+$ T lymphocytes was decreased by sunitinib treatment a tyrosine kinase that directly targets VEGFR, PDGFR and c-kit. In the same manner, anti-VEGF-A antibody (the mouse orthologue of bevacizumab) restrains PD-1 expression on tumor-infiltrating $CD8^+$ T lymphocytes. Administration of masitinib, a tyrosine kinase inhibitor acting on KIT, PDGFR and FAK but not on the VEGF/VEGF-R pathway, was not able to modulate PD-1 expression on T cells. Analysis of VEGF receptors on tumor-infiltrating $CD8^+$T cells revealed that PD-1^+ T cells express VEGFR1 and VEGFR2. In colorectal cancer patients, PD-1 expression was observed on $CD8^+$ T cells in PD-$L1^+$ hepatic metastases.
Conclusions: These results show that anti-angiogenic treatments targeting VEGFA/VEGFR decrease PD-1-expressing T lymphocytes in colorectal cancer. These results suggest that VEGF-A could be involved in PD-1 expression and maybe in the induction of T lymphocyte exhaustion in colorectal cancer. This point is currently under investigation. We and others have shown that anti-angiogenic molecules could modulate other immunosuppressive populations such as regulatory T cells and myeloid suppressive cells, anti-angiogenic molecules might be efficiently associated with immunotherapeutic strategies in colorectal cancer.
Conflict of interest: *Corporate-sponsored research: JT, MT: Roche and Pfizer research grants*

614 POSTER

CD4+CD25+ regulatory T cells and CD8+CD28− suppressor cells in elderly cancer patients

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Background: Immunosenescence is an important aspect in elderly cancer patients. In aging, T cell dysfunction and increasing CD4+CD25+ Regulatory T cells (Treg cells) have been reported. On the other hand, the status of these cells has not been uncovered so far in elderly cancer patients. In this study, we aimed to investigate Treg cells, CD8+CD28− suppressor cells, and other lymphocyte subpopulations in elderly cancer patients.
Material and Methods: Seventy-five cancer patients were included in the study. Data were obtained from our previous three studies about Treg, suppressive cells and other lymphocyte populations of breast, gastric and lung cancer patients. Total CD4+CD25+ Treg cells, CD8+CD28− suppressor cells, CD8+ memory cells, CD8+ naive cells, Natural Killer (NK) cells, CD8+ and CD4+ T cells had been investigated by flow cytometry. The parameters were compared between in patients over and under the age of seventy.
Results: Eighteen patients were older than 70 years of age (Elderly group) and fifty-seven patients were not (Control group). The percentage of CD4+CD25high cells in CD4+ T cells were higher in elderly cancer patients than control patients (13.01 ± 6.59 vs 8.43 ± 5.01;p:0.02). CD8+CD28− suppressor cells in lymphocytes were similar in both groups (18.12 ± 7.73 vs 18.03 ± 8.33;p:0.97). NK cells percentage was also elevated in elderly patients. CD8+ memory cells, CD8+ naive cells, CD8+ T cells, CD4+ T cells, and complete blood count parameters were not different between groups (Table).
Conclusion: Our data suggest that CD4+CD25+ Treg cells are increased in elderly cancer patients, but not CD8+CD28− suppressor cells. This may be a cause of age-related immunosuppression in cancer patients.
No conflict of interest.

Table: Lymphocyte subpopulations in cancer patients older and younger than 70 years

	Patients <70 years	Patients ⩾70 years	*p*
CD3 + cells in lymphocytes	71.79±11.21	65.53±9.69	0.079
NK cells in lymphocytes	7.41±7.22	12.74±9.46	0.048
CD8+ T cells in lymphocytes	25.35±9.58	26.59±9.04	0.672
Memory cells in CD8+ T cells	27.15±17.15	28.33±15.80	0.771
Naive cells in CD8+ T cells	9.24±7.62	10.95±13.23	0.821
CD8+ CD28− cells in lymphocytes	18.03±8.33	18.12±7.73	0.977
CD8+ CD28+ cells in lymphocytes	6.73±3.93	7.21±3.64	0.735
CD28−/CD28+ cell ratio in CD8+ T cells	3.94±3.55	2.68±0.89	0.749
CD4+ T cells in lymphocytes	37.40±11.10	29.22±11.78	0.061
CD4+CD25high cells in CD4+ lymphocytes	8.43±5.01	13.01±6.59	0.023

615 POSTER

Tumours modulate immune response of differentiated macrophages

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Interaction between tumour and immune cells either promotes or inhibits tumour progression. Studies reported that tumour associated macrophages have M2 phenotype that were proven to elicit tumour promoting functions. We hypothesised that exposure of differentiated macrophages to tumour lysates might alter their cytokine profile resulting in reduction of inflammatory response and induction of anti-inflammatory response. We generated two human macrophages populations by differentiating $CD14^+$ cells in either granulocyte macrophage colony stimulating factor (GM-CSF), (M1) or macrophage colony stimulating factor (M-CSF), (M2). Differentiated cells were phenotypically and functionally identified. Tumour cell lysates were employed to dissect their direct effect on cytokine production by these two populations. Our results revealed that, tumour lysates significantly ($p < 0.05$) inhibit TNF-α production of both populations while significantly ($p < 0.05$) inducing IL-10 production by M2 subtype. Furthermore, colorectal cell lysates switched M1 to M2 cells which is evident by their significant ($p < 0.01$) induction of IL-10 production of M1 cells. Results in this *in vivo* model added new evidence supporting the notion of 'tumour recruit macrophages to interfere with development of protective inflammatory response and induce the generation of tumour-promoting macrophage phenotype (M2)'.

No conflict of interest.

616 POSTER

Immunoreactivity to food antigens in patients with plasmacytoma and multiple myeloma

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Background: Increased immunoreactivity to certain food antigens (phytohemagglutinin (PHA) and cow's milk proteins (CMP)) was noticed in a number of patients with different types of haematological malignances, and it is considered partially responsable for immunological disorders observed in haematological malignancies.
Materials and Methods: This study involved 16 patients with plasmacytoma and 10 patients with multiple myeloma. The control group consisted of up to 50 healthy volunteers. Levels of IgA, IgG, IgM and IgE antibodies to food antigens were determined with ELISA test. Flow cytometry was performed for analysis of populations of white blood cells.
Results: Enhanced levels of anti-CMP antibodies were found in 13 out of 16 patients with plasmacytoma, and 5 out of 10 patients with myeloma. Immunoreactivity to PHA was increased in 8/16 plasmacytoma patients, respectively, which was not the case with patients with multiple myeloma. We found significant increase in IgE anti-CMP antibodies ($p < 0.009$) for plasmacytoma patients. Also, statistical significance was noticeable in increased levels of IgA and IgE anti-CMP antibodies ($p < 0.02$ and $p < 0.002$ respectively) in multiple myeloma patients. Decreased percentage of lymphocytes was observed in 5 patients with plasmacytoma and 5 patients with multiple myeloma. Of this number, enhanced levels of immunoglobulins to food antigens were found in 3 patients with plasmacytoma, and in 3 patients with myeloma.
Conclusions: Our results demonstrate that enhanced immunoreactivity to food antigens could contribute to accompanying disturbances in patients with haematological malignances. Involvement of larger groups of patients and further confirmation of this phenomenon will be necessary, and it is important to understand cause and mechanisms involved in immunoreacivity and the decrease in the percentage of lymphocytes.
No conflict of interest.

617 POSTER

Cancer-associated fibroblasts mediate tamoxifen resistance by secreting IL6 in ER positive breast cancer

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Background: Tamoxifen is an effective anti-estrogen drug for ER+ breast cancer, which has decreased 40% of recurrence and 30% of mortality. However, there are still about 33% of ER+ patients experienced tamoxifen resistance. Cancer-associated fibroblasts (CAFs), one major component of tumor microenvironment, have related to drug resistance, but whether and how they mediate tamoxifen resistance in ER+ breast cancer remain elusive.
Material and Methods: CAFs and normal fibroblasts (NFs) were isolated from fresh ER+ breast samples obtained from Ruijin hospital. Conditional medium (CM) were collected from cultured CAFs and NFs. Different secreted proteins were analyzed by RayBio human cytokine antibody Array. Cell proliferation was determined by XTT assay and colony formation assay. Protein expression was determined by western-blotting.
Results: CM from CAFs induced tamoxifen resistance in two ER+ cell lines, MCF7 and T47D. Moreover, higher level of interleukin 6 (IL6) was secreted from CAFs compared with NFs, and induced tamoxifen resistance in both cell lines. Also, this phenomenon was accompanied by ER-α downregulation and JAK/STAT3, AKT pathway activation, and epithelial–mesenchymal transition (EMT) was observed during this process. Interestingly, anti-IL6 treatment reversed CAF and IL6 mediated tamoxifen resistatnce.
Conclusions: CAFs secrete high level of IL6, mediate tamoxifen resistance through activating JAK/STAT3, AKT pathway and degrading ER-α by ubiquitination. Anti-IL6 treatment may reverse tamoxifen sensitivity in ER+ breast cancer cell lines, serving as a novel therapeutic agent for tamoxifen-resistant breast cancer patients.
No conflict of interest.

618 POSTER

NOG regulation of proliferation of breast cancer cells in cancer-bone microenvironment

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Background: Noggin has been known as an antagonist of bone morphogenetic protein (BMP) which has the role to regulate cell proliferation and migration. However, the functional role of NOG in the development and progression of breast cancer in context of microenvironment has not been fully elucidated. Here, we investigated that NOG gene expression in a various type of breast cancer cells and examined the effect on proliferation, migration and bone resorption.
Materials and Methods: The NOG gene expression was analyzed in breast cancer cell lines including MDA-MB-231, MCF-7, SK-BR-3, and T47D by Taqman assays. To investigate the role of NOG, high metastatic MDA-MB-231 cell was transfected with NOG small interfering RNA (siRNA) or non-target siRNA. Inhibition of NOG expression was confirmed by Taqman assays. To determine the cellular effects of NOG knockdown on the MDA-MB-231 cell, we performed cell proliferation assay with cell counting kit-8 (CCK-8) and cell count at 24, 48, 72 hr. Cell cycle analysis and apoptosis measured by flow cytometry (FACS) using the PI and Annexin V/7AAD staining kit, respectively. Also we examined the motility of NOG knockdown MDA-MB-231 cell with migration assay. Moreover, pit formation assay performed using co-culture systems with osteoclasts differentiated from Raw 264.7 cell with MDA-MB-231 cell treated by siRNA.
Results: We found that NOG was strongly expressed in osteolytic breast cancer cell MDA-MB-231 more than that of MCF-7, SK-BR3, and T47D. NOG knockdown mediated by siRNA in MDA-MB-231 cell represented decreased cell proliferation and growth rate. Furthermore, decreased NOG expressed MDA-MB-231 cell induced G0/G1 phase cell cycle arrest and increased early stages of apoptosis as compared with control. Also, suppression of NOG expression reduced migration activity of MDA-MB-231 cell. NOG knockdown MDA-MB-231 cell failed pit formation in cancer-osteoclasts co-culture model.
Conclusions: These data provides evidence for NOG promoted proliferation by regulation of cell cycle. Moreover, it showed the role on migration & osteolysis in cancer-bone model system. Taken together, NOG gene

have important role on breast cancer cellular process especially in bone metastatic microenvironment.
No conflict of interest.

619 POSTER

Tetraspanin CD151 regulates expression of fibroblast growth factor receptor-2 (FGFR2) in ductal carcinoma in situ cell line

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Background: CD151 is a member of evolutionary conserved transmembrane-4 superfamily. CD151 was the first tetraspanin associated with cancer development and its role in promotion of invasion and migration has been demonstrated in numerous *in vitro* and *in vivo* models. Clinically, high levels of CD151 are correlated with poor prognosis in a variety of tumours including breast cancer. Increased expression of CD151 was observed in ductal carcinoma *in situ* (DCIS), a premalignant form of breast cancer suggesting that CD151 may also play a crucial role at the early, proliferative stages of the disease. There is an increasing evidence that the FGF-FGFR2 signaling axis plays an important role in breast cancer. Elevated expression of FGFR2 transcripts was associated with a higher incidence of breast cancer. On the other hand *in vitro* and animal studies show that FGFR2 inhibits tumour progression. Here we demonstrate for the first time that expression and function of fibroblasts growth factor receptor-2 (FGFR2) in an immortalized breast epithelial cell line is regulated by tetraspanin CD151.
Material and Methods: FGFR2 expression was assessed by western blotting and qPCR in HB2 (CD151+) cell line and its variant HB2 (CD151−). CD151-dependent responses to various FGFs were evaluated in cells grown in 3D collagen. In order to reveal molecular pathways underlying CD151-mediated FGFR2 expression, cells were incubated with chemical inhibitors of a panel of kinases and analysed for the presence of FGFR2 protein.
Results: We found that CD151 knock-down in HB2 cells upregulated expression of FGFR2 at both mRNA and protein level, without affecting other FGF receptors. This was reflected in in inhibition of CD151-negative cells response to FGF2 (ligand for FGFR2) grown in 3D collagen. Analysis of signaling pathways likely to be responsible for these effects revealed that CD151 impairs activation of p38 kinase which controls FGFR2 expression level. Inhibition of p38 activity or its forced overexpression, impaired or elevated FGFR2 level, respectively.
Conclusions: The results demonstrate for the first time that tetraspanin CD151 interacts with the FGF-FGFR2 signaling axis in breast epithelial cells and regulates expression and function of FGFR2 gene and protein. Further *in vivo* and clinical studies are required to define the role of this process in breast cancer progression.
No conflict of interest.

620 POSTER

Hypoxia induced alterations on cell metabolism − an in vitro study in three different colorectal carcinoma cell lines

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Background: Recent clinical data indicate that tumor hypoxia negatively affects the treatment outcome of radiotherapy and chemotherapy in various cancers, emphasizing the need for noninvasive detection of tumor hypoxia. The application of ^{18}F-FDG PET imaging in oncology is based in the upregulation of glucose transporters and glycolytic enzymes, and tumor hyperglycolysis. On the other hand, ^{18}F-Fluorocholine (^{18}F-FCHO) is metabolized to form phosphatidylcholine, a major membrane phospholipid, because in malignant cells there is an increase on choline and phosphocholine synthesis. Once the biomedical processes that allow cancer cells to capture ^{18}F-FDG and ^{18}F-FCHO are different, these two radiopharmaceuticals can give us different information about the bioenergetics of colorectal cancer.
In this context, the main objective of this study is to determine the pattern of uptake of ^{18}F-FDG and ^{18}F-FCHO in three colorectal carcinoma cell lines in normoxia and hypoxia conditions and correlate these results with the expression of GLUT-1, −3 and p53.
Methods: Studies were performed in colorectal carcinoma cell lines (WiDr, C2BBe1 and LS1034). Uptake studies with ^{18}F-FDG and ^{18}F-FCHO were performed. After incubation in a cell suspension of 2×10^6 cells/ml (25 μCi/ml), samples were collected, radioactivity of pellets and supernatants was measured and percentage of uptake calculated. Experiments were conducted in normoxia (18% oxygen) and hypoxia (2% oxygen) environment. GLUT-1, −3, as well as p53 expression was assessed by flow cytometry and western blot, respectively.
Results: p53 protein quantification revealed that C2BBe1 cell line does not express p53 while WiDr and LS1034 do. Related to ^{18}F-FDG uptake, LS1034 and WiDr cell lines increased the uptake in hypoxic conditions in contrast with C2BBe1. When the cells were incubated with ^{18}F-FCHO, we observed that the uptake of all cell lines in hypoxic conditions was higher comparing with normoxic conditions. Concerning GLUT-1 and −3 expression we observed that hypoxia (2 and 48 hours) induced an increase of these glucose transporters.
Conclusions: With these results, we can conclude that in solid tumors, as colorectal cancer, the uptake of current radiotracers is influenced by tumor microenvironment. Besides that, characteristics like GLUTs, the main glucose transporters, can be responsible for these results. However, the genetic background also reveals be a key role in cells uptake.
No conflict of interest.

621 POSTER

The magnetite nanoparticles manifest self-dependent antitumor activity in the experiments in vivo

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At present ferrimagnetic nanoparticles (NP) are used in antitumour treatment for targeted drug delivery or as factors of magnetic fluid hyperthermia. The question about self-dependent antitumour activity of such NP is almost not studied.
The self-dependent antitumour activity of magnetite NP (Fe_3O_4) was for the first time shown in the experiments on 258 white outbred rats (200–300 g) *transplantable* tumour, *sarcoma 45* and *Pliss lymphosarcoma*.
Tumours were transplanted subcutaneously into the region of the rear side of the back. Before the start of treatment course experiment the tumour volume of *sarcoma 45* reached 0.7−1.3 cm^3, the tumour volume of *Pliss lymphosarcoma* reached 0.3−2.7 cm^3. The ferrofluid based on magnetite NP (10±2 nm) *was injected into the area adjacent to the tumour at a distance of 1.5 cm from the tumour borders* twice a week, 5−6 times in total. The dose of magnetite NP varied in different experiments. The dynamics of the tumour volume, changes in the tumour and adjacent tissues, as well as in the organs of the immune system, the quantity of NP in the liver, in the kidneys, and in the lungs were studied. The methods of light and electron microscopy as well as flow cytometry and X-ray absorption spectroscopy analysis were used. The Student's t-test and the Wilcoxon signed-rank test were used for the statistical analysis.
For the rats with *sarcoma 45* the maximum effect of magnetite NP was expressed in tumour regression in 70% of animals, including complete tumour regression in 43% of cases. For the rats with the *Pliss lymphosarcoma* the maximum effect of magnetite NP was expressed in the tumour regression in 50% of animals, in these cases complete tumour regression was noted in 40% of animals including the rats whose tumour volume before the start of treatment course exceeded 2.5 cm^3. The cases of the complete tumour regression were confirmed histologically, and also by monitoring the animals' state in the course of 8 months. The activation of system and local immune processes (increase of the limfoproliferative activity in the thymus and the spleen, the infiltration of the tumour tissue by immune cells and the appearance of morphological signs of different intercellular interactions, $p < 0.05$–0.01) was observed under the effective influence of magnetite NP. Toxic reactions were not noted.
We have examined the possible mechanisms, connected with the processes in the perifocal zone of the tumours, which can determine the self-dependent antitumour activity of magnetite NP.
No conflict of interest.

622 POSTER

Regulation of barrier function in human breast cancer can be controlled by the ROCK signalling pathway via interaction with SIPA-1

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Background: SIPA-1 (Signal-induced proliferation-associated gene 1) is a mitogen-inducible gene encoding a GTPase-activating protein for Rap1 and Rap2 that may be involved in metastatic progression. Recent years have highlighted the role that Tight Junctions (TJ) have in cancer metastasis. However, how changes in TJs of cancer cells are controlled is still uncertain. We have previously shown that SIPA-1 is significantly reduced in breast patients with poor prognosis & metastatic disease. This study examined SIPA-1 and its relationship to TJ function in human breast cancer cells.
Materials and Methods: Two breast cancer cell lines, MDA-MB-231 and MCF7, exhibiting high levels of SIPA-1 was chosen to knockdown endogenous SIPA-1 expression. Changes in TJ function was assessed using trans-epithelial resistance (TER) & paracellular permeability (PCP) under the influence of the mitogen/mitogen, HGF. Invasion, adhesion, growth & ECIS assays were also performed. Western blotting was used to confirm binding partners for SIPA-1. In vitro & in vivo models were used to assess the effect of ROCK inhibitor on knockdown cells.
Results: Knockdown cells exhibited significantly reduced response to HGF during both TER and PCP assays ($p < 0.001$) and there was a significant reduction in invasion, adhesion and growth ($p < 0.01$). Immuno-precipitation studies confirmed SIPA-1 as a binding partner for the ROCK signalling protein. Subsequent experiments with MDA-MB-231 cells revealed that neither HGF nor the ROCK inhibitor could exert an effect on migration or barrier functions in knockdown cells. HGF had no effect on protein levels of SIPA-1 in WT cells. Crucially, the in vivo model revealed that SIPA-1 knockdown cells had significantly reduced tumour growth in contrast to wild type tumours, that treatment with the ROCK inhibitor also inhibited tumour growth but that knockdown of SIPA-1 negated an additive effect with the ROCK inhibitor. Phosphorylation studies showed that the ROCK inhibitor caused serine phosphorylation of SIPA-1 in wild type cells, but that HGF had no effect on phosphorylation status. Neither factors affected threonine or tyrosine phosphorylation.
Conclusions: We have demonstrated for the first time that SIPA-1 is involved in the regulation of TJ in human breast cancer via the ROCK signalling pathway. A reduction in SIPA-1 expression leads to breast cancer cells with reduced aggressive phenotype and significantly increased TJ functions. Moreover, we have shown that SIPA-1 is involved in regulating barrier function via the ROCK signalling pathway. This leads to interesting possibilities for the role of SIPA-1 in human breast cancer.
No conflict of interest.

623 POSTER

HGF and the regulation of tight junctions in human prostate cancer cells

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Background: A major impact of Hepatocyte growth factor (HGF) on the development & metastasis of prostate cancer may be via its action on prostate stem cells or their progeny. Understanding the sequence of events in the above process would have important implications in understanding the biology of prostate cancer and in the development of new therapies. Tight Junctions (TJ) are key to the process of metastasis & have been previously shown to be regulated by HGF. This study sought to evaluate the effect of HGF on TJ function of human prostate epithelial cell lines, prostate-stem-cell- like cells and prostate cancer cell lines.
Materials and Methods: RWPE-1 (normal adult prostate parental epithelial cells), WPE-stem (a stem-cell-like derivative of RWPE-1) and 4 human prostate cancer cell lines (PC-3, DU-145, PZHPV-7, CaHPV-10) were used to assess HGF-induced changes in TJ function via trans-epithelial resistance (TER) & paracellular permeability (PCP). ECIS assays were also performed. RT-PCR, Western blotting and immunofluorescence were used to analyse changes in TJ molecule expression/distribution. An athymic murine tumour model was used to assess tumourigenicity.
Results: We found that there was a significant difference in behaviour between the stem-cell-like WPE-stem cells, the RWPE-1 cells & the cancer cell lines that was also HGF concentration dependent. As expected, HGF reduced the TER/PCP of the RWPE-1 cells & the prostate cancer cell lines ($p < 0.0001$ & $p < 0.005$); however, the response elicited indicated that the more invasive the cell line, the more HGF was able to effect a decrease in resistance over time, with PC-3 cells being most affected. ECIS confirmed these results, with different resistance profiles for each of the cell lines ($p < 0.043$). However, in the WPE-stem cells, the effect was biphasic, with the cells seemingly resistant to HGF modulated TJ disruption. Closer examination revealed that HGF effected a redistribution of ZO-1, −2 & −3 away from the TJ of confluent PC-3 cells with concurrent loss of claudin-1 & −5. Western blotting revealed loss in TJ protein expression of ZO-1 & −2 (confirmed with RT-PCR) with an apparent increase in Occludin (65kDa) & ZO-1 exhibiting two isoforms. In contrast to PC-3 & DU-145 cells, neither RWPE-1 nor WPE-stem cells were tumourigenic in an *in vivo* tumour model even in the presence of HGF.
Conclusions: We have demonstrated for the first time that HGF regulates the function of TJ in human prostate cells. Moreover, this regulation is dependent on the tumourgenicity of the cells, with the most aggressive cells being most susceptible and the stem-cell- like cells least susceptible. This opens up a fascinating avenue of research for the future. These data offer an intriguing glimpse of how TJ affect the behaviour of prostate cancer cells and how HGF modulates the expression and function of the molecules maintaining TJ structure & function.
No conflict of interest.

624 POSTER

Metastasis suppressor 1 (MTSS1), and epithelial to mesenchymal transition (EMT) in cancer progression

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Background: Acquisition of a mesenchymal-like cell phenotype is a hallmark of metastatic progression of most carcinomas. This dynamic process of epithelial to mesenchymal transition (EMT) allows polarised epithelial cells to assume a mesenchymal phenotype with enhanced migratory and invasive capabilities. Metastasis suppressor 1 (MTSS1), discovered in non-metastatic bladder cancer cell lines, but missing in metastatic bladder cancer, modifies interplay between the actin cytoskeleton and plasma membrane conserving intercellular contacts and is important in development, carcinogenesis and metastasis. This study aimed to discover any link between MTSS1, and the process of EMT in cancer progression.
Material and Methods: Two bladder cancer cell lines (EJ138 and RT112) and one breast cancer cell line (MCF-7) were studied. Genetic manipulation, utilising ribozyme technology, produced EJ138 and RT112 cells which over expressed MTSS1 and MCF-7 cells with knocked down expression of MTSS1. PCR and Western Blot analysis were performed on the wild type (WT) and manipulated cells to assess any link between MTSS1 expression and specific EMT markers. Electric cell-substrate impedance sensing (ECIS) technology was employed to investigate changes in cell motility in relation to MTSS1 expression.
Results: Over expression of MTSS1 in both bladder cancer cell lines lead to a loss of SNAI1 expression whereas knockdown of MTSS1 in the MCF7 breast cancer cell line resulted in upregulation of SNAI1. Similar results were seen for TWIST expression in the bladder cancer cells but not in the breast cancer cells. In the MCF7 cells E-cadherin expression inversely correlated with SNAI1 expression. The MCF-7-MTSS1 knockdown cells initially attached more slowly than the wild type cells but after wounding significantly attached more quickly ($p < 0.001$). Both bladder cancer cell lines over expressing MTSS1 attached more quickly than WT cells, with no significant difference seen in the migration capacity between RT112-MTSS1-Exp cells and the control RT112pEF cells, nor between EJ138-MTSS1-Exp cells and the EJ138pEF control cells.
Conclusions: The changes in EMT transcription factors SNAI1 and TWIST and in the cell-cell adhesion molecule E-cadherin, in all three cell types in relation to MTSS1 expression, together with differences in the motility of MTSS1 manipulated cells, point to a link between MTSS1 and EMT factors in these cancer types which bears further investigation.
No conflict of interest.

625 POSTER

Membrane proteome analysis of invasive human glioblastoma multiforme

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Glioblastoma multiforme (GBM) is the most aggressive and prevalent malignant brain tumour in adults. GBM is diffusely infiltrative and its poor demarcation from surrounding brain parenchyma makes complete surgical resection difficult and tumour recurrence inevitable. Tumour invasion of neighbouring tissues is facilitated by cell migration and degradation of the extracellular matrix (ECM). Invadopodia are discrete ECM-degrading structures recently described on GBM and play important roles in tumour invasion. The aim of the current study is to characterize the 'invasive potential' of a panel of established GBM cell lines using an invadopodia assay and perform comparative membrane proteomic analyses of highly invasive vs less-invasive cells.

Nine GBM cell lines were characterized based on their ability to produce invadopodia using a QCM gelatin invadopodia assay (Millipore). Glass slides were coated with Cy3-gelatin before seeding GBM cells for 24 h at 37°C. Fluorescence microscopy revealed areas devoid of Cy3-gelatin indicating gelatin degradation by GBM cell invasion. The membrane proteomes from GBM cells with different invasive potentials were enriched by differential ultracentrifugation and compared using isobaric tags for relative and absolute quantitation (iTRAQ) coupled with multi-dimensional liquid chromatography and tandem mass spectrometry (LC-MS/MS).
All 9 GBM lines produced invadopodia and degraded Cy3-gelatin. There was a significant difference between the most invasive (U87MG) and least invasive (LN229) cells (65%, percentage of total cell area; $p = 0.0001$). Overall, 1667 proteins were identified from duplicate runs, of which 76% mapped to membrane structures using the David bioinformatics database (http://david.abcc.ncifcrf.gov). The abundance of 34 proteins significantly correlated to the degree of invasion ($r^2 > 0.5$ or $r^2 < -0.5$; $n \geqslant 9$; $p < 0.05$). An invadopodia assay was used to characterize the invasive potential of GBM cell lines. Differentially abundant proteins identified by iTRAQ LC-MS/MS analysis are involved in cellular motility, cell-cell signalling and interactions and angiogenesis. Such, invadopodia-associated membrane proteins could be targets for novel anti-invasive therapies.
No conflict of interest.

626 POSTER

Exercise modulates redox-sensitive mechanisms in the blood–brain barrier microenvironment during metastasis development

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Background: Tumor cell extravasation into the brain requires passage through the BBB (blood–brain barrier) (BBB), which is a highly protected microvascular environment that is fortified with TJs (tight junction). Activated redox-sensitive small GTPases (Ras kinase) can target TJ proteins leading to disruption of the BBB and promoting tumor cell extravasation. There is evidence that exercise can alter the oxidation status of the brain microvasculature and protect against tumor cell invasion. However, the mechanism remains unclear.
Methods: Mice exercised voluntarily for five weeks using a running wheel. The average running distance was 9.04 ± 2.0 km/day. In order to study blood-borne brain metastasis formation we infused D122 cells (murine Lewis lung carcinoma) into mouse brain microvasculature through the internal carotid artery using a technique previously published in the lab. Mice were infused with $1x10^6$ tumor cells and observed for 48-hours or 2 weeks then brain tissues were collected.
Results: Oxidative stress measurements revealed a trend toward increased ROS (reactive oxygen species) in both the exercise and tumor cell injected groups, and a statistical correlation between running distance and ROS (DCF) in the high-running group. Ras activity was increased in the sedentary mice injected with tumor cells but was similar to control in the exercise tumor cell group. TJ (occludin and claudin-5) protein expression was similar between the exercise tumor and vehicle treated groups, however ZO-1 and junctional adhesion molecule-A protein levels trended toward increased expression in the tumor cell groups. Tumor cell bioluminescence was elevated in the sedentary group at 2 weeks compared with exercised mice.
Conclusions: These data indicate that initial steps in metastasis formation involve a localized increase in reactive oxygen species and activation of small GTPases. Also exercise may attenuate metastasis formation at later stages. Importantly, they suggest that exercise plays a role in modulating Ras signaling in the brain microvasculature.
No conflict of interest.

627 POSTER

Clinicopathological and prognostic significance of fibroblast growth factor receptor 1, 2, and 4 in gastric cancer

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Background: The overexpression of fibroblast growth factor receptor (FGFR) 2 has been known as a prognostic factor and a target of treatment in undifferentiated type gastric cancer. However, role of the other FGFRs is not elucidated enough. We investigated the correlations of FGFR1−4 expressions with clinicopathological features and prognosis in gastric cancer.
Materials and Methods: Tumor samples were obtained from gastric adenocarcinomas of 222 patients who underwent a gastrectomy from 2003 to 2007. The expression of each FGFR was analyzed in the tumor by immunohistochemistry. Parametric correlations were done between FGFR expressions and the clinicopathologic findings. A univariete and multivariate analysis were done with the disease specific survival.
Results: Cytoplasmic overexpression of FGFR1 was found in 66 (30%) of all tumors, FGFR2 in 114 (51%), FGFR3 in 142 (64%), and FGFR4 in 175 (79%). Overexpression of FGFR1, 2 or 4 was significantly associated with tumor progression, including the depth of tumor invasion, involved lymph nodes, distant metastasis, tumor stage and recurrent disease. Patients with overexpression of FGFR1, 2 or 4 had significantly worse survival ($p < 0.001$, $=0.0083$, and <0.001). In addition, co-overexpression of the three FGFRs was significantly associated with a poor survival than none or one expression of those expressions ($p < 0.001$ and $=0.0015$). Although the tumor stage was the most dominant prognostic factor (hazard ratio, 22.334; 95% confidence interval, 10.054–49.613; $P<0.001$), the co-overexpression of the three FGFRs was also an independent prognostic factor (hazard ratio, 1.707; 95% confidence interval, 1.022–2.851; $P = 0.041$). In subset analysis, patients with overexpression of FGFR1, 2 or 4 had also significantly worse survival in undifferentiated type ($p < 0.001$, <0.001, and $=0.0103$), and the co-overexpression of the three FGFRs was an independent prognostic factor (hazard ratio, 2.033; 95% confidence interval, 1.066–3.878; $P = 0.031$). But it was not an independent prognostic factor in differentiated type (hazard ratio, 1.062; 95% confidence interval, 0.437–2.582; $P = 0.894$), and patients with overexpression of FGFR4 had only significantly worse survival ($p = 0.0098$).
Conclusions: Overexpression of FGFR1, 2, or 4 was associated with tumor progression and poor survival.FGFR1 and 4 may become prognostic factors and targets of treatment as well as FGFR2 in gastric cancer especially in undifferentiated type.
No conflict of interest.

628 POSTER

Soluble METCAM/MUC18 blocks angiogenesis during the in vivo tumor formation of human prostate cancer LNCaP cells

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Background: Human METCAM/MUC18 is a key determinant in increasing tumor-take and tumorigenesis and initiating metastasis of human prostate cancer LNCaP cells. To study the mechanisms, in this report we further study the effect of enforced expression of truncated human METCAM/MUC18 proteins on tumor-take and tumorigenesis of LNCaP cells.
Material and Methods: The wild type and/or truncated human METCAM/MUC18-expressing LNCaP cells were subcutaneously co-injected with Matrigel to nude mice, and effects of expressing different forms of human METCAM/MUC18 on angiogenesis and tumor formation compared. The effect of expressing different forms of METCAM/MUC18 in LNCaP cells on the level of VEGF protein and the micro-vessel density in the *in vivo* tumors were determined.
Results: LNCaP clones/cells overly expressing the wild type or various cytoplasmic tail-deleted METCAM/MUC18 proteins had a higher tumor-take rate (80–100%) than the cells expressing vectors (50%). LNCaP clones/cells that overly expressed the cytoplasmic tail-deleted METCAM/MUC18 proteins appeared to have larger tumors than those that overly expressed the wild type protein. The tumors formed by the LNCaP clones/cells that overly expressed a soluble METCAM/MUC18 protein, in which both the cytoplasmic tail and the transmembrane domain were deleted, were not enriched with and not engulfed by massive blood vessels, whereas the tumors formed by the LNCaP cells that overly expressed the wild type or the cytoplasmic tail-deleted METCAM/MUC18 protein were enriched with and engulfed by massive blood vessels. Majority of the tumors formed by an equal mixture of the LNCaP cells, which expressed the wild type, and the cells, which expressed the soluble METCAM/MUC18, were not enriched with and not engulfed by massive blood vessels.
The VEGF level and the micro-vessel density in the tumors formed by LNCaP clones/cells that overly expressed the wild type or the cytoplasmic tail-deleted METCAM/MUC18 proteins were at least 2 fold higher than those in the tumors formed by the LNCaP clone/cells that overly expressed a soluble METCAM/MUC18 protein.
Conclusions: The ectodomain of the METCAM/MUC18 protein is necessary and sufficient, but the cytoplasmic tail is dispensable and may be inhibitory for angiogenesis and tumorigenesis of human prostate cancer LNCaP cells in nude mice. We suggest that human METCAM/MUC18 increases tumorigenesis and initiates metastasis of LNCaP cells by inducing vascularization inside and outside of tumors and hence mediates the hematogenous spread of tumor cells. We also suggest that peptides derived from human METCAM/MUC18 protein may be useful for blocking tumorigenesis and metastasis of human prostate cancer cells.
No conflict of interest.

629 POSTER

Inhibition of TGFβ induced EMT with metformin and salinomycin increases epithelial markers and reduces cell migration in lung adenocarcinoma cell lines

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Introduction: A central pathophysiological mechanism which is involved in the development of metastases is the epithelial-to-mesenchymal transition (EMT). EMT transforms epithelial carcinoma cells into mesenchymal like cells, characterized by increased cell migration and invasiveness. These functional conversions are dependent on stimulation by different cytokines, among those the Transforming Growth Factor β (TGFβ) seems to play a key role. Recently, metformin, an antidiabetic drug, and salinomycin, known for its apoptotic effect on cancer stem cells, have demonstrated an EMT inhibitory effect, although the exact mode of action still remains unclear. The presented experiments investigated how these substances inhibit TGFβ induced EMT in non-small cell lung cancer (NSCLC) cell lines.
Material and Methods: The NSCLC cell lines A549 and HCC4006 were stimulated with TGFβ (10ng/ml) for 48 h to induce EMT. Simultaneous addition of metformin or salinomycin was applied to inhibit the TGFβ induced EMT. Western blot analysis of E-cadherin and vimentin was performed to determine changes of EMT marker expression. Wound healing assay was conducted to determine effects on cell migration. The drug effects on cell viability were investigated by MTS assays.
Results: After TGFβ stimulation, cells underwent EMT, causing a down-regulation of E-cadherin and an upregulation of vimentin in Western Blot analyses. Moreover they showed an increased cell migration. Simultaneous application of TGFβ and metformin inhibited distinctly the execution of EMT and increased the E-cadherin expression. Similarly, salinomycin also inhibited EMT, although higher doses of salinomycin increased the vimentin expression in both cell lines. Furthermore metformin and salinomycin inhibited cell migration. Finally, with additional Western Blot analyses we provided possible evidence, that both substances do not block the binding of TGFβ to its receptor, but seem to interfere with intracellular pathways.
Conclusion: As EMT is involved in the metastatic process of cancer and in the development of chemoresistance, the profound knowledge and the manipulation of this mechanism could have some clinical implication. In summary, it was observed that metformin and salinomycin have the potential to block EMT and moreover inhibit EMT induced cell migration. Therefore our results implicate that both substances are novel intracellular EMT inhibiting drugs which might help to control the metastatic process in NSCLC.
No conflict of interest.

630 POSTER

Sialyl Lewis A and sialyl Lewis X antigens mediate oral cancer cell binding to recombinant E-selectin and TNF-alpha-stimulated endothelial cells

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Background: Distant metastasis is becoming a major cause of mortality among oral cancer patients. The carbohydrate epitopes sialyl Lewis A (sLeA) and sialyl Lewis X (sLeX) have been shown to play a role in the extravasation and metastasis of different cancer cells through interaction with E-selectin on endothelium. The aim of this study was to investigate whether sLeA/X are involved in the binding of oral squamous cell carcinoma (OSCC) cells to endothelial E-selectin.
Materials and Methods: The relative expression of the enzymes potentially involved in sLeA/X synthesis in OSCC cell lines was measured by quantitative real-time (RT)-PCR. sLeA/X cell surface expression was assessed by flow cytometry and immunofluorescence staining. Seventeen matched-pairs of primary and nodal metastatic OSCC tissue sections were evaluated immunohistochemically using anti-sLeA (clone KM231) and anti-sLeX (clone KM93) monoclonal antibodies (mAbs). The association between sLeA/X expression profiles and OSCC cell adhesion to recombinant E-selectin (rE-selectin) and TNF-α-stimulated human dermal microvascular endothelial cells (HuDMEC) was evaluated by static and flow adhesion assays, respectively. The effectiveness of various cell adhesion prevention mechanisms was tested using anti-sLeA/X mAbs, neuraminidase, fucosidase, IELLQAR®, swainsonine and siRNA.
Results: The metastatic OSCC cell line, TR146, expressed significantly more sLeA than the non-metastatic OSCC cell lines, SCC4 and Cal27, and this was at least partially related to expression of fucosyltransferase III (FUT3). Inhibition of FUT3 expression in TR146 cells using siRNA reduced sLeX but not sLeA levels. Immunohistochemistry analysis showed sLeA/X to be mainly expressed by well- to moderately-differentiated OSCCs. No association between sLeA/X expression and lymph node metastasis of OSCC was noted. TR146 cells bound to rE-selectin and TNF-α-stimulated HuDMEC in significantly greater numbers than SCC4 cells. The adherence of TR146 cells to rE-selectin was significantly reduced after incubation with anti-sLeA/X mAbs, neuraminidase and siRNA to FUT3. Treatment of TR146 cells with neuraminidase also resulted in a significant reduction in cell binding to HuDMEC under hydrodynamic flow conditions.
Conclusions: Increased levels of sLeX in metastatic OSCC cells results from increased expression of FUT3. Elevated expression of sLeA/X enhances OSCC cell binding to rE-selectin and TNF-α-stimulated HuDMEC.
No conflict of interest.

631 POSTER

PKC as therapeutic target in glioblastoma

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Background: Glioblastoma (GBM) is the most malignant and the most frequent primary brain tumour. Despite all the efforts, the median survival time for GBM patients remains approximately 12−14 months. Preclinical and clinical evaluation of novel therapeutic strategies is a priority in these tumours. Actually, the *gold standard* used in clinical practice in GBM treatment is temozolomide (TMZ) (Temodar®). TMZ has a poor relative lack of success, probably due to the genetic and cellular heterogeneity of these tumours and also to the development of chemotherapeutic resistance. Tamoxifen (Novaldex®) is a member of the estrogen receptor (ER) modulator family that has been successfully used in the treatment and prevention of breast cancer (Mandlekar*et al.,* 2001). However, recent findings have suggested the possibility of a new antitumor mechanism ER-independent that led to the use of tamoxifen in glioma treatment. It was demonstrated that tamoxifen could inhibit cell proliferation *in vitro* through inhibition of protein kinase C (PKC) activity in several cancers. Therefore, this study aimed to evaluate the effect of tamoxifen in cell signaling pathways associated with glioma proliferation and modulation of cytoskeleton organization.
Material and Methods: For that, U-118 glioma cells were incubated with different concentrations of tamoxifen and the evaluation of the cytotoxic effect was determined by MTT assay. Proliferation analysis was evaluated using a BrdU assay. p-PKC expression was evaluated by western blot. Fluorescence assay to actin-filament studies were also performed.
Results: The results indicated that in GBM cells treated with tamoxifen there was a significant down-regulation of p-PKC expression, and a reduction in the proliferation rate of U-118 cells. In addition, the results also showed that tamoxifen induced a disorganization of f-actin filaments indicating that this drug may interfere with glioma cell migration.
Conclusions: Based on the inhibition of p-PKC expression by tamoxifen these results indicated that PKC contributes to the aggressive behavior of U-118 glioma cells since it reduced glioma cells proliferation and disorganized f-actin filaments. Therefore, the role of PKC signaling pathway in glioma should be better elucidated in order to determine if PKC could be considered a new therapeutic target in this tumour.
No conflict of interest.

632 POSTER

The progression mechanism of hepatocellular carcinoma

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Background/Aims: To evaluate the progression of hepatocellular carcinoma (HCC), the ligand-stimulated receptor activity due to hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF) were studied.
Methods: In the specimens of 30 HCC patients and culture cells (PLC/PRF/5) the induction values of intracellular protein were estimated by western blot. And for culture cells, the viability was determined by test method with 3-[4, 5-dimethylthiazol-2-yl]-2, 5-dephenyl tetrazolium bromide (MTT).
Results: 1. Serum HGF levels were significantly higher in invasive gross type or in intrahepatic metastasis (IM)-positive tumours. 2. The mean expression value of HGF protein in tumour was 0.56±0.35, which was not

different from non-tumour tissue, 0.59±0.40. And there was no significant differences based on tumour profiles. 3. The value of c-Met in tumour tissue, 1.36±0.12, was clearly higher than in non-tumour tissue, 1.07±0.06. The c-Met expressions were significantly higher on invasive type of HCC on gross type, vessel invasion, IM presence and histological type. 4. On individual study about the relationship between the level of serum HGF and c-Met expression in tumour tissue, the presence of IM could be easily detected. Furthermore, the level of serum HGF after hepatectomy was significantly higher than the preoperative value, and individual study with c-Met expression was associated with early recurrence. 5. The c-Met tyrosine phosphorylation in culturing cells was increased by 20 ng/ml HGF, and extracellular signal-regulated kinase (ERK) was also activated. Although VEGF receptor (Flk-1) was phosphorylated in response to VEGF, phosphorylated ERK was not detected. 6. Over 5.0 μM hydrogen peroxide (H2O2) caused rapid phosphorylation of both ERK1/2 and c-Jun NH2-terminal kinase (JNK) at 1 hour and cell death in a dose-dependent manner after 24 hours. 7. In first 6 hours, H2O2 induced cell death for 58.4±6.8%, whereas the presence of 100 ng/ml VEGF improved the survival rate to 77.2±4.2. 8. VEGF significantly decreased H2O2-induced cell death after 12 hours, whereas HGF (20 ng/ml) did not have a similar effect. 9. H2O2-induced phosphorylation of ERK and JNK was also reduced by VEGF (100 ng/ml). In contrast, HGF did not have an effect for H2O2-induced action for ERK and JNK.

Conclusion: The induction of c-Met and VEGF might be important to make IM and to survive respectively in the progress of HCC.

No conflict of interest.

633 POSTER

Small interfering RNA mediated down-regulation of ribonuclease reductase M2 subunit reduces cell proliferation, migration and invasion of clear cell renal cell carcinoma in vitro

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Background: Ribonuclease reductase (RRM2) is an enzyme essential for the process of DNA synthesis. Overexpression of *RRM2* has been identified in numerous types of cancer including breast, colon, cervical and liver. Clear cell renal cell carcinoma (ccRCC) is the most common type of adult kidney tumour accounting for 75% of renal cell neoplasms. It is responsible for 2% of cancer related deaths worldwide. Our preliminary studies using Affymetrix® microarray analyses showed that *RRM2* was up-regulated up to 5 fold in ccRCC human tissues compared to normal human kidney tissues. However, the functions of *RRM2* in human ccRCC have not been clarified. The aim of this study is to investigate the effect of *RRM2* gene knockdown on proliferation, migration and invasion of human ccRCC cell line cells.

Materials and Methods: Down-regulation of *RRM2* in primary ccRCC (Caki-2, RCC-KP) and secondary metastases (Caki-1) cell line cells was achieved using pre-designed *RRM2* small interfering RNA (siRNA) at a final concentration of 20 μM for 72 h, alongside scrambled siRNA was used as a negative control. *RRM2* gene knockdown was assessed by real-time qPCR and Western Blot analyses. Cell proliferation and viability assays were carried out. *In vitro* scratch and Trans-well assays were done to investigate the effect of *RRM2* down-regulation on ccRCC cell migration. Effect of *RRM2* gene knockdown on cell invasion was assessed using Trans-well invasion assay.

Results: At least 80% *RRM2* gene knockdown was observed by quantitative RT-PCR and Western blot analyses. SiRNA mediated knockdown of the *RRM2* gene resulted in a reduction in cell proliferation ($P \leqslant 0.005$) without a concurrent reduction in cell viability in each cell line. *RRM2* knockdown had significant effect on reduction of cell invasion of primary ccRCC cell lines (Caki-2 and RCC-KP) ($P \leqslant 0.05$) but not secondary metastases Caki-1 cell line cells by Trans-well invasion assays. Furthermore, *In vitro* scratch and Trans-well assays showed a significant decrease in ccRCC cell migration of each cell line.

Conclusions: In summary, down-regulation of *RRM2* in ccRCC inhibits cell proliferation, migration and invasion of primary ccRCC cell lines. It indicates that overexpression of *RRM2* may be associated with ccRCC progression; thus suppressing its function may be a potential therapeutic strategy in ccRCC.

No conflict of interest.

634 POSTER

Supplementation with selenoglycoproteins suppresses early events in brain metastatic tumor formation via a mechanism involving NF-kB

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Background: Selenium is an essential trace element known to have a significant influence on biological systems. Beneficial impact of selenium on human health is attributed to its antioxidant activity and, in therapeutic aspects, to anticarcinogenic, anti-inflammatory and antiviral features. Feeding mice with selenium (Se) enriched yeast for 20 weeks markedly decreased growth of brain metastatic tumors. In order to identify components responsible for this protective effect soluble selenoglycoproteins (SGP) were extracted from Se-enriched yeast at pH 4.0 (SGP40) and 6.5 (SGP65).

Materials and Methods: To determine influence of SGPs on adhesion and migration of cancer cells through human brain endothelium, co-cultures of brain endothelial cells (hCMEC/D3) with lung (A549) or breast (MDA-MB231) cancer cells were treated with SGP40 or SGP65. hCMEC/D3 cells were cultured on collagen-coated transwell inserts (transmigration) or 48-well plates (adhesion) until reaching confluence. Labeled tumor cells were added in the amount of $5x10^5$ cells/ml onto endothelial monolayers. Fluorescence was measured as a marker of cell migration or adhesion at 485-nm excitation and 530-nm emission wavelengths. We then employed electrophoretic mobility shift assay (EMSA) to determine the influence of the SGPs on NF-κB activation.

Results: SGP40, but not SGP65 inhibited adhesion and migration of tested tumor cell lines through endothelial cell monolayers compared to the vehicle-treated control. SGP40 effectively suppressed TNFα-stimulated NF-κB activation in brain endothelial cells. While SPG65 also inhibited NF-κB DNA binding activity, these effects were less robust than those of SGP40. Surprisingly, pretreatment with SGP40 or SGP65 did not affect TNFα-induced expression of ICAM-1 and VCAM-1, suggesting the involvement of another adhesion mechanism. To further evaluate the active components responsible for the unique properties of SGP40, a series of experiments were performed using compounds identified to be present in Se-enriched yeast. Several of the compounds showed high activity, decreasing adhesion of cancer cells to brain endothelium and suppressing NF-κB activation.

Conclusions: The findings indicate that specific selenium compounds have the ability to inhibit adhesion and transendothelial migration of tumor cells via a process, which is likely to involve NF-κB activation.

Conflict of interest: *Corporate-sponsored research: Research supported in part by Alltech*

635 POSTER

The effect of the Wilms tumour suppressor protein (WT1) on regulating cellular morphology and gene expression in endometrial stromal cells

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Background: The Wilms tumour suppressor gene (WT1) is a transcription factor that functions as a key regulator of development and differentiation. WT1 encodes four major protein isoforms (WT1 +/+, +/−, −/+ and −/−), each denoted by the presence or absence of two alternative splice sites. An increase in WT1 mRNA and protein has been shown to cause a mesenchymal to epithelial transition (MET) during kidney development, aberrant function can lead to the paediatric malignancy Wilms tumour. Recently, WT1 has also been shown to be expressed within the endometrial stromal cells (ESCs) of the uterus.

Methods and Results: Using Real-time PCR, western blotting, cell culture and immunofluorescence a MET is shown to occur in ESCs, through changes in the morphology, mRNA and protein levels of the mesenchymal marker vimentin and epithelial markers E-cadherin and cytokeratin. This is demonstrated to occur during maximum levels of WT1 expression. The WT1 isoforms are shown to induce an ESC MET, through transient transfection of each WT1 isoform into ESCs. The WT1 +/+ and −/− isoforms are shown to induce the expression and bind to the promoter of E-cadherin, providing a possible role for the induction of MET. Methoxyprogesterone acetate (MPA) is also shown to effect the WT1 isoform regulation of a range of target genes, indicating a possible synergism between WT1 and MPA activated factors.

Conclusions: An ESC MET is shown to occur in ESCs at maximal WT1 expression. The ESC MET is demonstrated here to be induced by WT1 isoforms through MET markers E-cadherin, cytokeratin and vimentin and the formation of an epithelial morphology. This WT1 mediated ESC MET is thought to occur through a direct WT1 regulation of the E-cadherin

promoter. This study therefore aids the understanding of WT1 in ESCs and may prove to be useful as a possible biomarker for endometrial malignancies.
No conflict of interest.

636 POSTER

Investigation of a mechanistic link between 15-Lipoxygenase-1 (15-LOX-1) and Metastasis Associated Protein 1 (MTA1) in human colorectal carcinoma cell lines

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Background: Metastasis Associated Protein 1 (MTA1) is a member of the nuclear remodeling and histone deacetylase (NuRD) complex that is known to repress the expression of several tumor suppressor genes. 15-lipoxygenase-1 (15-LOX-1), a member of the inflammatory eicosanoid pathway, has been shown by us and others to have an anti-tumorigenic role in colon cancer. *ALOX15* was recently shown to be repressed by the NuRD complex. Previously we have reported that ectopic expression of 15-LOX-1 in colon cancer cells reduced MTA1 expression, indicating the presence of a crosstalk and a negative correlation between 15-LOX-1 and MTA1 expressions.
To understand the mechanism behind this crosstalk, we have hypothesized the involvement of nuclear factor kappa B (NF-kB). MTA1 can be transcriptionally upregulated by NF-kB, while we and others have shown that 15-LOX-1 can inhibit the activity of NF-kB.
We have ectopically expressed 15-LOX-1 in colon cancer cell lines and examined the expression of MTA1 and NFkB p65 subunit in a panel of 5 colon cancer cell lines and the transcriptional regulation of MTA1 by NF-kB. We have also checked whether there is a correlation between the expression of 15-LOX-1 and MTA1 by analyzing publicly available human colorectal cancer gene expression datasets.
Materials and Methods: Cells were transiently transfected a 15-LOX-1 expression vector or the empty vector. Protein levels of 15-LOX-1, MTA1 and NFkB p65 were detected by Western blot analysis. NF-kB recruitment to the promoter of MTA1 was determined by chromatin immunoprecipitation and luciferase assays. Publicly available colorectal cancer dataset GSE41258 was obtained from Gene Expression Omnibus (GEO) and analyzed with GeneSpring GX 11.0.
Results: HT-29 and LoVo cells transfected with the 15-LOX-1 vector showed a decrease in nuclear levels of NF-kB p65 and MTA1 expression. Recruitment of p65 onto its consensus sequence at the MTA1 promoter was reduced in 15-LOX-1 expressing cells. Moreover, the expression of MTA1 and 15-LOX-1 was negatively correlated particularly in the Stage 3 and Stage 4 colorectal cancer patients.
Conclusion: 15-LOX-1 may inhibit MTA1 expression at least partly via reduced recruitment of NF-kB on to the MTA1 promoter. Based on recent reports by us and others on the role of MTA1 as a master regulator of cellular transformation in several tumor types, these data may help in understanding the regulation of MTA1 and open ways for therapeutic applications in the future.
No conflict of interest.

637 POSTER

Promoter methylation of the BRCA-1 gene in premenopausal breast cancer patients in West Sumatera-Indonesia

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Background: Breast cancer is the most common type of cancer in Indonesian women. Around 39,831 new cases of breast cancer happens annually with the incidence of 36.2 per 100,000 women. Several researches reported that the mean age of Indonesian breast cancer patients are younger than 50 years old. The peaks of the incidence occur on the age of 48 years old and rarely are hereditary breast cancer (less than 2%). The aim of the research is to evaluate the relationship between the promoter of BRCA-1 gene with premenopausal breast cancer and its correlation with ER, PR, HER-2, BRCA-1 and Ki-67 expression.
Materials and Methods: This study is an observational study with cross-sectional design. Size and samples are 32 premenopausal breast cancer patients listed on the registration of breast cancer from department of the Division of Oncology, Dr. M. Djamil Padang General Hospital, West Sumatera. Breast cancer tissues are examined by histopathology and immunostaining for histopathological type and expression of ER, PR, HER-2, BRCA-1 and Ki-67. To determine the methylation of the promoter BRCA-1 gene, methylation specific bisulphide PCR are used. Data are analyzed using Chi-Square test.
Results: 32 patients with average age of 42.09 years, median 44.5 years, standard deviation of 5.7, oldest age is 50 years old and the youngest is 31 years old. The results of immunostaining are ER+ (34.4%), PR+ (12.5%), HER-2+++ (18.8%) and Ki-67+ (43.8%), positive methylation specific PCR are found in 20/27 patients (74%). The result of Chi-Square test found a significant relationship between age and methylation ($p = 0.037$). There was no significant association between methylation of ER ($p = 0.178$), PR ($p = 0.593$), BRCA-1 ($p = 0.266$), HER-2 ($p = 1.000$) and Ki-67 ($p = 1.000$).
Conclusion: Promoter methylation of BRCA-1 gene are in premenopausal breast cancer patients in West Sumatera (70%), but does not have significant relationship with the expression of ER, PR, HER-2, Ki-67 and BRCA-1. Age has a significant relationship with the occurrence of methylation promoter BRCA-1 gene in premenopausal breast cancer patients in West Sumatera.
No conflict of interest.

Poster Session (Sat, 28 Sep)
Translational Research

638 POSTER

Anti-60S ribosomal protein L29 antibody; new anti-cancer agent discovered from human sera

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Background: Incidence of hepatocellular carcinoma (HCC) is lower in autoimmune hepatitis (AIH) than chronic viral hepatitis. In AIH, serum immunoglobulin G (IgG) levels are associated with the clinical features. In this study, we searched IgG showing anti-tumour effect in sera of AIH patients.
Material and Methods: Total IgG was extracted from sera of AIH patients by using protein G. Anti-tumour effects of the total IgG were evaluated by MTT assay using human HCC Huh7 cells and PLC/PRF/5 cells. Autoantigens in membrane proteins of Huh7 cells were screened by immunoprecipitation followed by liquid chromatography-mass spectrometry (LC-MS) shotgun analysis. Signalling pathways were analysed by western blotting.
Results: In one AIH patient without any cancers, addition of total IgG extracted from her serum to the culture inhibited the proliferation of huh7 cells and PLC/PRF/5 cells, and decreased intracellular levels of β-Catenin and Cyclin-D1. In this patient, autoantigens in membrane proteins were screened, and 60S ribosomal protein L29 (RPL29) was identified from the MS/MS spectra and the SwissProt database using the Mascot Search engine. RPL29 expression in human HCC cell lines including Huh7, PLC/PRF/5, Hep3B, HepG2, HLE, HLF and SK-Hep-1 were identified by Western blot. Next, in the other 25 AIH patients, we investigated the correlation between serum anti-RPL29 levels by indirect ELISA using recombinant RPL29 and anti-tumour effects of total IgG extracted from their sera. Serum anti-RPL29 levels were significantly correlated with anti-tumour effects of total IgG extracted from their sera ($P < 0.0001$). On the other hand, addition of recombinant RPL29 to the culture cancelled anti-tumour effects of total IgG extracted from sera of AIH patients showing higher serum anti-RPL29 levels. Additionally, these anti-tumour effects of total IgG extracted from sera of AIH patients were shown by MTT assay using human pancreatic cancer AsPC-1 cells and Panc-1 cells.
Conclusions: Anti-RPL29 antibodies showing anti-tumour effect were discovered from human sera. Anti-RPL29 inhibits cancer cell proliferation via down-regulation of Wnt/β-Catenin signalling pathway. Serum anti-RPL29 may be one of immune systems by which the human does not develop cancers. RPL29 will be a potential target for cancer therapy and cancer vaccine.
No conflict of interest.

639 POSTER

Local irradiation to enhance the anti-tumour effect of immunotherapy with the FP-IL12 fusion protein

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Background: The fusion protein FP-IL12 (α-histone-antibody with interleukin 12) binds to necrotic tissues. Upon binding IL12 promotes a Th1-based anti-tumor immune response. Irradiation is an effective inducer of

necrotic cell death in tumours. We hypothesize that irradiation of tumours leads to increased binding of FP-IL12 via radiation-induced necrotic cell death and thereby to an enhanced anti-tumour effect of the fusion protein.
Material and Methods: The human rhabdomyosarcoma (A204) and prostate cancer (PC3) models were studied in vitro and xenografted in NSG (nod-scid-gamma) mice (72 tumours). Radiation sensitivity was assessed by colony forming assays. In vivo necrosis was determined with small-animal MR using the ADC values (control, single doses of 0.5 Gy, 2.0 Gy and 8.0 Gy; fractionated doses of 5 x 2.0 Gy and 3 x 5.0 Gy). Binding of the FP-IL12 fusion protein was evaluated with small-animal PET imaging (DOTA- Cu-64 labelled FP-IL12) with and without irradiation as well as ex-vivo-biodistribution and autoradiography. Tumour growth delay assays in humanized NSG mice with xenografted A204 are ongoing.
Results: A204 (D37 1.0 Gy) and PC3 (D37 1.9 Gy) differ in their intrinsic radiation sensitivity. Accordingly, radiation-induced tumour necrosis was found only in A204 with changes in ADC values after 8 Gy of +51% $\pm$ 21% and no change in PC3 with −6% $\pm$ 5%. In A204 a radiation-dose effect for necrosis-induction was observed with change in ADC values increasing from +16% $\pm$ 14% after 2.0 Gy to +51% $\pm$ 21% after 8.0 Gy. An enhanced up-take of FP-IL12 in A204 tumours was detected by PET and ex-vivo-biodistribution. Tumour-to-muscle-ratio (TMR) increased from 5.4$\pm$3.2 in unirradiated tumours to 14.8$\pm$5.2 after 8.0 Gy ($p = 0.03$). In PC3 tumours no increase in TMR was observed. Autoradiography revealed homogenous FP-IL12 binding in the tumours.
Conclusions: Local irradiation increased the tumour-specific binding of the immunotherapeutic fusion protein FP-IL12. The anti-tumour effect of this combination is currently investigated in A204 bearing mice. The observed relationship of FP-IL12 binding with necrosis-induction supports the concept that local tumour irradiation might enhance anti-tumour immunotherapy. The successfully established humanized tumour-mouse model provides a valuable tool for translational studies investigating the combination of radiotherapy and immunotherapy.
This work was funded by the PATE program, grant 2007−0−0, University of Tübingen.
No conflict of interest.

640 POSTER

HER2 status in breast cancer patients: A comparison between borderline positive HER2 and strongly positive HER2 tumors

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Introduction: Amplification or over-expression of the *HER2* gene occurs in approximately 30% of breast cancers. It is strongly associated with increased disease recurrence and a worse prognosis. In recent years HER2 status has evolved to become an important biomarker and therapy target. The aim of this study was to compare the group of borderline positive HER2 (++) status patients with strongly positive HER2 (+++) status group according to clinicopathological features, cardiotoxicity and treatment response.
Material and Methods: This retrospective study was conducted on HER2 positive breast cancer patients treated in Clinical and Experimental Oncology Department, Maria Sklodowska-Curie MemorialCancer Center and Institute of Oncology in Gliwice Branch in Poland (COI). The analysis included 167 early and metastatic breast cancer patients treated with trastuzumab between 2006–2012. HER2 overexpression was assessed using an immunohistochemical method (IHM). HER2 gene amplification was additionally assessed by FISH in 17% patients.
Results: In analyzed group, 17 (10%) patients were borderline HER2 positive (HER2++) tumors. Most of them were treated with trastuzumab in adjuvant seting (65%). In these study all HRE2 borderline tumors were ductal invasive adenocarcinoma. There were not find any differences between both groups in positive steroid receptor status (ER+/PR+) (47% vs 46%). The comparison between HER (++) and HER (+++) status had shown that HER (++) tumors were at lower advance stage of disease at diagnosis (54% vs 18%) $p = 0.002$. Distant metastases was observed only in strongly positive HER2 patients (8%). Skin metastases also were more often detected in this group (14% vs 6%). The decrease of LVEF occurred in the same rate in both groups (6% vs 5%). Acute cardiac side effects were presented only in strongly positive HER2 (+++) status group (2%) $p = 0.953$. Contralateral breast cancer occurred more often in borderline positive HER 2 (++) status patients ($p = 0.02$). Disease recurrence was significantly more frequent in strongly positive HER2 status patients (72 % vs 36%) $p = 0.006$. The Disease progression was significantly more frequent in strongly positive HER2 status patients (57% vs 27%) $p = 0.02$.
Conclusion: Borderline positive HER2 breast cancer patients are in lower advance stage at diagnosis and have better outcome than strongly positive HER2 tumors. They are less predisposed to the development of cardiac side effects.
No conflict of interest.

641 POSTER

Comprehensive pharmacogenetic profiling of advanced colorectal cancer

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Background: Inherited genetic factors may influence a patient's response to, and side effects from, chemotherapy and biological therapies. Here, we sought to generate a comprehensive inherited pharmacogenetic profile for advanced colorectal cancer (aCRC).
Materials and Methods: We analysed 260 potentially functional coding region and promoter variants in genes within the 5-FU, capecitabine, oxaliplatin, EGFR and DNA repair pathways in 2183 patients with aCRC treated with oxaliplatin-fluoropyrimidine chemotherapy $\pm$ cetuximab (from the MRC COIN and COIN-B trials). Primary outcomes assessed were 12-week response, skin rash (SR) (for those receiving cetuximab), dose-reduction or delay in treatment due to any toxicity and peripheral neuropathy (PN).
Results: In patients treated with chemotherapy + cetuximab, 5 and 4 coding region variants in the EGFR pathway were associated with response and SR, respectively. The most significant associations were with variants in members of phosphatidylinositol 3-kinase regulatory subunit. In patients treated with chemotherapy $\pm$ cetuximab, 8 coding region variants in the 5-FU, capecitabine, oxaliplatin or DNA repair pathways were associated with response, 8 with any toxicity and 5 with PN. The most significant associations for response were with variants in DNA repair genes and, for any toxicity, with two common and independent variants in DPYD. Given previous observations that rare variants in DPYD affect toxicity, we undertook a comprehensive analysis of both common and rare DPYD variants. Carriers of the common variant V732I and/or the rare variants D949V and IVS14+1G>A, which accounted for 10.6% of all patients, had an increase in any 12-week toxicity (OR=1.64, 95% CI 1.23–2.18, $P = 0.0007$) which included neutropenia (OR 2.30, 1.52–3.48, $P = 0.0002$).
Conclusions: Despite having considerable power to detect alleles of small effects (>85% power to detect OR=1.3), none of the associations remained significant after rigorous correction for multiple testing. We suggest that common DPYD variants may be worth re-considering in future screens for tolerance to 5-FU.
Conflict of interest: *Corporate-sponsored research: This study was part funded by an unrestricted research grant from Merck Serono (to T.S.M. and J.P.C.)*

642 POSTER

DMET (Drug Metabolizing Enzymes and Transporters) microarray analysis of colorectal cancer patients with severe 5-Fluorouracil-induced toxicity

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Background: 5-Fluorouracil (5-FU) is still a milestone anti-cancer drug, on the other hand, its use is often limited by the occurrence of severe toxicity. Even if the detrimental effect of some dihydropyrimidine dehydrogenase (*DPYD*) and thymidylate synthase (*TYMS*) polymorphisms is well known, no genetic predictor of severe toxicity has yet been validated. For the first time, we studied the genetic background of 5-FU-induced toxicity using the Affymetrix DMET™ Plus GeneChip, a pharmacogenetic array that interrogates 1936 variants in 231 genes involved in drug metabolism, excretion and transport.
Material and Methods: Among 119 colorectal cancer patients gathered from 2004 to 2006, we analyzed 25 patients who experienced a severe gastrointestinal toxicity (G3 or G4); control group consisted of matched patients who did not disclose adverse events (G0 or G1). Toxicity was classified according to the NCI-Common Toxicity Criteria (v.3.0). Genomic DNA from peripheral blood was analyzed with DMET™ Plus GeneChip (Affymetrix, Santa Clara, CA), appropriateness of data was evaluated with DMET™ Console and statistically relevant variants were assessed with DMET-Analyzer.
Results: No significant difference was found with respect to the 18 *DPYD* and 6 *TYMS* variants investigated by DMET™. In contrast, 11 variants in 10 new genes resulted significantly different between toxicity cases and controls, with the *CHST1* rs9787901 having the strongest inverse association ($p = 0.0008$), followed by the *GSTM3* rs1799735 ($p = 0.008$). Moreover, the number of subjects carrying the C/C genotype of the

CHST1 rs9787901 together with the AGG/- of the *GSTM3* rs1799735 was significantly higher in the group exhibiting severe toxicity compared to controls (p = 0.016). CHST1 belongs to the keratin sulfotransferase family and plays a central role in lymphocyte homing at sites of inflammation. The high frequency of the C allele in the total population might account for the elevate occurrence of gastrointestinal toxicity, ranging from milder to the most severe forms, and could also suggest that the co-presence of other variants is needed to promote severe toxicity. The *GSTM3* rs1799735 of the gluthatione S-transferase family could be one of them.
Conclusions: Though our data need to be confirmed in a larger cohort and extended to other types of toxicity, this exploratory study indicates the DMET™ array as a valid approach to discover new genetic variants involved in 5-FU-induced toxicity.
No conflict of interest.

643 POSTER

Association of killer immunoglobulin-like receptor and HLA class-I gene polymorphisms with the incidence and the clinical course of epithelial ovarian cancer

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Background: Inhibitory and activating killer immunoglobulin-like receptors (KIRs) regulate the function of NK cells and subsets of T cells. The HLA class-I molecules are the ligands for the inhibitory KIRs, while the specificity of the activating KIRs is mainly unknown. Both the *KIR* and *HLA* genotypes are highly polymorphic. It has been assumed that the *KIR* and *HLA* genotypes may confer susceptibility to ovarian cancer and influence the clinical course of the disease.
Material and Methods: The DNA of 179 patients was analyzed for 14 *KIR* genes and 126 samples were additionally typed for *HLA class I*. The control group consisted of 200 healthy individuals, including 83 women, who were analyzed separately.
Results: The *KIR2DS2* has been found to occur significantly less often in ovarian cancer patients than in the female controls (38.6% vs. 62.6%; p = 0.0004) and in the entire control group (vs. 55.5%; p = 0.002). The combination of *KIR2DL2+/KIR2DS2-* has been found to be present in 24.7% of the patients, whereas no such combination has been observed in the controls (p < 0.0001). The *HLA-C1* was significantly more frequent in patients (85.7%), compared with the female controls (67.5%; p = 0.003) and the entire control group (71%; p = 0.002). The *HLA-C1-/HLA-C2+* combination occurred in 13.5% of the test group patients and in 29% of the controls (p = 0.001). The frequency of *KIR2DS4* was higher in endometrioid cancer patients, compared with those with serous histology (67.9% vs. 35.7%; p = 0.004), mucinous histology (30.8%; p = 0.04) and the controls (29.5%; p = 0.002).
Conclusions: The genotype of *KIRs* and their ligands is associated with the susceptibility to epithelial ovarian cancer. In particular, the *KIR2DL2+/KIR2DS2-* combination is associated with an increased risk of the disease, as is the presence of *HLA-C1*. The *KIR2DS4* is linked to an increased incidence of endometrioid cancer. The results obtained need to be confirmed in independent patient populations. Our findings may be used for genetic screening and the protocols of cellular immunotherapy.
No conflict of interest.

644 POSTER

Circulating tumor cells (CTCs) in metastatic castration-resistant prostate cancer patients treated with cabazitaxel: A Dutch Uro-Oncology Study Group side-study

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Background: A circulating tumor cell (CTC) count of ⩾5 CTC/7.5 mL blood is a strong adverse prognostic factor in metastatic castration-resistant prostate cancer (mCRPC) patients before start of and during treatment with docetaxel and abiraterone. For patients treated with cabazitaxel (CBZ), this has yet to be confirmed. In this study, we prospectively evaluate the prognostic value of CTCs during CBZ therapy. Additionally, RNA is stored for future development of a gene-expression profile to predict CBZ sensitivity.
Methods: This study is a side-study of a phase II trial, initiated by the Dutch Uro-Oncology Studygroup and supported by an educational grant from Sanofi. In total, 226 patients will be randomized to CBZ/prednisone ± budesonide to investigate the effect of budesonide on CBZ-induced diarrhea. At baseline and after two cycles of CBZ, blood is obtained from patients who provided additional informed consent. CTC enumeration and isolation are both done from 7.5 mL by the CellSearch System® (Veridex, Raritan, USA). For development of a predictive gene-expression profile, RNA is stored at −80ºC. The profile will be developed as in our prior breast cancer studies [Sieuwerts, Clin Cancer Res, 2011]. A panel of genes will be selected based on changes in expression under treatment pressure and will be tested for the ability to predict CBZ sensitivity and resistance at an early stage.
Results: We here report CTC results in the first 31 patients enrolled. Of these, 28 patients (90%) had ⩾1 CTC and 19 patients (61%) had ⩾5 CTC at baseline. A CTC count at both time-points was available in 19 patients. Median CTC count dropped from 19 (IQR 3−61) at baseline to 4 (IQR 0−19) after 2 cycles. In 6/12 patients (50%) with ⩾5 CTC at baseline and a second CTC count available, there was a decrease to <5 CTC after 2 CBZ cycles and in 3/7 patients (43%) with <5 CTC at baseline there was an increase to ⩾5. Associations with clinical parameters and outcome will follow.
Conclusions: CTCs can be detected in 90% of mCRPC patients starting CBZ. In 50%, CTC counts decreased from ⩾5 CTC at baseline to <5 CTC after 2 CBZ cycles, while in 43% there was an increase from <5 to ⩾5. Future goals of this study are to associate CTC counts with clinical parameters and outcome and to develop a gene-expression profile to predict CBZ sensitivity at an early time-point.
Conflict of interest: *Corporate-sponsored research: Sanofi*

645 POSTER

Identification and quantification of AKT isoforms and phosphoforms in breast cancer using a novel, ultrasensitive nanofluidic immunoassay

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Background: Breast cancer subtype-specific molecular variations can dramatically affect patient responses to existing therapies. It is thought that differentially phosphorylated protein isoforms might be a useful prognostic biomarker of drug response in the clinic. However, accurate detection and quantitative analysis of cancer-related protein isoforms and phospho-isoforms in tumors is limited by current technologies.
Methods: Using a novel, fully automated nanocapillary electrophoresis immunoassay (NanoPro™1000) designed to separate protein molecules based on their isoelectric point, we developed a reliable and highly sensitive assay for the detection and quantitation of AKT isoforms and phosphoforms in breast cancer.
Results: This assay enabled measurement of total and activated AKT1/2/3 across a breast cancer cell line panel, using protein produced from as few as 56 cells. AKT1 and AKT2 were found to be expressed in all cell lines, whereas AKT3 was mainly expressed in basal cells, which resemble the most aggressive, triple-negative breast cancers in the clinic. Importantly, we were also able to assign an identity to the phosphorylated S473 phosphoform of AKT1, the major form of activated AKT involved in multiple cancers including breast, and a current focus in clinical trials for targeted intervention. Using this assay, we were able to detect and measure qualitative and quantitative changes in AKT isoforms and phosphoforms in cells that were treated with AKT and PI3K inhibitors.
Conclusions: The ability of our AKT assay to detect and measure AKT phosphorylation from very low amounts of total protein will allow the accurate evaluation of patient response to drugs targeting activated PI3K-AKT using scarce clinical specimens. Moreover, the capacity of this assay to detect and measure all three AKT isoforms using one single pan-specific antibody enables the study of the multiple and variable roles that these isoforms play in AKT tumorigenesis.
No conflict of interest.

646 POSTER

Investigation of biomarkers for assessing activity of the HSP90 inhibitor AT-13387 in circulating tumor cells of ALK positive patients

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Background: Crizotinib is an effective treatment in ALK-translocated NSCLC patients; however the clinical success of this therapeutic approach is limited by the development of drug resistance. Both the EML4/ALK fusion and mutated ALK are sensitive HSP90 clients, making inhibition of HSP90 another potential approach for treating ALK-driven tumors. A key to successful development of HSP90 inhibitors in the clinic is the ability to identify predictive biomarkers of response. Demonstrating the feasibility of using Circulating Tumor Cells (CTCs) as a surrogate for invasively-obtained tumor material in the assessment of HSP90 client protein levels would provide a valuable guide in the development of these agents. AT13387 is a potent fragment-derived second generation HSP90 inhibitor currently in clinical trials. We evaluated the impact of AT13387 treatment in the lung ALK-positive cell line, H2228.
Material and Methods: Experimental conditions were established for the detection of HSP70 (a marker of tumor drug engagement) and ALK proteins by immunofluorescent staining (IF) in AT13387-treated and untreated H2228 and A549 (negative control) cells. Optimal IF conditions were first determined on slides. AT13387-treated and untreated H2228 and A549 cells were then spiked in blood from normal donors and enriched on filters using the ISET (Isolation by Size of Epithelial Tumor cells) device. Epithelial to mesenchymal transition (EMT) markers were also examined in AT13387-treated and untreated cells.
Results: A highly significant induction of HSP70 was detected in both AT13387 treated (0.8 μM for 24 hrs) H2228 and A549 cells while very little HSP70 was detected in untreated cells. As expected, ALK protein expression was detected in untreated H2228 cells and not in untreated A549. Levels of ALK protein were notably decreased in AT13387 treated H2228 cells. Studies to clarify the relationship between the effect of AT13387 treatment and the induction of EMT markers are ongoing.
Conclusion: The HSP90 inhibitor AT13387 has anti-tumor activity in ALK-driven NSCLC models. These results suggest that CTCs are amenable to biomarker analyses such as quantification of HSP70 and ALK protein levels, which could be useful as PD biomarkers of AT13387 activity in the clinical setting. This hypothesis is currently being tested by the incorporation of CTC enumeration and characterization in the Phase I/II clinical trial of AT13387 in combination with crizotinib in the treatment of NSCLC (NCT01712217).
No conflict of interest.

647 POSTER

Loss of membranous expression of the intracellular domain of EpCAM is a frequent event and predicts poor survival in patients with pancreatic cancer

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Background: EpCAM is a widely used immunohistochemical marker for epithelial human malignancies and recently the new EpCAM-specific antibody Catumaxomab has been approved for the treatment of malignant ascites in cancer patients. Antibodies to target EpCAM are usually directed against its ectodomain (EpEX) but do not detect the intracellular domain (EpICD) and do not discriminate between full-length and cleaved variants.
Material and Methods: We developed an anti-EpICD antibody to compare membranous EpEX *vs.* EpICD expression by immunohistochemistry. Concurrent EpEX and EpICD expression were investigated retrospectively in paraffin-embedded primary tumor and normal tissue samples from a series of patients with pancreatic adenocarcinoma on a tissue microarray. In total 317 paired samples of pancreatic tissue from 88 patients were analyzed for membranous EpEX and EpICD expression and were correlated with clinicopathological parameters and clinical outcome.
Results: In non-cancerous pancreatic tissue, a high concordance of membranous EpEX and EpICD expression was observed and the full-length EpCAM variant ($EpEX^+/EpICD^+$ phenotype) was highly predominant. In tumor samples, most cases were EpEX positive. Loss of membranous EpICD expression ($EpEX^+/EpICD^-$ phenotype) was observed in one third of tumor samples and these patients had a significant shortened disease-free and overall survival independently from other prognostic factors.
Conclusion: This study demonstrates for the first time, that loss of membranous EpICD expression is a frequent event and predicts poor prognosis in patients with pancreatic cancer. Based on these observations, additional studies evaluating the predictive and prognostic value of the expression of different membranous EpCAM variants are clearly warranted in epithelial cancers.
Conflict of interest: *Advisory board: Gilbert Spizzo served as consultant and advisory board member for Fresenius Biotech*

648 POSTER

Establishment of a diagnostic system using next generation sequencing for RET rearrangements in non-small cell lung cancer

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Background: Recent advances of molecular-targeted treatment have revealed drastic effects in appropriate genetically defined patient populations. In addition to *EGFR* mutations and *ALK* rearrangements, *RET* rearrangements were recently identified as a novel driver mutation in approximately 2% of non-small cell lung cancers (NSCLCs). Although exact selection of the beneficial population is needed, rapid and efficient diagnostic methods for detecting *RET* rearrangements are not established yet.
Material and Methods: A target enrichment system (SureSelect ®, Agilent) capturing selected 133 cancer-related genes, including *RET, ALK, ROS1* and genomic regions of genes expected to be fused with them, were performed with genomic DNA extracted from LC2/ad, a lung adenocarcinoma cell line with a *RET* rearrangement, and formalin-fixed paraffin-embedded specimens of its xenograft in mice. The captured DNA was sequenced using the MiSeq System ®, Illumina, and gene alterations were detected by a customized algorithm. Clinically resected 43 NSCLC specimens including ones with *RET, ALK* or *ROS1* rearrangements were also analyzed. Confirmed whole exon sequencing data of 29 samples among them were used for further evaluation of the concordance of mutation detection.
Results: At least 50 ng of genomic DNA of each sample was sequenced at an average coverage of 420 x. The concordance rate for detection of single nucleotide variants with another analysis was 97%. RT-PCR- and/or FISH-confirmed 4 cases of *RET*, 5 cases of *ALK* and 5 cases of *ROS1* rearrangements were precisely detected and different break points of each cases were identified.
Conclusions: This novel molecular diagnostics has potential utility for detecting *RET* rearrangements with limited amounts of NSCLC samples.
No conflict of interest.

649 POSTER

Clinical feasibility study of a novel sorting system for detecting PIK3CA mutations from captured circulating tumor cells in patients with breast cancer

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Background: Circulating tumor cells (CTCs) are cells that originate from a primary solid tumor and are found transiting the circulatory system. CTCs are expected to provide useful clinical information on biology of their primary, as 'liquid biopsy.' We have developed a novel cell-sorting system equipped with a disposable microfluidic chip (On-chip Sort, On-Chip Biotechnologies, Tokyo, JAPAN). At AACR 2013, we previously reported about its CTC enumeration capability when performed in a clinical setting. Currently, On-chip Sort enables recovery of more CTCs than conventional cell sorting systems for further characterization.

PIK3CA encoding the p110α catalytic subunit of the PI3K protein is the oncogene showing the highest frequency of gain-of-function mutations in breast cancer (approximately 20%). Therapeutics that target key nodes in the PI3K signaling pathway are currently being developed, and stratifying patients based on their PIK3CA mutation status is becoming more important. Detecting the PIK3CA mutation status from CTCs is challenging, although there is a need to detect them non-invasively.
Material and Methods: In a preclinical study, a BT-20 human breast cancer cell harboring PIK3CA mutation (H1047R) was spiked into the blood from healthy donors. After samples were negatively enriched using anti-CD45-coated magnetic beads, the spiked cancer cells in the samples were captured by On-chip Sort. The captured tumor cells were subjected to mutation detection by ARMS/Scorpion PCR assay. A clinical feasibility study was then conducted in patients with breast cancer.
Results: On-chip Sort performed recovery of the spiked BT-20 cancer cells (50 cells in 4 ml of blood)in a preclinical experiment. Successively, we were able to detect the PIK3CA mutation from the captured cells. In a clinical feasibility study, 4 blood samples from breast cancer patients were collected regardless of the PIK3CA mutation status and were evaluated. All the samples were successful in capturing CTCs by On-chip Sort. ARMS/Scorpion PCR assay detected the PIK3CA mutation (H1047R) from one of the samples (25%).
Conclusions: The preclinical study and the results of the clinical feasibility study suggested the possibility of the On-chip Sort assay to detect PIK3CA mutations from peripheral blood of patients with breast cancer. Further investigation is going to be conducted to evaluate the correlation of PIKCA mutation in captured CTCs and primary lesions.
No conflict of interest.

650 POSTER

Molecular characterization of circulating tumor cells recovered from metastatic pancreatic cancer patients using ApoStream™, a new antibody-independent dielectrophoretic device

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Background: Pancreatic adenocarcinoma (PAC) remains the fourth most common cause of cancer-related mortality due to late diagnosis and limited treatment options. The available diagnostic tools and biomarkers for PAC fail at early detection and suffer from low sensitivity and specificity. Advances in the recovery and characterization of circulating tumor cells (CTCs) offer hope for the development of noninvasive techniques for earlier disease detection, monitoring response to therapy, and identification of druggable targets and biomarkers. While CTC enumeration provides prognostic information in patients with various cancer types, the biological characterization of CTCs may offer insight into the molecular determinants of disease progression and sensitivities or resistance to treatment regimens. Epithelial cell adhesion molecule (EpCAM) and cytokeratin (CK) dependent CTC technologies fare poorly in the metastatic PAC setting due to altered phenotypes acquired during epithelial mesenchymal transition (EMT). The links between EMT, KRAS, plectin-1, mesothelin and metastatic progression of PAC are emerging and underscore the need for biomarker information in real time.
Material and Methods: We used ApoStream™, a novel, antibody-independent device which uses dielectrophoretic technology in a continuous flow system to isolate CTCs from the blood of metastatic PAC patients and determine their phenotypic identities to elucidate population heterogeneity and characterize pancreatic specific markers (CA19-9, *KRAS*, plectin-1 and mesothelin). This prospective study will evaluate thirty patients. Paired blood samples from 10 metastatic PAC patients were analyzed by CellSearch® and ApoStream™. Collected cells were immunostained using antibodies against CK, CD45, DAPI, CA19-9, plectin-1 and mesothelin. A multiplexed immunofluorescent assay and laser scanning cytometry (LSC) analysis were applied to enumerate CTCs and identify cell phenotypes based on combinations of CK, CD45, plectin-1 and mesothelin marker expression.
Results: The detection of $CK^+/CD45^-/DAPI^+$ cells was comparable between CellSearch® and ApoStream™ with counts ranging from 1−10 CTCs/7.5 mL blood in 50% of patients. In addition, ApoStream™ recovered $CK^-/CD45^-/DAPI^+$ cells in 100% of patients with counts in the range of 12–166 cells/7.5 mL of blood. CA19-9^+ cells were identified in both $CK^+/CD45^-/DAPI^+$ and $CK^-/CD45^-/DAPI^+$ subpopulations isolated by ApoStream™. *KRAS*, plectin-1 and mesothelin analysis on CTCs will be presented.
Conclusions: ApoStream™ recovered classical and putative CTCs with multiple phenotypes in patients with metastatic PAC. Preliminary data is encouraging and if confirmed in a larger sample size of PAC patients, ApoStream™ combined with molecular characterization could prove to be a sensitive method for isolating and detecting biomarkers in CTCs of PAC patients.
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No conflict of interest.

651 POSTER

A phase II clinical trial of neoadjuvant therapy with zoledronic acid for operable breast cancer

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Background: The neoadjuvant use of bisphosphonates has been reported to increase rates of pathological response in patients with operable breast cancer. We conducted a study to determine whether treatment with zoledronic acid (ZOL) would improve outcomes in such patients when it was added to standard neoadjuvant chemotherapy (NAC).
Methods: From April 2010 to June 2012, 30 patients with stage IIA, IIB, IIIA, or IIIB, Her2-negative operable breast cancer were eligible for the study. Written informed consent was obtained from each patient before starting chemotherapy. The patients received NAC (4 cycles of CEF: intravenous epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2, and fluorouracil 500 mg/m^2 on day 1, then 12 cycles of weekly paclitaxel 80 mg/m^2) with ZOL. The ZOL was administered immediately after each cycle of NAC in a 4-mg dose by intravenous infusion every 3 to 4 weeks. The primary end point of the study was pathological response (pPR, rate of grade 2−3 by the Japan Breast Cancer Society Criteria) rate. The secondary end points were pathological complete response (pCR) rate, breast conservation (BC) rate, axillar lymph node complete response (ALNC) rate, adverse effects and the changes in the numbers of disseminated tumour cells (DTC), circulating tumour cells (CTC), and circulating endothelial cells (CEC). We evaluated the efficacy and safety of ZOL in the NAC in operable breast cancer patients by use of Fisher's exact test.
Result: 29 patients (luminal A: 20 patients, triple negative: 9 patients) completed surgery after NAC, and pathological analyses and the numbers of CTC and CEC were assessed. Two patients had progressive disease during NAC, with brain metastasis and bone metastasis, respectively. The pPR rate, pCR rate (triple negative: 3 patients), BC rate and ALNC rate was 31.0%, 10.4%, 27.6%, and 31.0%, respectively. CTC were detected in 3 patients at baseline, and CTC had changed to positive in one patient in D15 of the first cycle, then after NAC, all four patients changed to negative. CTC were negative in two patients at baseline, but after NAC, changed to positive. There were no factors associated with the change rates of CTC. CEC after NAC increased from baseline significantly.($p < 0.001$) The increase rates of CEC were not significantly different among permenopausal and postmenopausal, PR and non-PR, and luminal and triple negative patients. Adverse events (AE) associated with ZOL included fever in 13.3%, fatigue in 3.3%, hyponatremia in 6.7%, and increased creatinine in 3.3%, there were no severe AE to discontinue treatment.
Conclusion: These data suggested ZOL in combination with NAC might not have a significant direct anti-tumour effect. Change of CEC would be a biomarker for neoadjuvant chemotherapy, but further analyses would be necessary. We will add the report about DTC on the meeting.
No conflict of interest.

652 POSTER

RAC1b mRNA expression and prognosis in advanced non-small cell lung cancer treated with first-line chemotherapy

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Introduction: Chemotherapy is the standard treatment for advanced non-small cell lung cancer (NSCLC) patients, except for those harboring EGFR mutations or EML4-ALK rearrangements. RAC1b, a RAC1 spliced variant, is over-expressed in NSCLC and impairs apoptosis by activation of nuclear-factor-kB. We evaluated the role of mRNA RAC1/RAC1b ratio as a predictor of chemotherapy efficacy in advanced NSCLC.
Methods: The expression of RAC1 and RAC1b was examined by real time reverse transcription quantitative PCR (RT-qPCR) from 104 NSCLC patients treated with platinum-doublets. We used RAC1/RAC1b ratio

(rRAC1b) to capture the RNA splicing RAC1b variant and its correlation with RAC1 expression in each patient. The mutations of *EGFR* (exons 19 and 21), *KRAS* and *BRAF* were determined using standard PCR protocols.
Results: Patient demographics: Median age 62 (range 40−81), histology − adenocarcinoma (AD) and large cell (LC) (60%), squamous cell (SCC) (40%).
Mutations in *KRAS, BRAF* and *EGFR* were found in AD and LC (17/62) and in SCC (6/42) p = 0.22.
Median rRAC1b was 0.892 (range 0.8–0.953). We found a significant association with histology and rRAC1b, but no association between age, gender, mutational status and rRAC1b. Median rRAC1b was higher in AD and LC (0.901) vs SCC (0.879) (p = 0.002). When analyzed by tertiles, we found significantly poor median survival in SCC patients with higher rRAC1b (high-4.9 months vs intermediate-10 months vs low-18.3 months) (p = 0.014), but not in AD and LC subtypes. The multivariate regression analysis identified high rRAC1b as a poor prognostic marker for PFS (p = 0.027); HR: 3.3 (95% CI 1.14−9.4) and OS (p = 0.007); HR: 6.059 (CI 1.6–22.3) in SCC.
Conclusions: High rRAC1b constitutes a marker of poor PFS and OS in SCC of the lung treated with first-line chemotherapy.
No conflict of interest.

653 POSTER

Thymidylate synthase (TS) polymorphisms (Pol) in genomic DNA as a clinical outcome predictor in patients (pts) with advanced non-small cell lung cancer (NSCLC) receiving pemetrexed (Pem)

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Background: TS is the main biological target of the antifolate Pem. Some TS Pol may confer a short survival and a poor response to antifolate-treated colorectal cancer pts. Whether TS genotype has an independent prognostic/predictive impact on non-Asian advanced NSCLC pts treated with Pem is still to be determined.
Methods: Twenty-five advanced NSCLC pts treated with Pem-based regimens (1st, 2nd or 3rd line) were included. Genomic DNA was isolated from peripheral blood prior to treatment. The variable number of tandem repeat (VNTR) Pol, the G>C single nucleotide Pol (SNP) and the TS 6-bp insertion/deletion (6/6) in the 3' untranslated region (UTR) Pol were analyzed and correlated with response rate (RR), progression-free survival (PFS), overall-survival (OS) and toxicity (Tx).
Results: Regarding the VNTR Pol, most of the pts showed 2R/2R or 3R/2R Pol (17 pts; 68%), and 8 pts (32%) showed 3R/3R or 3R/4R Pol. A SNP (G>C) in VNTR was observed in 18 pts (72%). The Pol found in the 3′UTR region were +6/+6 in 12 pts (48%), +6/-6 in 11 pts (44%) and −6/-6 in 2 pts (8%). In the subgroup of T3-T4 pts, there was a significantly higher RR among those showing 3R/3R Pol than those with 2R/2R Pol (100% vs 83.8%; p = 0.029). The genotype +6/+6 predicted a higher RR among active/former smokers (A/FS) compared to +6/-6 (100% vs 37.5%; p = 0.026). A 3R/3R Pol followed by 2R/2R and 2R/3R Pol predicted a superior RR in pts without EGFR mutations (p = 0.018). Overall, a trend towards a better PFS in pts showing 2R/2R Pol was found (p = 0.076). The cohort's median overall survival (OS) was not reached during follow-up. The most frequent Tx was grade (G)1 anemia (28%) and nausea (20%) and G2 leucopenia (40%). G3−4 anemia (4%), leucopenia (16%), neutropenia (4%), astenia (8%) and dyspnea (4%) were uncommon but more frequent in pts with 2R/2R Pol (p = 0.545).
Conclusions: In this cohort of NSCLC pts 3R/3R Pol among T3-T4 pts and unmutated EGFR pts, and +6/+6 bp among A/FS pts significantly predicted a higher RR to Pem and may aid in treatment selection. Tx was not significantly correlated with a specific TS genotype. These interesting preliminary data warrant further validation in larger prospective series.
No conflict of interest.

654 POSTER

Sensitivity to glutamine deprivation is dependent on the interplay between epigenetic regulation of Glutamine synthetase (Glul) and induction of autophagy

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Background: We identified Glutamine synthetase (Glul), key enzyme in the biosynthesis of glutamine, as subject to methylation-dependent transcriptional silencing in breast cancer cell lines and therefore as a potential target for synthetic lethality strategies. We determined the functional relevance of modulating Glul levels in breast cancer. As autophagy is a protective response to conditions of nutrient deprivation, we investigated whether glutamine deprivation was initially inducing an autophagic response in breast cancer cells.
Methods: The promoter region of Glul was analysed using methylation microarrays (Illumina 450K Methylation BeadChip), bisulphite sequencing and pyrosequencing. This was correlated with expression using qRT-PCR and Western Blot. Sensitivity to glutamine deprivation and autophagy induction was assessed using fluorescence and MTT assay respectively after culturing cells in media without glutamine and chloroquine administration. Formalin-fixed paraffin-embedded tissue from a series of 115 stage I−III primary breast cancers with linked clinical outcome data were randomly selected from the Cuneo Tissue Bank for analysis of GLUL promoter methylation and immunohistochemistry.
Results: Dense methylation of the CpG-island of Glul was detected in 46% of cell lines across all subtypes and linked with expression of Glul. We defined three subsets of cell lines; unmethylated cell lines, methylated with non-expressing (sensitive to deprivation) and methylated with expressing Glul (resistant to deprivation). When Glul is completely silenced azacytidine and trichostatin treatment induced its up-regulation. All methylated cell lines reacted to glutamine deprivation inducing autophagy as early as 2 h after glutamine starvation. Chloroquine administration was sufficient to restore glutamine deprivation sensitivity in those methylated cell resistant to the treatment. Dense methylation (26%) of the CpG island of Glul was found in 30.4% of patients, with an additional 46.9% of patients showing partial methylation (6−26%).
Conclusions: This is the first report of methylation-dependent transcriptional silencing of Glul expression in cancer with an autophagic response. We are also the first to investigate the distribution of Glul methylation and protein levels in a series of patient samples.
No conflict of interest.

655 POSTER

Oncogenic microRNAs in sera reflect diagnosis and treatment of breast cancer patients

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Background: Breast cancer is the most frequent female cancer with very different outcomes. New approaches are needed in order to improve prognosis of breast cancer using routine blood testing. MicroRNAs are new class of small and stable molecules that are produced by tumor cells and are detectable in sera with remarkable stability. Aim of this project is to compare expression of microRNAs according to diagnosis and therapy of breast cancer and their differences in high-risk vs. low-risk breast cancer.
Materials and Methods: We prospectively collect sera from patients with histologically confirmed breast cancer from 2010 year. For analysis we choose 56 consecutive women, breast cancer clinical stage I to III. Negative prognostic factors were determined: triple negativity (N = 4), grade III (N = 12), Ki-67 over 15% (N = 13). High-risk group 25 patients, low-risk group 31 patients. Serum samples were collected 1-day before surgery, 14−28 days post-surgery, 14−28 day following either chemo- or radio-therapy, and during clinical relapse. We used sera from 21 healthy controls. For total RNA isolation 200 mL sera were used followed by specific reverse transcription and TaqMan qPCR on 7900HT instrument. Oncogenic microRNAs miR-19a, miR-155, miR-181b, miR-24 were normalized on level of miR-let7a. These microRNAs were reported to be involved in breast cancer pathogenesis (Zhang 2011, Sun 2012, Volinia 2006, Du 2013).
Results: The four oncogenic microRNAs are detectable in the patient sera and are significantly elevated compared to healthy controls. Trend to a decrease of the microRNAs between pre-operative and post-therapeutic samples was observed. MiR-19a was initially (sampling 1−2) elevated

(2−25 fold) in 30 (54%) patients. MiR-155 was elevated (2−29 fold) in 33 (59%) patients. MiR-181b was elevated (2−5 fold) in 23 (41%) patients. MiR-24 was elevated (2−18 fold) in 25 (45%) patients. In whole group 10 patients (18%) displayed elevation in all four oncogenic miRNAs. In high-risk group was detected elevation in all four miRNAs in 30% patients. And interestingly, in three relapsed patients oncogenic microRNAs were detected and their changes were significantly different. We compared subgroup with negative prognostic factors (triple negativity, grade III, Ki67) and displayed significantly increased expression in some microRNAs compared to low risk patients with significantly different changes after therapy.

Conclusions: The oncogenic microRNAs appear to reflect breast cancer growth and therapy and are possibly useful for tumor monitoring. Results confirm their different expression and changes in high vs. low-risk breast cancer. Prognostic power will be known with longer follow-up. Detection of microRNAs is rapid and reproducible and can be useful for majority of breast cancer patients.

No conflict of interest.

656 POSTER

Steroid receptors in neuroendocrine tumors of the lung

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Background: Primary neuroendocrine tumours (NET) of the lungs include typical carcinoids (TCs), atypical carcinoids (ACs), large cell neuroendocrine carcinomas (LCNECs) and small cell lung cancer (SCLC). Knowledge about the biology and prognostic markers of NET of the lungs is scarce. It is well known that sex steroids contribute to cell proliferation in various human tissues but information about their expression as well as data on amplification or overexpression of *c-erbB-2* gene in NET of the lung is limited. Based on these data, we aimed at characterising the expression of steroid receptors and Her2 in a broad cohort of probes from NET of the lungs, correlate this with known neuroendocrine markers and evaluated their possible use as prognostic or eventually predictive markers.

Materials: A total of 192 tumour specimens of NET of the lungs were collected, which comprised 60 biopsies of SCLC, 58 of TC, 42 of AC and 32 of LCNEC. A tissue microarray was built. Analysis by immunohistochemistry for the following markers was performed: ERα, ERβ, AR, PR, TTF1, Synaptophysin, ChromograninA and Mib-1. HercepTest33 was used to determine Her2 positivity. Her-2 FISH positivity was evaluated based on HER-2/CEP17 ratio.

Results: Neuroendocrine markers were found to be diffusely expressed in all tumour subtypes as previously described. ERβ was found to be expressed in more than 60% of tumor probes in all tumour entities. Survival data were available from 126 patients. Based on ER expression, no survival differences were detected between tumour types, but a multivariate analysis on SCLC patients showed a survival benefit in the subgroup of male patients whose tumours expressed ERβ ($p = 0.008$) and all SCLC patients whose tumours expressed both ER and ChromograninA ($p = 0.02$).

Conclusions: Here we could demonstrate that ERβ expression is very frequent through all NET of the lungs. Its relevance as favourable prognostic marker for SCLC was found in male patients and in all patients expressing also ChromograninA. Our results suggest including ERβ as marker for a prospective analysis for SCLC and underline the challenges for differential diagnosis between these tumours and metastases of neuroendocrine tumours from other origin.

No conflict of interest.

657 POSTER

Comparison between HER2 extracellular domain in serum and HER2 overexpression in breast cancer tissue

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Background: Human epidermal growth factor receptor 2 (HER-2) is an important prognostic factor and an indicator for targeted therapies in HER-2 overexpressing breast cancer (BC). Immunohistochemistry (IHC), fluorescent in situ hybridization (FISH) and chromogenic in situ hybridization (CISH) are reliable ways to identify HER-2. Each technique requires access to tumor tissue and high-quality tissue samples. HER-2 extracellular domain (ECD) may be shed to the serum and be detected in patients with BC. The importance of serum ECD in BC is not yet determined. The first aim of this study was to explore the correlation between serum ECD and tissue HER-2 expression. The second aim was to compare ECD levels with clinical and pathological features in primary BC patients.

Materials and Methods: In this prospective study only patients with stage I−III BC were included. Serum ECD levels were measured by ADVIA Centaur automated assays before surgical resection of the tumor. Tissue HER-2 was detected by IHC and CISH test. Serum ECD >15ng/ml was considered to be positive.

Results: Eighty patients with breast tumors were included. Stage I−III BC was diagnosed in 64 patients, Ductal carcinoma in situ in 9 patients and benign tumors in 7 patients. HER-2 overexpression in tumor tissue was observed in 8 of 64 patients (16.4%). Mean value of serum ECD was 10.9 ng/ml (range: 6.7 to 21.5). Four (6.2%) of the 64 patients had preoperative ECD high levels and in 60 (93.8%) patients lower levels of ECD were found. No significant relationship was found between ECD levels and tissue HER2 overexpression. ECD was significantly higher in women aged >40 than in women aged <40. There was no significant relation between ECD and tumor size, stage, histological grade, lymph node involvement, estrogen (ER) and progesterone (PR) receptors.

Conclusion: The sensitivity of HER2 ECD for the diagnosis of HER2 overexpression in primary breast cancer is poor. No significant correlation was found between ECD levels and tissue HER2 expression, clinical and pathological characteristics of primary BC.

No conflict of interest.

658 POSTER

Serum cytokine/angiogenic factors (CAFs) and toxicity in BEP treated testicular germ cell tumor patients

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Background: BEP (bleomycin, etoposide, cisplatinum) is a standard treatment in patients with testicular germ cell tumors (TGCTs). Toxicity of this chemotherapy can affect treatment compliance and decrease quality of life of patients as well. Our endpoint was to find out correlation between toxicity and CAFs in patients with TGCT receiving standard BEP treatment.

Methods: We enrolled 50 patients with TGCTs treated by BEP chemotherapy. All patients received G-CSF support after chemotherapy (48 patients pegfilgrastim, 2 patients filgrastim). Fifty one plasma CAFs were analyzed before the 1st (50 patients) and before the 2nd cycle of chemotherapy (28 patients) using multiplex bead arrays. Toxicites of grade 2 and higher were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. We analysed toxicity, which occured in more than 5% of patient population. Toxicities were correlated to pretreatment and also postreatment values of CAFs. Spearman's correlation test was used to analyze the relationship between toxicity and CAFs. We considered $p < 0.05$ to be significant.

Results: Toxicities with frequency of more than 5% were neutropenia, nausea, anorexia, insomnia and singultus. Elevated pretreatment levels of MCP-3 significantly correlated with neutropenia ($p = 0.045$). Neutropenia had also positive correlation to postreatment values of SDF1-a ($p = 0.033$). Increased pretreatment levels of TGF-b1, TGF-b3, FGF correlated with nausea, elevated pretreatment values of MIP-1b, RANTES, MCP-1MCAF, MIP-1a, FGF, TGF, IL-4,IL-5, IL-7, IL-8, IL-13, IL-17, GM-CSF ($p < 0.05$) were associated with anorexia. We observed no correlations with postreatment CAFs and non-hematological toxicities.

Conclusions: We suppose, that CAFs can provide prognostic information of toxicity related to BEP beyond standard measurements and can be included in patogenesis of toxicity as well. For patients with TGCTs, the ability to receive full doses of chemotherapy could improve survival rates. This data should be considered in further studies evaluating CAFs levels as prognostic information and predictive to toxicity related to BEP in TGCTs patients. This work was supported by the Slovak Research and Development Agency under the contract No. APVV-0016−11.

No conflict of interest.

659 POSTER

Morphometric analysis of malignant epithelial structures for assessment of invasive breast cancer survival

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Introduction: Breast cancer is a heterogeneous disease and it is therefore essential to accurately prognosticate metastasis risk at primary diagnosis in order to avoid adverse effects in low risk patients who will not benefit from systemic cytotoxic therapy. As reliable prognostic risk-assessment parameters are still elusive, we set out to investigate the potential of the image analysis on the rare group of patients untreated with systemic therapy.
Methods: The group of primary operable breast node negative carcinoma was diagnosed in 1993 and treated with surgical therapy alone (natural course of disease), with the minimum follow-up of 12 years. Such group is particularly informative in a prognostic sense as systemic therapy is likely to modify outcome. High-risk group (distant metastasis occurrence within 3 years) and low-risk group (no metastasis during the entire follow up time of 12 years) were selected as extremes and tumour tissue sections stained with the anti-human cytokeratin monoclonal antibody AE1/AE3. Slides were scanned by use of the Nano-Zoomer Hamamatsu scanner and 68 RGB images at 50x magnification imported into Image J software, and subjected to textural, box-count and lacunarity analysis.
Results: Three of the eight morphometric parameters tested were significantly different between the groups: outline box dimension, textural contrast and entropy. The outline box dimension was higher ($p = 0.001$), while texture contrast ($p = 0.031$) and entropy ($p = 0.016$) were significantly lower in patients with high risk when compared with patients with low risk of distant metastasis occurrence.
Conclusion: On the basis of these pilot data we propose that morphometric analysis may have a potential for clinical deployment as a prognosticator in invasive breast cancer. The prognostic value of the above morphometric parameters within the entire patient group ($n = 85$) will be reported at the meeting.
No conflict of interest.

660 POSTER

Single nucleotide polymorphism (SNP) profile indicating increased risk of head and neck squamous cell carcinoma (HNSCC)

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Background: Known etiological external factors can only partially explain the incidence of (HNSCC). Individual genetic variations may lead to susceptibility to HNSCC and influence the clinical outcome. Single Nucleotide Polymorphism (SNP) are inherited genetic variations derived from a single nucleotide. This study attempts to establish a correlation between SNP profile and risk of HNSCC.
Material and Methods: Forty four candidate genes were selected based on our previous study and theoretical implications in the development of cancer. These genes were analyzed with respect to 46 known SNPs in 103 HNSCC patients and 113 healthy controls. The tissue used for DNA analysis in both groups was peripheral blood or biopsy material in some of the patients.
Results: Statistically significant differences ($p \leqslant 0.05$) in the frequency of SNP between patients and controls were found in seven separate genes; ABCA1, MTHFR, TNFa, ESR, FAS, IL12RB2, Casp8 and EGF. These genes are involved in processes pertaining to cell cycle control, DNA repair, metabolism, inflammation and immune response.
Conclusion: Our results indicate that a susceptibility to HNSCC may be associated with variations in SNP. Further investigation, not only with respect to risk of disease, but for putative implications for prevention measures, prognosis and response to treatment including side effects is warranted.
No conflict of interest.

661 POSTER

Are serum tryptase and c-kit expressing cells novel bio-markers or molecular pharmacological targets in colo-rectal cancer patients?

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Background: Experimental data suggest that mast cells (MCs) accumulate near tumour cells before angiogenesis onset and that they are required for primary tumour progression. Mast cells contain several classical proangiogenic factors, such as VEGF, FGF and, also, non classical proangiogenic factors, such as tryptase. Tryptase can stimulate angiogenesis binding protein activated receptor-2. MCs can release tryptase following c-Kit membrane activation. Here, we detect tryptase serum concentration in 71 colorectal cancer patients (CRC) before and after radical surgery resection and c-Kit expressing cells in primary tumour tissue to achieve their possible clinical-biological value.
Material and Methods: Patients with stage B and C CRC were selected according Astler&Coller classification. Samples of blood were taken from CRC patients 1 day before and after surgical resection. Venous blood was dispensed into a tube for serum (Becton Dickinson Hemogard Vacutainer Systems, Plymouth, UK). Serum blood samples were centrifuged at 1,500*g* for 10 minutes and then aliquoted and frozen at −80ºC. Tryptase levels were measured using the UniCAP Tryptase Fluoroenzymeimmunoassay (Pharmacia,Uppsala, Sweden). Moreover, primary tissue section were immunostained with a primary anti c-Kit antibody (A4502**;** Dako, Glostrup, Denmark) by mean of immunohistochemistry. Tissue sections were than evaluated by mean of an immage analysis system (Quantimet 500, Leika).
Results: Mean$\pm$s.d. tryptase level was 6.57$\pm$4.51 μg/L and 4.92$\pm$3.71 μg/L pre and post-tumour surgical resection, respectively. A statistically significant difference between pre and post-tumour surgical resection tryptase level concentrations was found ($p = 0.000$) by student t-test. A significance association between pre-tumour surgical tryptase level and mast cell expressing c-Kit cells was, also, observed ($r = 0.82$, $p = 0.000$). There wasn't association among tryptase levels, c-Kit expressing cells and pricipal clinical-pathological features.
Conclusions: Our results showed higher serum tryptase levels CRC patients before surgical treatment, demonstrating that tryptase can be released from c-Kit positive cells infiltrating primary CRC tissue. Conversely, tryptase levels decreased after surgery. We suggest that tryptase may play a role as a novel bio-marker in CRC patients. Based on these evidences, we hypothesize that available c-Kit inhibitors may play a role targeting stromal tumour MCs. Finally, tryptase inhibitors, such as gabexate and nafamostat mesilate, might be evaluated in future clinical trials as a new anti-angiogenetic approach.
No conflict of interest.

662 POSTER

Cell line microarrays for immunohistochemical assay validation: Reliable controls for the evaluation of EGF receptors and pathway molecules

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Background: Immunohistochemistry (IHC) is a strong tool to analyse the distribution and expression of biomarkers in diseased or healthy tissues. Therefore, IHC has to be valid in terms of target specificity and reproducibility. An accurate validation of antibodies is normally done by Immunoblotting, ELISA and IHC. For all validation approaches appropriate positive and negative controls are necessary, which are often not easily available.
Material and Methods: Indivumed developed cell line control slides comprising positive and negative controls for the validation of IHC assays, using secondary cell lines. All cell lines have been selected for their predicted expression or absence of target proteins and were evaluated by immunoblotting, Mesoscale Discovery Technique (MSD) and NanoPro assays. Subsequent to the confirmation of the specificity of applied antibodies and confirmation the predicted expression of target proteins in selected cell lines, formalin-fixed paraffin embedded (FFPE) cell lines were validated in IHC. The validation was performed in terms of presence and absence of positive staining results as well as the staining patter of positive

controls, which should be in accordance to the predicted subcellular distribution.
Results: The control slide panel includes controls for the detection of EGF receptors family (EGFR, HER2, HER3) as well as their activated phosphorylated forms (pEGFR, pHER2, pHER3). Furthermore, pathway molecules as well as their related phospho-proteins are included in this panel (Akt/pAkt, MAPK/pMAPK, mTOR/pmTOR, pMEK, p70s6K, pGSK3β).
Conclusion: Since IHC assays are crucial diagnostic tools their reproducibility and specificity need to fulfil highest standards. To ensure the reproducibility and specificity of IHC assay Indivumed's control slides can be applied as run controls in routine diagnostics. On-slide controls become more and more required for therapeutically relevant diagnostics. To ensure the identical analytical conditions for controls and samples of interest, tissue slices can be mounted on Indivumed's controls slides (On-slide control). In case of anti-EGFR and anti-HER2 IHC, which is used to determine the applicability of targeted drugs in cancer therapies, Indivumed's EGFR and HER2 control slides can be used as on-slide control. In addition to assay validation in routine diagnostic cell line control slides are valuable for a specificity testing of antibodies in research applications.
No conflict of interest.

663 POSTER

CHK2 expression as predictor factor for tumor aggressiveness and shorter survival in metastatic colon cancer patients

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Background: The DNA checkpoint pathway damages have been explored to better understand the process of carcinogenesis. Checkpoint kinase 2 (CHK2) activity increased following DNA damage induced by ionizing radiation, chemotherapeutic agents, or other compounds that harm DNA directly or indirectly. Reduced expression of CHK2 and activated CHK2 could be an important inactivating mechanism contributing to the development of colorectal neoplasm. However, during progression of neoplasia, activated CHK2 could contribute to the invasiveness of tumor. The purpose of this study was to evaluate CHK2 expression in metastatic colon cancer and correlate this with K-RAS status, clinicopathological features and patient survival.
Material and Methods: Tissues were obtained from 58 patients with confirmed metastatic colon cancer diagnosis, treated with capecitabine and oxaliplatin chemotherapy as standard doses. Patients included had, at least, 2 years post diagnosis of clinical following. K-RAS status was analyzed by RT-PCR and TMA immunohistochemistry was the technic used to detect CHK2 expression. Statistics analysis used SPSS 17 software and p-value <0.05 was considered statistically significant.
Results: CHK2 was positive in 69% samples and mutate K-RAS was found in 48.3% patients. There was association between expression of CHK2 and lymph node status, being more frequent in higher categories of lymph node involvement, p = 0.001. The overall survival of CHK2 negative patients was higher (72.17 versus 59.55 months, p = 0.155) and the same was observed with progression-free survival (19.27 versus 13.33 months, p = 0.293). The survival curves were different according to CHK2 expression in patients with or without lymph node involvement, being lower in patients with CHK2 positive, p = 0.028. Patients with K-RAS wild type and CHK2 positive had lower overall survival than those CHK2 negative, p = 0.031. Multivariate regression analysis identified performance status (p = 0.001), synchronous metastasis (p = 0.037), tumor cell differentiation (p = 0.029) and expression of CHK2 (p = 0.020) as independent factors to overall survival.
Conclusions: CHK2 positive expression in colon cancer was associated with tumor aggressiveness, reduced overall survival and progression free survival. Further studies with CHK2 expression could detail the activity of this pathway in colon carcinogenesis, and its possible application as a biomarker in clinical practice.
No conflict of interest.

664 POSTER

USP2 promotes cell migration and invasion through the regulation of MMP2 in triple negative breast cancer

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Background: Triple negative breast cancer (TNBC), accounts for approximately 12−15% of all breast cancers, frequently have the worse prognosis among breast cancer subtypes. However, not all TNBCs exhibit dismal survival rates, there are still some TNBCs with long disease free survival. The aim of this study was to find out which genes contribute to the different prognosis.
Material and Methods: Ten breast tissue samples of TNBC, including 4 with metastasis and 6 without metastasis in two years after surgery, were obtained during surgery and subjected to Affymetrix gene chip (human genome U133). We found the ubiquitin-specific protease 2(USP2) was one of the up-regulated genes in the metastatic group, and it is also up-regulated in LM2–4175, a aggressive MDA-MB-231 subpopulation, than other TNBC cell lines. We built the USP2 knock-down cell model on LM2–4175 to figure its role in migration and invasion by transwell assay. Protein expression was analyzed by Western Blot. USP2 protein in tissue was detected by immunohistochemistry in a formalin-fixed paraffin-embedded human breast sample.
Results: Knocking-down USP2 expression by siRNA decreased migration and invasion in LM2–4175. The level of matrix metalloproteinase-2 (MMP-2) was also found downregulated simultaneously. On the other hand, transfect USP2 into MDA-MB-468 enhanced migration and invasion, and also increased the expression of MMP2. In 107 human breast tumors, cytoplasmic positive immunostaining was detected in tumor glands; whereas in normal breast epithelium, USP2 expression was negative. More importantly, USP2 was highly expressed in TNBC compared with other subtypes.
Conclusions: These findings suggest overexpression of USP2 enhances the migration and invasion by upregulating MMP-2 production in vitro. USP2 are expressed in tumor glands, especialy in TNBC, but not expressed in normal tissue. USP2 probably represents a therapeutic target in TNBC.
No conflict of interest.

665 POSTER

Drug sensitivity markers for approved kinase inhibitor drugs from cell panel profiling

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Background: Measuring drug responses in tumour cell line panels can help to identify molecular responder subtypes that predict drug sensitivity. This can then guide the design of further *in vivo* tests and clinical trials. Recently, the potential for finding responder subtypes has greatly increased with the determination of the genetic background of cell lines, and this has contributed to the development of many targeted therapies, including the kinase inhibitors (also known as TKIs).
Materials and Methods: We have established a panel of 44 genetically well-characterized cell lines, that originate from a diversity of tissues and which represent the most frequently occurring oncogenic drivers in cancer (www.ntrc.nl). The panel gives highly reproducible, high quality data, which facilitates prediction of responder cancer genotypes. We have profiled all clinically approved kinase inhibitor drugs, a set of experimental kinase inhibitors, and a representative set of classic chemotherapeutic agents. Using high throughput proliferation assays, we determined in parallel the inhibitory response for all drugs on all 44 cell lines of our panel. The data were linked to the genetic background of the cells by Anova analysis.
Results: Responses in our cell line panel confirm known associations. For instance, the B-RAF inhibitor vemurafenib is most potent on cells that carry B-RAF mutation. For clinically approved kinase inhibitors that have a more broad biochemical selectivity panel (so-called spectrum selective inhibitors), it was found that no single genetic change was predictive for response. Instead, more complex subsets of mutations correlated with drug sensitivity.
Conclusions: We have tested all approved kinase inhibitor drugs on our panel of 44 well-characterized cancer cell lines. The resulting response patterns generate hypotheses about responder populations for these modern precision drugs that could eventually lead to extended applications in newly defined patient populations. As a next step, we will systematically investigate the efficacy of combinations of kinase inhibitors and classic chemotherapeutic agents.
Conflict of interest: *Other substantive relationships: employees of the Netherlands Translational Research Center B.V.*

666 POSTER

Analysis of arrayCGH data suggests that chromosomal copy number variation is increased in aggressive cancers when compared to less aggressive cancers

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Background: Array-comparative genomic hybridization (arrayCGH) technology is frequently used in cancer to identify chromosomal abnormalities.

The aim of our study is to identify if there is a correlation between an increase in the number of chromosomal abnormalities and the more aggressive phenotype associated with some cancers.
Materials and Methods: Using Gene Expression Omnibus data repository (http://www.ncbi.nlm.nih.gov/geo) we downloaded the cancer data generated using the Agilent-014693 Human Genome CGH Microarray 244A platform, the most commonly used arrayCGH platform. These data comprised over 550 samples across 10 distinct cancer types (prostate, melanoma, ovarian, lung, colon, mesothelioma, cervical squamous cell carcinomas, glioblastoma, breast and chronic lymphocytic leukemia (CLL)). In addition the breast cancer data was divided into hormone positive; HER2 (Human Epidermal Growth Factor Receptor 2) amplified and triple negative samples. The Bioconductor package snapCGH in conjunction with limma was used to identify insertions or deletions across the entire genome in each sample. The average per chromosome alteration was then compared across the different cancers. The more or less aggressive cancers were those cancers with greater than or less than 50% 5 year survival rates respectively, based on 5 year survival data from Cancer Research UK.
Results: The frequency of chromosomal alterations was identified in each of 10 cancers studied, including the three breast cancer subtypes. The more aggressive cancers (ovarian, lung, mesthelioma, glioblastoma and colon,) on average had higher levels of chromosomal alterations that less aggressive cancers (breast, prostate, cervical squamous cell carcinoma, CLL and melanoma). For example, there are a significant number of chromosomal alterations in ovarian versus breast cancer (p-value = 0006) and lung versus prostate cancer (p-value = 4.8e-07). Indeed, a difference was noted between the breast cancer subtypes, where the more aggressive triple negative subtype has a higher frequency of chromosomal alterations in comparison to the more benign hormone positive tumours (p-value = 0.001).
Conclusions: From this analysis it would appear that more aggressive cancers have a higher number of chromosomal abnormalities. Although the reasons for some cancers being more aggressive are not well defined, the increased number of chromosomal abnormalities could potentially contribute to their more aggressive phenotype.
No conflict of interest.

667 POSTER

Phase I/II clinical trial using A24- or A02-restricted cancer/testis antigen- and/or VEGFR1/2-derived peptide-vaccine cocktails for various types of cancers

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Background: We have investigated safety and efficacy of A24- or A02-restricted cancer epitope- or VEGFR1/2-derived peptide vaccines against various human cancers in this phase I/II clinical trial (UMIN000002857).
Method: A2402-restricted cancer/testis antigen-derived peptides, URCL10, KOC1, TTK, which are highly expressed among lung, esophageal and pharyngeal cancers, A0201-restricted cancer/testis antigen-derived peptides, URCL10, and A2402-restricted or A0201-restricted VEGFR1/2-derived peptides, were used for this clinical trial. HLA-matched peptide-vaccine cocktails, each mixed with montanide as a vaccine adjuvant, were prepared by URLC10 (A24/A02), KOC1 (A24), TTK (A24), VEGFR1/2 (A24/A02) for lung, esophageal or pharyngeal cancer patients, or by VEGFR1/2 (A24/A02) for gastric, pancreatic, biliary-tract, or colorectal cancer patients. Each patient had refractory disease after standard treatments, and had given written informed consent for this clinical trial. Vaccination had been conducted weekly for each patient before PD. Primary endpoint is RECIST evaluation, and secondary endpoints are safety (adverse events), Overall survival, Responsive rate, TTF, Immunological responses by peptide vaccination (CTL response) examined by Elispot assay.
Results: Sixty-eight patients were enrolled in this trial. Among them, 8 patients were excluded before vaccination and 60 patients had undertaken vaccination by peptide cocktail described above with average of 7.7 times. Thirty-three patients reached to RECIST evaluation after 8 vaccinations, and 19 patients were diagnosed SD, while 13 were PD. Grade-3 adverse events were observed in 5 patients and all of them were thought to be a possible outcome of disease progression. Median overall survival was 143.0 days. Exploratory studies showed that patients with positive CTL from more than 2 peptides had prolonged survival (hazard ration 0.407, from 0.224 to 0.740 in 95% CI).
Conclusions: Peptide-vaccine cocktail is feasible for patients with refractory diseases after standard therapy in various cancers. Patients with positive CTL responses from multiple peptides can be beneficial from peptide cocktail examined in this trial. Results obtained in this trial encouraged us to move to later phase of clinical studies by multiple peptide cocktails.
No conflict of interest.

668 POSTER

Immunological biomarkers as surrogates for clinical response for dendritic cells vaccine therapy for non-small cell lung cancer and renal cell carcinoma

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Background: Immunological biomarkers have the potential to predict clinical outcome after cancer vaccine therapy. However, at present no single parameter is likely to achieve any significant degree of use. The aim of our study was to determine phenotypical and functional characteristics of T cells and evaluate dendritic cell (DC) vaccine-induced immune responses which are associated with clinical benefit.
Material and Methods: The study was conducted within the framework of two randomized clinical trials of DC-vaccine efficacy in 120 patients with IIB−IIIA stage of non-small cell lung cancer (NSCLC) and in 16 patients with IV stage of renal cell carcinoma (RCC). NSCLC patients were randomly assigned to receive surgery (S) plus DC-vaccine or S only; RCC patients − to receive S plus IFN-a and DC-vaccine or S plus IFN-a. The original construction of DC-vaccine (DC loaded with mechanical activated lyophilized microparticles of tumor cells) was used. Patients received one-two courses (4−5 intravenous injections per course) of DC-vaccine with 6 month interval in adjuvant setting. Patients were monitored for immune function measures before and 1 month after each DC-vaccine administration.
Results: Median DFS for NSCLC patients was 25 vs 6 months in DC-vaccine and control groups respectively ($p = 0.02$). Median OS for RCC patients was 18.4 months in DC-vaccine group in comparison with 13 months in control group. At 24 months, signs of disease progression were noted in 10 vs 25% of NSCLC patients (HR = 2.6; 95% CI: 0.60–7.93; $p = 0.009$) and in 33% vs 43% of RCC patients ($p = 0.21$) in DC-vaccine vs control groups respectively. The most pronounced changes in the immune system have been defined only after fourth DC-vaccine injection. In disease free groups of patients these changes consist in the significant reduction of T-reg number and their ability to secrete TGF-β, significant increasing the $CD8^+IFN^+$ number, Th1-polarization of immune responses, significant increasing of the RANTES/MIP-1α mRNA ratio ($p < 0.001$). A significant increase of T-regs number, mRNA TGF-β level, MIP-1a/RANTES ratio was associated with therapy failure. Significant increase of the $CD4^+$ memory cell number after 2nd course DC-vaccine (10 administrations) was observed.
Conclusions: T-regs and $CD8^+IFN^+$ number, level of mRNA TGF-β, MIP-1a/RANTES mRNA ratio are the most important immunological biomarkers which associated with clinical outcome after DC-vaccine therapy in NSCLC and RCC patients.
No conflict of interest.

669 POSTER

Oncolytic vaccinia virus combined with standard TNF/Melphalan chemotherapy delays tumour growth and prolongs survival in a rat sarcoma isolated limb perfusion model

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Background: Isolated Limb Perfusion (ILP) is an established surgical technique for the treatment of locally advanced extremity melanoma and sarcoma. Oncolytic virotherapy is a promising novel cancer therapy that has been limited by its inability to reach tumour cells in sufficient titres. Extending ILP methodology to include administration of cancer-selective oncolytic viruses allows for targeted, direct delivery of virus to cancer cells, increasing viral uptake through TNFα mediated disruption of the tumour vasculature and initially evading both immune and reticuloendothelial clearance. This represents an exciting approach to improving both oncolytic viral delivery and the therapeutic efficacy of ILP. In addition, it raises the possibility of using a locoregional therapy to prime a systemic anti-tumour immune response.
Methods: Single agent and combinatorial activities of melphalan, tumour necrosis factor-alpha (TNF-α) and oncolytic vaccinia virus (GLV-1 h68) were assessed *in vitro* against a range of melanoma and sarcoma cell lines.
Then, a reliable model of hyperthermic, oxygentated lower limb perfusion was developed in a Brown Norway rodent. Next an orthotopic model of advanced lower limb extremity sarcoma was constructed using a syngenic sarcoma cell line (BN175). These models were then amalgamated to test

treatment efficacy of single agent and combination therapy with TNFα, Melphalan and the oncolytic vaccinia virus (GLV-1 h68) in vivo. Furthermore the locoregional and systemic biodistribution of GLV-1 h68 after delivery by ILP alone and in combination with TNFα and melphalan was evaluated using viral plaque assays and quantitative PCR.
Results: The combination of melphalan and GLV-1 h68 was synergistic *in vitro* when assessed using the median-dose effect principle of Chou and Talalay. ILP with virus was well tolerated with no increase in side effects compared to standard ILP therapeutics. In an advanced disease model, the triple therapy significantly delayed tumour growth and enhanced survival when compared to other treatment regimens ($p = 0.0001$) (Table 1). Live vaccinia virus was recoverable at high titres from perfused regions, but at lower levels from distant organs.
Conclusions: The addition of GLV-1 h68 to existing TNFα/melphalan-based ILP strategies increased survival in an immunocompetent rat model of advanced extremity sarcoma. Further evaluation and clinical translation of this model has been granted ethical approval and will be evaluated in a Phase I study. This will be conducted in the pre-existing surgical ILP programme at The Royal Marsden Hospital.

Table 1. Median survival (n = 8 per group) post treatment with ILP.

ILP Treatment Group	Median survival post engraft (days)
Control	11
Melphalan only	14
Vaccinia Virus only	15
TNF/Vaccinia Virus	16
TNF/Melphalan	16
Melphalan/Vaccinia Virus	19
TNF/Melphalan/Vaccinia Virus	24

Conflict of interest: *Ownership: Aladar A Szalay is President, CEO and a shareholder of GeneLux corporation. Yong A Yu is an employee and shareholder of Genelux Corporation. Corporate-sponsored research: Kevin Harrington receives funding from GeneLux Corporation in support of laboratory research.*

670 POSTER

Peptide-mediated siRNA delivery: Chronic myeloid leukemia therapy targeting the BCR/ABL fusion gene

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Background: Chronic Myeloid Leukemia (CML), a myeloproliferative disorder caused by a single genetic mutation, that originates the BCR-ABL gene with constitutive tyrosine kinase activity, is an excelent pathology for RNA silencing therapy (siRNA), which has been pointed as a promising therapy technology. We developed a siRNA-based therapeutic approach in which the siRNA is delivered by Dengue Virus Capsid Protein-derived peptides against CML. Previous results showed that the Dengue Virus Capsid protein was a valid template to design Cell Penetrating Peptides (CPP) − pepR and pepM − as drug delivery systems of nucleic acids.
Objectives: To use siRNA molecules to target BCR-ABL gene expression and act as a therapeutic approach for CML. Design and synthesize siRNA molecules that target specifically the BCR-ABL fusion region were designed. To test effective siRNA delivery by both pepM and pepR in a BCR-ABL$^+$ cell line (Human B-cell precursor leukemia BV-173 cell line).
Methods: pepR and pepM ability to transfect siRNA we evaluated using an anti-TLR3 siRNA in Baby Hamster Kidney (BHK-21) cells, followed by expression levels quantification by RT-PCR. Positive BCR-ABL$^+$ Cell Line (BV-173) transfection was tested with a GFP encoded plasmid with pepR or pepM, and evaluated by confocal microscopy. Anti-BCR-ABL siRNA design was performed using a siRNA design web-tool using BCR-ABL mRNA sequence as template. The siRNA effect against BCR-ABL after transfection by pepM or pepR was evaluated by RT-PCR in BV-173 cell line in a time course from 48 h to 120 h after transfection.
Results: Both pepM and pepR are able to deliver functional siRNA into mammalian cells (BHK-21) and, positive GFP expression was observed in BV-173 cell line by confocal microcopy using both peptides. The design of the siRNA targeting the BCR-ABL fusion region retrieved 148 potential siRNA sequences, reduced to 10 BCR-ABL specific sequences after comparison with the *wt* BCR and ABL, being selected 5. Positive efficacy of siRNA transfection was tested using a commercial transfection agent. Significant decrease in expression levels of BCR-ABL gene was observed for siRNA #3 and #4 and mix #1−#5 (60 h after transfection). Successful BCR-ABL gene silencing was observed when delivered by pepM with maximum decrease at 120 h. PepR delivery was unsuccessful.
Conclusions: The design of the siRNA molecules was successful with significant decrease in BCR-ABL gene expression levels, which reveal a potential output for an alternative CML gene therapy.
No conflict of interest.

671 POSTER

Anticancer drugs effect on NK cell-mediated cytotoxicity via the regulation of NKG2D ligand expression in non-small-cell lung cancer cells

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Background: A nucleoside analog Gemcitabine inhibits DNA replication, resulting in apoptosis in cancer cells, while an EGFR-tyrosine kinase inhibitor Gefitinib interrupts signalling through the EGFR in cancer cells with EGFR driver mutation. Both Gemcitabine and Gefitinib have shown impressive activity in terms of clinical benefit for patients with non-small-cell lung cancer (NSCLC), however, almost all patients develop resistance to these drugs. Although much research is focusing on the mechanisms of drug resistance in tumor cell, the role of anticancer drugs in tumor escape from the host immune system is poorly understood. Here we demonstrate Gemcitabine enhances NK group 2 member D (NKG2D) ligand MHC class I-related chain A and B (MICA/B) and UL16 binding protein (ULBP), resulting in enhancement of NK cell-mediated cytotoxicity, while Gefitinib downregulates these molecules, resulting in attenuation of NK killing, in NSCLC cells.
Material and Methods: A possible influence of anticancer drugs (Gemcitabine and Gefitinib) on expressions of MICA/B and ULBP1−3 in non-small-cell lung cancer cell lines (A549, PC-9, and RERF-LC-AI) was investigated by flow cytometry. NK cell-mediated cytotoxicity against cancer cells was assessed by ^{51}Cr release assay and flow cytometry based CD107a degranulation assay.
Results: Treatment with Gemcitabine promoted MICA/B, ULBP1−3 in both A549 and RERF-LC-AI cells but not in PC-9 cells. Gemcitabine induced MICA/B expressions were blocked by ATM-ATR inhibitor caffeine in A549 cells. On the other hand, Gefitinib downregulated both MICA/B and ULBP2 in PC-9 cells, but did not in other lines. As expected, Gemcitabine enhanced NKG2D ligands induced NK cell-mediated cytotoxicity, and anti-NKG2D blocking antibody attenuated Gemcitabine induced NK killing in A549 cells. In contrast, Gefitinib attenuated NK killing in PC-9.
Conclusions: We conclude that each anticancer drug effects on NK cell-mediated cytotoxicity against tumor cells in different way via the regulation of NKG2D ligands expression.
No conflict of interest.

672 POSTER

Ex vivo activated autologous NK cells efficiently lyse tumor cells from metastatic colon carcinoma patients: A perspective for immunotherapeutic approaches

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Background: Over the last decade the development of new treatments for advanced disease improved survival of metastatic colorectal (mCRC) patients, but therapies are still associated with a poor prognosis and significant morbidity. Immune-based therapies could limit treatment related adverse effects, such as morbidity and/or mortality. The functional behavior of natural killer (NK) cells makes them appealing potential effectors for cancer immunotherapy, however in mCRC patients only anecdotal experiences have been reported so far.
In this study we evaluated the capacity of autologous NK cells, freshly or after cytokine activation, to lyse mCRC cells and the expression of ligands for adhesion and triggering NK receptors involved in CRC recognition and killing to clarify the mechanisms involved in tumor susceptibility or resistance to NK cells.
Methods: 23 mCRC patients who underwent surgery on tumor or metastases were enrolled so far. mCRC cells were isolated and expanded *in vitro* and, after evaluation of pathologic characteristics to confirm their

neoplastic origin, were analyzed for the expression of HLA class I and of ligands for NK triggering receptors. NK cells were purified and analyzed for the presence of receptors involved in NK-mediated cytotoxicity. The expression of NK receptors and levels of cytotoxic activity against patients mCRC cells were also evaluated after overnight (ON) activation of NK cells with IL-2 and IL-15.
Results: mCRC cells were successfully expanded from 20 out of 23 samples. Results of experiments performed in 10 patients documented a substantial inability of patients freshly NK cells to lyse mCRC cells (<5% lysis at E:T ratio of 20:1). ON cytokine activation results in an greatly increase of NK cytotoxicity in all patients evaluated (IL-2: mean 28%; range:10−71; IL-15: mean 40%; range 16−76 at E:T ratio of 20:1). NKp30 and NKp46 are highly expressed by patients NK cells and are further up-regulated after ON activation, while TC expressed variable levels of most NK ligands.
Conclusions: Further experiments are in progress to evaluate the effect of a more days activation on cytotoxic activity and on the up-regulation of NK receptors and the possibility to augment the susceptibility at lysis of mCRC cells.
Reported preliminary data on the ability of *ex vivo* activated autologous NK cells to lyse patients tumor cells can offer the possibility of designing immunotherapy approaches for mCRC patients with a worse prognosis.
No conflict of interest.

673 POSTER

microRNA-15b expressed in lung cancer-infiltrated CD8-positive memory T cell inhibit cell apoptosis by repressing DEDD

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Background: CD8+ T cells are key members of adaptive immunity against tumorigenesis. As subset of CD8+ T cells, effector T cells (Te) and memory T cells (Tm) have different biological activities. The former can kill tumour cells but come into apoptosis in a certain period and the latter is static with the ability of self-renewal. Previous studies showed that microRNAs (miRNA) played critical roles in regulating adaptive immunity. This study aimed to identify the different expression of miRNAs between Te and Tm cells in tumour-bearing mice and to sort out the target miRNAs which can be regulated to improve anti-tumour activities of CD8+ T cells.
Methods: miRNA expression profiling was performed on CD8+ Te and Tm cells from mice with Lewis lung carcinoma. Differentially expressed miRNAs were chosen and analysed by qRT-PCR. Then, flow cytometry, ELISA, and CFSE kit were used to evaluate the biological effects of target miRNA on apoptosis, cytokine secretion, phenotype, and proliferation of CD8+ T cell. The possible downstream target genes of this miRNA were also analysed.
Results: Analysis of miRNA microarray and qRT-PCR showed that the level of miRNA-15b was higher in CD8+ Tm cells than in Te cells. Higher expression of miRNA-15b was observed in CD8+ T cells from tumour-bearing mice than those from healthy ones. Transfection of CD8+ T cells with miRNA-15b mimics could prevent T cells from apoptosis by inhibiting the translation of DEDD (Death Effector Domain-containing DNA binding protein). Moreover, ectopic miRNA-15b could inhibit the activation of CD8+ T cells via repressing the production of IL-2 and IFN-γ and expression of CD69 and promote CD44 expression through unknown pathways.
Conclusion: Up-regulation of miRNA-15b in tumour environment might negatively regulate anti-tumour immunity through inhibiting function of CD8+ T cells. miRNA-15b might be a potential therapeutic target for immunotherapy.
No conflict of interest.

674 POSTER

A translational research program to evaluate the synergistic activity of CRLX101, a nanopharmaceutical in phase 2 clinical trials, with antiangiogenic therapies mediated through HIF-1 alpha inhibition

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Background: Antiangiogenic drugs reduce blood flow to tumors and thereby inhibit tumor growth by starving tumors of oxygen and nutrients. However, antiangiogenic drugs have achieved limited success as monotherapies, in part because of their induction of hypoxia and the concomitant up-regulation of hypoxia-inducible factor 1α (HIF-1α), now well implicated in the promotion of tumor angiogenesis, invasion, metastasis, and cancer stem cell formation. We describe here a translational research program to investigate whether the efficacy of antiangiogenic drugs can be improved through combination with CRLX101, a camptothecin (CPT) containing nanopharmaceutical that inhibits both topoisomerase-1 and HIF-1α.
Material and Methods: We will present preclinical and clinical projects conducted across several major research institutions intended to demonstrate the anti-HIF-1α activity of CRLX101, the capacity of this drug to block the epithelial–mesenchymal transition (EMT) and the formation of cancer stem cells, and the synergistic activity of CRLX101 given in combination with antiangiogenic drugs. We will further describe two ongoing clinical trials evaluating these hypotheses, one at the University of Pennsylvania in advanced renal cell carcinoma (RCC) and one at the Massachusetts General Hospital in relapsed ovarian cancer following progression through prior platinum-containing chemotherapy.
Results: A single dose of CRLX101 durably inhibits HIF-1α protein levels across multiple tumor types. Evaluation of CRLX101 in combination with bevacizumab, aflibercept or pazopanib in the A2780 ovarian xenograft tumor model demonstrates synergistic inhibition of tumor growth inhibition as well as increases in the rate of long-term survivorship. While all three antiangiogenic drugs alone increased HIF-1α protein levels, levels were inhibited in response to combination with CRLX101. In clinical evaluations, a CRLX101-bevacizumab combination appears safe and well tolerated with no dose limiting toxicities observed to date. Notable tumor decreases and long periods of progression free survival have been noted among patients treated with CRLX101-based mono and combination therapy.
Conclusions: Results generated through this translational research program suggest that CRLX101 can overcome HIF-1α-mediated acquired resistance to antiangiogenic drugs, supporting the use of CRLX101 in combination with antiangiogenic drugs as an exciting new paradigm for the treatment of cancer.
Conflict of interest: *Advisory board: Kerbel is scientific advisor for Cerulean Pharma. Corporate-sponsored research: Kerbel and Wicha have received Cerulean Pharma sponsorship for research, and Keefe and Krasner have received Cerulean Pharma sponsorship for clinical trials. Other substantive relationships: Garmey, Lazarus, Peters and Eliasof are shareholders in Cerulean Pharma*

675 POSTER

Context and tumor cell dependent consequences of autophagy inhibition revealed by targeting ATG4B

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Background: Autophagy is an adaptive cellular response to stress that plays an important role in resistance to cancer therapies. While being the most advanced autophagy inhibitor in clinical testing, hydroxychloroquine has pharmacodynamic and pharmacokinetic shortcomings that limit its use as an anticancer agent. Therefore, the development of more potent and more specific autophagy inhibitors is a very active area of research, and the cysteine protease ATG4B (also named autophagin-1) is a particularly interesting drug target in this respect. However, the role of ATG4B during cancer therapy is poorly documented.
Methods: By utilizing a dominant negative mutant of ATG4B (i.e., $ATG4B^{C74A}$), we derived syngeneic pairs of autophagy-deficient versus autophagy-competent PC-3 and C4−2 human prostate cancer cells. We analyzed the autophagic properties of these cells, and studied their behavior in proliferation and colony formation assays following chemotherapy and radiation therapy, respectively. Finally, we studied the in vivo growth properties of tumor xenografts and their response to doxorubicin chemotherapy.
Results: Autophagy inhibition due to $ATG4B^{C74A}$ expression was more pronounced in C4−2 cells compared to PC-3 despite similar expression levels of endogenous ATG4B and of $ATG4B^{C74A}$ in both cell lines. While ATG4B inhibition sensitized C4−2 to doxorubicin and radiation therapy in vitro, conversely $ATG4B^{C74A}$ expression promoted resistance to doxorubicin and radiation in PC-3. On the other hand, $ATG4B^{C74A}$ expression did not modulate the effects of docetaxel in PC-3 or C4−2. Of note, the diametrical response of $ATG4B^{C74A}$ expressing C4−2 versus PC-3 cells to doxorubicin observed in vitro did not predict the response of corresponding tumor xenografts. In a reversal of patterns $ATG4B^{C74A}$ expression promoted resistance of C4−2 tumors to doxorubicin, whereas PC-3 tumors were sensitized to doxorubicin by ATG4B inhibition.
Conclusions: Our findings position ATG4B as a valuable alternative treatment target to the use of hydroxychloroquine. However, the data also

add to a growing body of evidence that the clinical translation of autophagy inhibitor therapy will be challenging. The outcome of autophagy inhibition appears to be highly tumor, drug and context dependent. Our cell models are a promising tool to study the molecular mechanisms of such differential responses, and to ultimately identify predictive markers of response to ATG4B inhibition.
No conflict of interest.

676 POSTER

Study of different mutations in chronic myeloid leukemia in India and their co-relation with drug resistance

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Background: Emergence of ABL point mutations is the most frequent cause for imatinib resistance in CML. Aim of our study is to investigate two potential resistance mechanisms i.e., mutations of the BCR-ABL tyrosine kinase domain (TKD) and Additional chromosomal abnormalities (ACA), during TKI treatment in CML.
Materials and Methods: Karotyping and BCR-ABL TKD mutation screening are performed in 120 imatinib resistant CML patients who were on imatinib at the time of loss of hematologic response (HR), cyto-genetic(CyR) or molecular response (MR). Imatinib-Resistance Mutation Analysis (Qualitative) were detected by Nested RTPCR and Sanger's Sequencing. In 120 cases, 39 received escalated imatinib, 38 nilotinib and another 43 dasatinib.
Results: In 120 BCR-ABL positive imatinib, nilotinib and dasatinib resistant cases, 11 different BCR-ABL TKD mutations were detected. Analysis revealed no mutations in 49 cases, M351T 12 cases, G250E 14 cases, F317L 11 cases, M244V 8 cases, E255K 7 cases, V379I 4 cases, F359V 3 cases, H396R 3 cases, Y253F 3 cases, E355G 3 cases, T315I 3 cases. 11 novel mutations (F317L, G250E, M244V, Y253F, E255K, M351T, F359V, H396R, V379I, E355G, T315I) conferring imatinib resistance, 10 nilotinib-resistant mutation (M244V, F359V, T315I, E355G, G250E) and 8 dasatinib-resistant mutation (H396R, F317L, H396R, T315I, M351T) were seen in our patient population. T315I was found more frequently in patients on dasatinib than on imatinib therapy.
Conclusions: T315I which confers resistance to all TKIs was detected only in 3/120 patients who demonstrate loss of response in our population. As compared with other western studies, the incidence of T315I mutation was very low in our study. In addition analysis of mutation patterns at baseline may help in stratifying patients for treatment. For cases with TKI resistance, mutation and ACA screening may play a role in identifying patients with poorer prognosis. In our practice if nilotinib-resistant mutation was detected, dasatinib was preferred and if a dasatinib-resistant mutation was detected, nilotinib was preferred. We are planning for using bosutinib, panotinib and omacetaxine (SC route) in third line therapy in imatinib resistant different mutation positive chronic myeloid leukemia.
No conflict of interest.

677 POSTER

Protein phosphatase 2A reactivation by PME-1 depletion and multi-kinase inhibition: a novel combination therapy for glioblastoma

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Glioblastoma multiforme (GBM) is a devastating disease with negligible prognosis. Although deregulated kinase pathways have been identified as drivers of GBM progression, inhibition of receptor tyrosine kinases (RTK) or serine/threonine kinases (STK) has not been successful GBM therapy (Chen et al., Cell. 2012). Tumor suppressor protein phosphatase PP2A is the major negative regulator of STKs and oncogenic phospho-proteins, and is inhibited in many cancers. Several PP2A inhibitor proteins are known to be overexpressed in cancers (Westermarck et al., Trends Mol Med. 2008). PP2A inhibitor, protein phosphatase methylesterase 1 (PME-1) is shown to promote the proliferation and progression of glioblastoma in patient samples (Puustinen et al., Cancer Res. 2009). Here, we study the RNAi based PME-1 depletion as a potential PP2A reactivation strategy to induce synthetic lethality with kinase inhibitors in GBM.
Small scale screening of small molecule compound library targeting different parts of the human kinome, and further screening lead to the identification of a group of structurally related multi-kinase inhibitors with marked synthetic lethality in PME-1 depleted GBM cells. Many of these inhibitors are in clinical development for various cancer types. The efficacy of these compounds in combination with PME-1 siRNA is demonstrated in a series of GBM cell lines *in vitro,* including CD133-enriched GBM cells. The *in vivo* assessment of this therapy combination in tumor xenograft mouse model is in progress.
We propose the activation of specific PP2A complexes and, thereby, inhibition of oncogenic PP2A target phospho-proteins as a mechanism behind increased chemosensitivity of PME-1 depleted GBM cells. We have identified histone deacetylase HDAC4, as such a potential PME-1 regulated PP2A target. The siRNA based HDAC4 silencing phenocopies the synthetic lethal cell killing as seen in PME-1 depleted cells. Furthermore, the HDAC4 expression correlates with the PME-1 status as well as disease progression in human astrocytic glioma patient samples.
In summary, we have identified PME-1 or HDAC4 depletion and multi-kinase inhibitor combination as a potential new therapy for glioblastoma. These results may also have direct clinical implication in patient stratification for treatment with multi-kinase inhibitors currently in advanced phases of clinical trials. Generally these results emphasize the potential of concomitant inhibition of kinase signaling and reactivation of their antagonist protein phosphatases as a cancer therapy approach.
No conflict of interest.

678 POSTER

Potential functional implications of NSSR1 in endometrial carcinogenesis

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Introduction: NSSR1 (Neural salient serine/arginin rich protein) is a member of the serine/arginin rich protein family and acts as a repressor of alternative splicing processes. Initially NSSR1 expression was detected in neural tissues. Later, NSSR1 expression was found in tissues of reproductive systems, e.g. testes, uterus, epithelial endometrium and glands suggesting a potential functional role in regulation of gene expression in these organs. Overexpression was found as a characteristic of tumor cell lines. High NSSR1 expression levels distinguish malignant from physiological ovarian tissues. NSSR1 is one potential novel target gene that might play crucial roles in endometrial carcinogenesis and metastasis. Functional in vitro analyses were designed to investigate potential alterations in expression profiles of NSSR1. In detail, typical microenviromental epiphenomena of solid tumors (hypoxia, extracellular acidosis) as well as therapeutic approaches (hyperthermia) were mimicked in cell culture models.
Materials and Methods: Endometrial cancer cell lines were cultured to more than 80% confluence. Experimental setup mimicked hypoxic conditions, extracellular acidosis or hyperthermia vs. regular conditions (control). mRNA expression levels of NSSR1 were analyzed by quantitative RT-real-time PCR, followed by statistical analyses. Protein expression levels were determined by Western blot and immunocytochemistry. Protein expression levels were determined by Western blot and immunocytochemistry.
Results: Functional analysis revealed variable effects of hypoxia, acidosis and hyperthermia on the mRNA and protein expression of NSSR1 in regard to different cell lines. Acidic conditions induced a significant up-regulation of NSSR1 mRNA expression in all endometrial cell lines, under hypoxia and hyperthermia differing response reactions were observed in the cell lines tested. In contrast; NSSR1 protein translocated from the nucleus to the cytoplasm after acidosis and hypoxia, and variant responses were observed after hyperthermia.
Conclusion: Hypoxia, extracellular acidosis and heat shock response are known as tumor microenviromental epiphenomena or exogenous stresses. We have demonstrated their effect *in vitro*, and based on our results we reached a better understanding of molecular NSSR1 gene regulation under these conditions.
No conflict of interest.

679 POSTER

Potential functional role of EZH2 in endometrial carcinogenesis

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Introduction: Endometrial cancer represents the most common gynecological malignancy in the western world and the eighth leading cancer related cause of death in women. EZH2 is one potential novel target gene that might play crucial roles in endometrial carcinogenesis and metastasis. Functional *in vitro* analyses were designed to investigate potential alterations in expression profiles of EZH2. In detail, typical microenviromental epiphenomena of solid tumors (hypoxia, extracellular acidosis) as well as therapeutical approaches (hyperthermia) were mimicked in cell culture models. The polycomb group protein EZH2 acts as a transcriptional repressor and controls cellular memory and methylation processes. So far, the factor was found highly expressed in malignant vs. physiological tissues in several tumor entities. In particular, EZH2 over expression was described in various tumors with epithelial origin, e.g. endometrium, bladder, urothelial tissues, colon, esophagus, gastric tissue. Recently, it has been found that EZH2 overabundance is clearly associated with tumor aggressiveness and with an ascending histological grade and /or advanced stages of tumor progression, hence correlating with poor prognosis and reduced patient survival.
Materials and Methods: Endometrial cancer cell lines were cultured to more than 80% confluence. Experimental setup mimicked hypoxic conditions, extracellular acidosis or hyperthermia vs. regular conditions (control). mRNA expression levels of EZH2 were analyzed by quantitative RT-real-time PCR, followed by statistical analyses. Protein expression levels were determined by Western blot and immunocytochemistry.
Results: Acidic conditions as well as hyperthermia were identified as strong inductors of increased EZH2 expression levels in all cell lines tested. In contrast, hypoxia uniformly caused a down-regulation of EZH2 expression. EZH2 protein localization switched from complete nuclear expression under regular culture conditions to nearly complete deficiency of nuclear protein under hypoxia, acidosis and hyperthermia.
Conclusion: The obtained results clearly indicate the regulatory effects of acidosis, hypoxia and hyperthermal treatment on both, the mRNA and protein expression levels of EZH2. Thus, this factor might be of important relevance for tumor progression and metastasis with inferential therapeutic implications.
No conflict of interest.

680 POSTER

Variable DNA methylation profiles and protein expressions in breast cancer patients

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Background: During the process of tumorigenesis many tumour suppressor genes are inactivated that lead to the decreasing of relevant protein expressions and functions. The aim of this study was to investigate the role of epigenetic inactivation through evaluation of DNA methylation in promoters of 11 cancer associated genes in relevant protein expression changes in breast cancer patients. We selected genes responsible for self-sufficiency in growth signals (*ESR1*, *PGR B, RASSF1A, SOCS1, SYK and APC*) or inhibiting of cell invasion and metastases forming (*CDH1, TIMP3, ADAM23, CXCL12 and BRMS1*). Promoter methylation in these genes could cause decreasing of corresponding protein expression that will contribute to invazivity and metastasis forming processes in breast cancer.
Material and Methods: DNA methylation levels in paraffin embedded tumour tissues and blood cell samples from 34 patients with invasive breast carcinomas and peripheral lymphocytes from 50 control women were quantitatively evaluated by pyrosequencing. Protein expressions were estimated by immunohistochemical analyses using histoscore (intensity of staining x % of stained cells).
Results: The higher levels of promoter methylation in cancers were shown in *RASSF1A*, *APC*, *CXCL12*, *ADAM23 and PGR B* up to 86, 86, 64, 53 and 48%, respectively. The methylation levels in genomic DNA of patients and controls were significantly different in *APC*,*CXCL12*, *ESR1, PGR B and TIMP3* genes. Moreover, the significant differences between methylation levels in tumours and genomic DNA of patients were observed in *APC*, *ADAM23, CXCL12*, *ESR1, CDH1, RASSF1A, SYK, BRMS1* and *SOCS1* genes. Variable spectrum from high to none expressions were presented in tumour tissues in all of evaluated proteins; however, the significant negative association between protein expression and DNA methylation level in tumours was found for *APC* gene only.
Conclusion: DNA methylation profiles observed in our group of breast carcinomas are cancer specific, but they are not the only cause that affects the silencing of evaluated genes and decreasing of relevant protein products.
This study was supported by the Slovak Research and Development Agency under the contract No. APVV-0076−10, Research and Development Operational Programme (ERDF), contract No.26240220058 and Scientific Grant Agency, contract No. 2/0120/13.
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681 POSTER

Antidromic NFATc1 and p53 signaling at the edge of differentiation and stemness in pancreatic cancer

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Background: The current concept suggests a direct link between EMT and stemness induction in pancreatic cancer, thereby coupling cell motility and de-differentiation with self-renewal capacities and drug resistance. Both key features of cellular plasticity are controlled by distinct intracellular signaling and transcription pathways. We have shown that activation of the NFATc1 transcription factor promotes pancreatic cancer development and metastasis through its ability to integrate extrinsic stimuli into coordinated gene regulation.
Aim: To assess whether NFATc1 controls transcription of EMT genes and stemness in PDAC, particularly upon p53 inactivation.
Material and Methods: We generated mouse strains with combined pancreas-specific expression of NFATc1, $p53^{R172H}$ and $Kras^{G12D}$ using Cre-Lox technology. These mice showed a highly aggressive tumor growth (median survival of <50 days). Mouse primary tumour cells were used to identify NFATc1 targets by gene expression profiling and pathway analyses (ChIP seq, miRNA analyses and GSEA). NFATc1 mediated EMT and stemness were assessed in human and murine pancreatic cancer models using migration and spheroid assay as well as xenograft mouse models.
Results: Here, we identified antidromic NFATc1 and p53 signaling pathways in transcriptional control over EMT and stemness. We show that p53 activation prevents cells from EMT in a miR200 dependent manner. However, disruption of the tumor suppressor pathway enables NFATc1/Sox2 chromatin complex formation and transcription of EMT programmes, resulting in highly invasive and metastatic PDACs. Finally, re-expression of miR200c or NFATc1 inactivation suppresses EMT/stemness genes and re-sensitizes PDAC to chemotherapy.
Conclusion: Antidromic NFATc1 and p53 signaling pathways control key features of cellular plasticity and tumor progression at the level of gene transcription. These findings implicate key roles for NFATc1 in transcriptional regulation of differentiation and self-renewal in PDAC.
No conflict of interest.

682 POSTER

Genetic and pharmacological targeting of mast cells inhibits inflammation-associated gastric tumourigenesis

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Background: Mast cells (MC) are innate immune cells, which are important in microbial defence and allergic responses. The role of MCs in tumourigenesis and cancer progression is less well understood. Elevated MC numbers in the tumour stroma were correlated to human gastric cancer progression and promotion of angiogenesis. In this study we explore the role of MCs in tumourigenesis and tumour maintenance in a spontaneous mouse model for gastric cancer.
Material and Methods: Here we study the role of MCs in the $gp130^{FF}$ knockin mouse model, a validated preclinical model for Stat3-dependent inflammation-associated gastric cancer. MC-dependent tumour formation was investigated in the MC-deficient compound $gp130^{FF}$;$ckit^{wsh/wsh}$ mutant mice. To establish whether MCs are potential therapeutic targets, we also treated tumour-bearing $gp130^{FF}$ mice with either Cromolyn (MC degranulation inhibitor) or a dual inhibitor for the c-fms and c-kit receptor kinases (MC and macrophage (MΦ) inhibitor).

Results: We find increased numbers of MCs in the submucosa of gastric tumours and adjacent unaffected submucosa in gp130^{FF} mice compared to gp130^{wt} mice. Genetic depletion of MCs in gp130^{FF};ckit$^{wsh/wsh}$ mice led to a substantial decrease in tumour mass and tumour numbers. Furthermore, therapeutic treatment of tumour bearing mice with Cromolyn decreased the overall tumour weight compared to vehicle treated mice. MC depletion and inhibition were associated with decreased MΦ numbers. Pharmacologic targeting of both MCs and MΦs with a dual inhibitor completely blocked tumour growth of gp130^{FF}-driven gastric tumours. This anti-tumour effect was independent of the Stat3 and mTOR signalling status, which is required for the growth and maintenance of these tumours. Instead genetic and therapeutic targeting of MCs reduced cancer cell proliferation and tumour vascularisation.
Conclusion: The decreased tumour burden of the MC-deficient gp130^{FF};ckit$^{wsh/wsh}$ compound mice suggests that MCs play a critical role in the formation and maintenance of inflammation-associated gastric cancer. Furthermore, pharmacologic targeting of MCs and dual inhibition of MCs and MΦs impedes gastric tumour growth independent of the activation status of Stat3 and mTOR, the two major cancer promoting signalling pathways in gp130^{FF} mice and in a majority of human gastric cancers. Therefore, MCs represent a novel therapeutic target for inflammation-associated gastric cancer.
No conflict of interest.

683 POSTER

Immunological subtypes in breast cancer are prognostic for invasive ductal but not for invasive lobular breast carcinoma

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Background: Classical patient and tumor characteristics are currently the benchmark of personalized breast cancer (BC) management. However, this risk stratification proved suboptimal and recent evidence stated immune and molecular profiling of BC to be a crucial contribution. Most studies are performed on the BC population as a whole, failing to observe differences between invasive ductal (IDC) and lobular (ILC) BC. Despite increasing evidence that IDC and ILC are distinct entities, they are still treated in similar manners. The purpose of this study was to investigate the relevance of the tumor immune response in the major histological subtypes of BC to further potentiate tailored therapy.
Methods: 714 patients who underwent primary surgery in our center between 1985–1996, with or without AST were included. Immunostains were done for classical HLA type I, non-classical HLA-E and HLA-G, Treg, NK-cells and CTL for the composition of the immune profiles. Additionally, Caspase-3 and Ki67 were stained to objectify the apoptotic and proliferative rate in the tumor. Missing data were imputed with multiple imputations; 25 iterations were generated and results were combined using Rubin's Rules. Multivariable logistic regression was used to assess differences between IDC and ILC. The association with disease-free period (DFP) was analysed with Cox proportional hazard models, stratified for IDC and ILC.
Results: No significant difference was found between IDC (90.6) and ILC (9.4) regarding the association with tumor immune subtyping ($p = 0.4$). However, for DFP our data showed that tumor immune subtyping is prognostic ($p = 0.002$) in IDC, but not for ILC. In contrast to ILC, IDC patients more frequently expressed high levels of Caspase3 and Ki67, which was of prognostic value (Caspase3:$p = 0.02$; Ki67:$p = 0.03$). Intermediate immune susceptible IDC expressing high levels of Caspase3 or Ki67, showed worse DFP than low expression hereof (Caspase3:$p = 0.004$; Ki67:$p = 0.002$), this was not seen for ILC or in high or low immune susceptible tumor types for neither IDC nor ILC.
Conclusion: Tumor immune characteristics and host immune responses are prognostic indicators in IDC, but not in ILC. Therefore, IDC and ILC are separate entities and may be better managed as such.
No conflict of interest.

684 POSTER

Clinical relevance of VEGF, VEGFR, PDGFR, HIF and ERCC1 gene polymorphisms on thymic malignancies outcome

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Background: Improving our understanding of the molecular biology of thymic malignancies represents a key challenge in the treatment of these rare tumors.
Material and Methods: The genomic DNA of 57 consecutive patients (31 females and 26 males; 43 thymomas and 14 thymic carcinomas) submitted to total thymectomy at our Institution was extracted from paraffin-embedded tissue.
We selected polymorphisms in the following genes: Hypoxia Inducible Factor-1 alpha (HIF1a: rs2057482T>C, rs1951795A>C, rs2301113C>A, rs10873142C>T, rs11158358G>C, rs12434438G>A, rs11549465C>T, rs11549467G>A), Vascular Endothelial Growth Factor-A (VEGF-A: rs2010963G>C, rs699947A>C), VEGF Receptor 2 (VEGFR-2: rs2305948C>T, rs1870377T>A), VEGFR-3 (rs307826T>C, rs307821C>A), Platelet-Derived Growth Factor-A (PDGFR-A: rs35597368C>T) and Excision Repair Cross-Complementing 1 (ERCC1: rs11615A>G).
Gene polymorphisms were determined by Real-Time PCR using TaqMan assays.
Results: The allele frequency of PDGFR-A rs35597368 T (95.24%) was significantly higher than general population (86%, $p = 0.012$), while the frequency of alleles HIF1-A rs2057482C (76.98%), rs1951795C (68.25%), rs2301113A (68.55%), rs10873142T (68.85%), rs11158358C (74.6%), rs12434438A (65.87%), rs11549465C (83.33%) were significantly lower than those of the control group (90%, 87%, 82%, 87%, 86%, 84%, 92%, respectively, $p < 0.01$).
VEGFR-3 rs307821C was significantly higher in thymomas vs. thymic carcinomas (79.5% vs 72%, $p = 0.0371$).
The following factors were significantly correlated with a better overall survival: VEGFR-3 rs307826T, VEGFR-2 rs1870377T, PDGFR-A rs35597368T/C, HIF1a rs2301113A/C, rs2057482C/T, rs1951795C, rs11158358G/C and rs10873142T/C, ERCC1 rs11615A ($p < 0.05$).
Conclusions: To the best of our knowledge this is the largest monocentric study analyzing the angiogenetic variants in thymic tumors representing a further asset in the definition of high-risk patients after curative resection. The selection tool deriving from this analysis may allow an optimal use of innovative treatment strategies including targeted agents such as sunitinib and sorafenib.
No conflict of interest.

685 POSTER

The role of the COP9 signalosome during HIPEC: consequences for clinical application

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Peritoneal carcinomatosis (PC) is a common manifestation in patients with colorectal cancer and has long been considered to be with no curative treatment options. Local treatment strategies have been developed combining cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). The most frequently used chemotherapeutic agent mitomycin C (MMC) has alkylating properties. It inhibits DNA synthesis by interstrand cross-linking and generating double-strand breaks. The DNA damage induces repair mechanisms including the COP9 signalosome (CSN), a regulator of the ubiquitin proteasome system (UPS). The CSN is a protein complex composed of 8 subunits (CSN1-CSN8). It regulates the degradation of important regulatory proteins via the UPS. It controls protein stability of DNA damage repair effectors and is involved in cell cycle regulation. It determines the activity of tumor suppressor proteins such as p53. The coordinated expression of CSN subunits is modulated by miRNAs of the let-7 family. miRNA let-7 binds to the mRNA of CSN subunits and acts as a negative regulator of their expression.
We investigated the role of the CSN during the treatment with MMC. Treatment of colon cancer HT29 cells with different concentrations of MMC in medium heated to 42°C for 1 h or 4 h increased CSN subunit expression. Significant apoptosis was measured only after 4 h. We hypothesize that the increase of the CSN is part of the DNA damage response program, which counteracts apoptosis and decreases the efficiency of HIPEC. One possibility to increase the effect of MMC is to block CSN expression with miRNAs. Therefore, to accelerate apoptosis we transfected HT29 cells

with miRNA let-7 mimic. miRNA mimics act as endogenous miRNAs and block the expression of the CSN. After transfection with miRNA cells were incubated with different concentrations of MMC for 4 h. Our data shows that let-7 miRNA mimic prevented the increase of CSN subunits induced by MMC treatment.
We conclude that let-7 mimic impairs the DNA damage response and potentially increases the efficiency of HIPEC.
No conflict of interest.

686 POSTER

Vinflunine promotes the differentiation of bladder tumour cells by the induction of e-cadherin based cell-cell contacts and β-catenin inhibition

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Background: Vinflunine (VFL) is a third-generation, semi-synthetic vinca alkaloid that, similar to other microtubule-targeting drugs, suppresses microtubule (MT) dynamics both *in vitro* and in living cancer cells. VFL is an option treatment for patients with transitional-cell-carcinoma (TTC) progressing after first-line platinum-containing chemotherapy. In the last ten years, it was established the impact of MT dynamics on E-cadherin-based cell-cell contacts. E-cadherin is the prototype and best characterized member of adherens junctions in mammal's epithelial cells and is regarded as a tumour suppressor. Its loss is associated with poor prognosis in carcinoma, and it is considered as a hallmark of epithelial–mesenchymal transition (EMT). In this work we investigate the effect of VFL in bladder TCCs during EMT.
Material and Methods: Five bladder transitional carcinoma cell lines (HT1376, 5637, SW780 and UMUC3) were analysed after VFL treatment. By MTT assay, cell viability was determined and the effect on cell phenotype by contrast phase microscopy was examined under increasing concentrations of VFL. Western blotting and qRTPCR were performed to explore VFL effect on the expression protein and miRNAs markers implicated during EMT.
Results: By phase contrast, we have shown that VFL treatment exerts its action on the reversion of the mesenchymal to epithelial phenotype. We have also analyzed the effect of VFL on EMT protein markers. In E-cadherin-expressing bladder tumour cells it was detected an up-regulation of epithelial marker, such as E-cadherin, accompanied to the downregulation of mesenchymal markers, such as N-cadherin; moreover, Hakai, a posttranslational regulator of E-cadherin was also downregulated by VFL. miR-200 family members are also strongly associated to epithelial differentiation during EMT. miR-200a and miR-141 were upregulated by VFL further confirming its action in the regulation of EMT. Moreover, as β-catenin is connected to E-cadherin at cell-cell contacts and it is also reported to influence the microtubule network; therefore our results shows the effect of VFL on β-catenin degradation and also the molecular mechanism by which VFL can regulate EMT through β-catenin action.
Conclusion: Our results show that VFL induces E-cadherin and modulates β-catenin levels exerting its action on the EMT process, opening a new research approach, particularly promoting the differentiation of bladder tumour cells and reverting the epithelial–mesenchymal transition.
No conflict of interest.

687 POSTER

Capillary morphogenesis gene 2 inhibits growth of breast cancer cells and is inversely correlated with the disease progression and prognosis

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Background: Capillary morphogenesis gene 2 (CMG2) was identified as a gene being up-regulated in capillary morphogenesis. It is also known as a receptor of anthrax toxin. It has been shown to be involved in the cell adhesion and motility which are also critical capacities of cancerous cells for their dissemination. Present study aims to examine the expression of CMG2 in a breast cancer cohort and its implication in the disease progression.
Materials and Methods: Breast primary tumours and background tissues were collected immediately after the surgery and stored at −80°C with approval by the local ethics committee and written consent from patients. The expression of CMG2 in 127 breast cancer tumour samples and 33 normal mammary tissues was determined using real time PCR. Knockdown and over-expression in breast cancer cells were established using constructed plasmid vectors carrying either anti-CMG2 ribozyme or full-coding sequence of human CMG2. The effect on growth of breast cancer cells was examined using *in vitro* and *in vivo* models.
Results: The CMG2 transcript levels were reduced in advanced tumours compared with its expression in tumours of early stage according to their TNM staging. The reduced expression was associated with poorer overall survival, $p = 0.004$ compared with patients had higher expression. The knockdown of CMG2 resulted in an increased *in vitro* growth of MDA-MB-231 cells which express this gene at relatively higher level. This is consistent with the finding from MCF-7 cells express lower level of CMG2 and exhibited an inhibition on the growth following over-expression of CMG2. The over-expression of CMG2 also demonstrated an inhibitory effect on *in vivo* growth of breast cancer cells.
Conclusion: Reduced expression of CMG2 is associated with disease progression and poor prognosis of breast cancer. CMG2 has inhibitory effect on growth of breast cancer cells. Further investigation is required to shed light on the prognostic and therapeutic potential of targeting this molecule.
No conflict of interest.

688 POSTER

Polymorphisms in estrogen metabolizing genes in gallbladder cancer

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Background: Gallbladder Cancer (GBC) is more common in females suggesting that sex hormones may play a role in its etiopathogenesis. We hypothesised that genetic polymorphisms in Estrogen Metabolising Enzymes (EMEs) are linked with susceptibility to GBC.
Material and Methods: We selected three single nucleotide polymorphisms(SNPs)- *CYP1A1 Msp1*, *CYP1A1 Ile462Val* and *CYP1B1 Val432Leu* involved in estrogen metabolism for this study. 142 patients of GBC and 142 age and sex matched healthy controls were included in this study. Clinical data was collected from patients along with 5 ml blood venous blood samples from both patients and controls. High molecular weight DNA was extracted by salting out method. SNP analysis in the three genes was based on PCR-RFLP method. Binary logistic regression was used for all analysis variables to estimate risk as the odds ratio (OR) with 95% confidence intervals (CIs) using age and sex as covariates. Tests of statistical significance were two sided and *P* values were considered significant at <0.05 level.
Results: No significant association between risk for GBC and the presence of SNPs in the three EME genes studied. The age- and sex adjusted ORs for the CYP1A1 *TC* and *CC* genotypes were 0.74 and 1.5 (95% CI=0.4−1.3 and 95% CI=0.3−4.9, respectively) using the *TT* genotype as reference group. The age- and sex adjusted ORs for the *CYP1A1 Ile462Val IleVal* genotype was 1.3 (95% CI=0.6−2.4) using the *Ile*/*Ile* genotype as reference group. The age & sex adjusted ORs for the *CYP1B1 Val432Leu Leu*/*Val* and *Val*/*Val* genotype were 1.38 (95% CI=0.7−2.6) and 1.68 (95% CI=0.9–28.9) using the *Leu*/*Leu* genotype as reference group. However, an increased association between risk of GBC in patients who consumed tobacco & non vegetarian food and *CYP1A1 Msp1* gene polymorphism was seen. The frequency of *TC* and *CC* homozygote genotypes were dissimilar in GBC patients who consumed tobacco when compared to patients who did not consume tobacco and were statistically different in the two groups in the *TC* genotype ($p = 0.009$) but not in the *CC* genotype ($p = 0.387$). The age & sex adjusted ORs for the *CYP1A1 TC* and *CC* genotypes were 3.34(95% CI=1.36–8.65) and 0.43(95% CI=0.34–15.8) respectively, using the *TT* genotype as reference group. Similarly, the frequency of *TC* and *CC* homozygote genotypes were dissimilar in GBC patients who consumed non vegetarian food when compared to patients who consumed vegetarian food and were significantly different in the two groups in the *CC* genotype ($p = 0.045$) but not in the *TC* genotype ($p = 0.19$). The age and sex adjusted ORs for the *CYP1A1 TC* and *CC* genotypes were 1.63(95% CI=0.77–3.43) and 9.18(95% CI=1.05–79.9) respectively, using the *TT* genotype as reference group. Similarly, the *C* allele was significantly associated with gallbladder cancer in non vegetarians ($p = 0.016$) and the age and sex adjusted OR was 2.07 (95% CI=1.14–3.76) with *T* allele as the reference.
Conclusions: Similar studies with larger number of patients may show significant association if adequately powered to detect smaller associations. Similarly, polymorphisms in other EMEs need to be studied to look for possible associations with risk of GBC.
No conflict of interest.

689 POSTER

Effect of sample DNA impurities on MLPA

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Background: MLPA® (Multiplex Ligation-dependent Probe Amplification) is a PCR-based technique that allows copy number detection of up to 50 different genomic sequences in one reaction. MLPA can be also used for methylation and point mutation detection and requires only 50 ng DNA input. MLPA is routinely used in tumour diagnostics and in cancer research. One of the critical factors for MLPA is the quality of DNA, which depends on the tissue source and on DNA extraction procedure. As tumours occur in all types of tissues with each tissue having certain chemical content, various potentially inhibitory substances can be co-extracted with DNA and affect the downstream molecular applications. Hence, it is important to know to what extent these substances affect the MLPA reaction. Here we have estimated concentrations of several substances in DNA sample, present in human tissues or added during tissue processing, that have a negative influence on the MLPA reaction.
Materials and Methods: MLPA was performed on 50 ng of human genomic DNA in the presence of various amounts of inhibitory substances: sodium chloride, calcium(II) chloride, iron(III) chloride, EDTA, haemoglobin, heparin and melanin. P377-A1 probemix that contains 54 MLPA probes was used for all the tests. Data analysis was performed using Coffalyset.Net software and overall variability of MLPA probes was assessed. The MLPA reaction was considered affected when at least three probes showed >30% variation.
Results: The highest concentration of the inhibitory substance in DNA sample where MLPA is not affected was determined: sodium chloride (20 mM), calcium (II) chloride (2 mM), iron (III) chloride (0.1 μM), EDTA (2 mM), haemoglobin (100 ng/μl), heparin (0.02 U/ml) and melanin (3.0 ng/μl).
Conclusions: It is important to consider the nature of biospecimen, such as chemical content of tumour tissue and processing of it, for MLPA analysis on copy number, methylation and point mutation detection. DNA purification methods should be used that eliminate the presence of naturally occurring substances such as heparin and melanin in the DNA samples tested. Our experience with various methods will be presented. Furthermore, simple precautions to be made during DNA purification and handling will be presented that can eliminate the presence of inhibitory concentrations of substances such as sodium chloride and EDTA.
No conflict of interest.

691 POSTER

Targeting cancer stem cells with platinum anti-cancer drug-incorporated polymeric micelles

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Background: Within tumor populations are subsets of 'cancer stem cells', cells that overexpress the glycoprotein CD44v, a marker for stem cell-like qualities as it involved in cell differentiation, cell proliferation and cell migration. These types of cells are more likely to re-initiate both tumor growth and metastasis if left un-eradicated after therapy.
Two polymer-encapsulated platinum nanocarrier micelles, NC-6004 (cisplatin-encapsulating) and NC-4016 (DACHPt-encapsulating) are currently in clinical trials as alternatives to their conventional cisplatin and oxaliplatin 'free drug' counterparts. In this report, we show that these polymer-Pt micelle nanocarrier drugs can target cancer stem cell populations in tumor masses, an occurrence that contributes to their effect on tumor growth suppression.
Materials and Methods: Upon treatment with cisplatin, oxaliplatin, NC-6004 or NC-4016, OSC19 and HSC2 (oral squamous carcinoma, CD44v-expressing cells) subcutaneous tumors were measured and then analyzed for CD44v expression (IHC or western blot) or for Pt content (ICPMS). For *in vitro* studies, cells were treated with polymer-Pt micelles or free Pt drugs for 48 hours before analysis for CD44v content (flow cytometery, Alexa488-anti-CD44v9 antibodies).
Results: Treatment with polymer-Pt micelles suppressed growth rates of subcutaneous CD44v-expressing OSC19 and HSC tumors, as well as reduced the expression of CD44v within the tumor masses. Minimal or adverse effects on tumor progression were observed by treatment with free Pt drugs at comparable doses. As previously reported, polymer-micelle-assisted delivery can improved accumulation of Pt drug into tumor sites, which could have aided in their superior anti-tumor effect. Furthermore, it was found that cellular internalization of whole polymer-Pt micelle complexes followed by slow release of Pt from the micelle compartment was important for CD44v suppression, as opposed to internalization of free drug *via* permeation through the cell membrane.
Conclusions: A major problem for cancer therapy is the existence of chemoresistant and dormant cancer cells within a tumor population. Conventional free Pt anticancer drugs are ineffective at eradicating these populations, thereby increasing the chances of post-therapy relapse and metastasis. Here we show that polymer-micelle nanocarrier-mediated delivery of Pt drugs can overcome this resistance by reducing the expression of cancer stem cells within solid tumors.
No conflict of interest.

692 POSTER

Effect of dosing time on sunitinib pharmacokinetics

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Background: There is increasing evidence that biochemical processes that determine the pharmacokinetics (PK) of drugs are subject to a circadian rhythm. Sunitinib, an active multi-targeted tyrosine kinase inhibitor used for RCC, GIST and pNET, is mainly metabolized by CYP3A4 into its even active metabolite, which is further converted into several inactive compounds. The aim of this study was to investigate a possible circadian rhythm in sunitinib PK.
Materials and Methods: We performed PK studies in mice and humans treated with sunitinib. Six groups of 18 mice were administered sunitinib through gavage in 4 hour (h) intervals. In each group, blood for PK analysis was collected at 6 time points after gavage. In patients, a prospective randomized cross-over study was performed. Patients were randomized to take sunitinib at 8 AM during the 1st course and at 6 PM during the 2nd course in arm A, or *vice versa* in arm B. During both courses patients were hospitalised for 24 h for blood withdrawal at multiple time-points for PK measurements. Primary endpoint in both studies was the difference in area under the curve (AUC) of sunitinib + metabolite between dosing times. Paired t-test was used for statistical analysis.
Results: A clear 12 h rhythm in AUC was seen in mice (table). The AUC increased with 32% when sunitinib was administered at 12 noon, compared to 8 AM (see table). In the study in human 21 patients were included so far (arm A n = 10, arm B n = 11) of whom 12 patients had PK sampling during 2 treatment cycles. Preliminary data indicate that there is a difference in trough levels (C_{trough}) of sunitinib + active metabolite between morning *vs* evening dosing (mean C_{trough} respectively 49 ng/mL and 61 ng/mL, p = 0.006). Thus far, no clear difference in AUC was seen between morning *vs* evening intake of sunitinib.
Conclusions: These observations indicate that sunitinib PK follows a 12 h rhythm in mice. In humans, a difference in trough levels was seen between morning and evening dosing. Taken together, these data suggest that sunitinib PK may be subject to circadian rhythmicity. Further research is necessary to reveal the underlying molecular mechanisms.
No conflict of interest.

Table: AUC at different dosing times of sunitinib in mice

Dosing time	AUC_{0-inf} (ng·h/mL)
8 AM	8944
12 noon	11850
16 PM	11134
20 PM	9774
12 midnight	11183
4 AM	11317

693 POSTER

Hepatitis A virus cellular receptor (1HAVcR1) enhances the aggressive behaviour of breast cancer cells and is linked to hepatocyte growth factor (HGF) regulation of the tight junction complex

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Background: HAVcR1 acts as a cellular receptor for the hepatitis A virus and has been indicated in atopic & allergic diseases. It has recently been shown that HAVcR1 may have a role in cancer & is involved in the regulation of tight junctions (TJ) in human endothelial cells via interaction with ZO-1 &

ZO-2, both proteins involved in TJ assembly. This study sought to discover the role of HAVcR1 in human breast cancer.
Material and Methods: HAVcR-1 expression was assessed by Western blotting, immunohistochemistry & RT-PCR in MDA-MB-231 & MCF7 human breast cancer cell lines. A hammerhead ribozyme transgene was used to knockdown HAVcR-1; moreover, forced expression was obtained by insertion of a transgene into wild type cells. TJ function was assessed using trans-endothelial resistance (TER) & paracellular permeability under the influence of HGF (40ng/ml). ECIS (electrical cell impedance sensing) was used to evaluate changes in attachment, migration & barrier integrity. Breast cancer primary tumours (n = 114) & matched background tissue (n = 30) were processed for frozen sections (IHC) & RNA extraction (for analysis by Q-PCR).
Results: HAVcR1 was expressed in MDA-MB-231 & MCF7 human breast cancer cells. HGF increased localisation of HAVcR1 to cell membranes. Successful knockdown resulted in cells with increased TJ function ($p < 0.05$) & no response to HGF. ECIS revealed that knockdown cells had reduced attachment, migration & increased barrier function & were not affected by HGF. Closer investigation using phosphorylation studies revealed that HGF hyper-phosphorylated HAVcR1. HAVcR1 expression was significantly higher in tumour tissues, node positive tumours & in patients with poor prognosis ($p < 0.02$). Patients with metastasis & who died from breast cancer had significantly higher levels of HAVcR1, compared with patients who remained disease free over a 10 year follow-up ($p < 0.027$). Survival analysis revealed a significant relationship between high levels of HAVcR1 & poor overall survival ($p = 0.0057$) as well as disease-free survival ($p = 0.0279$).
Conclusions: In human breast cancer cells HAVcR1 is involved in TJ regulation via HGF. HAVcR1 is associated with poor prognosis & survival in patients with breast cancer & is therefore a potential prognostic factor & therapeutic target. These results demonstrate for the first time that HAVcR-1 may have a previously undiscovered role in the regulation of TJ integrity in human breast cancer.
No conflict of interest.

694 POSTER

The DNA repair inhibition by Dbait enhances the treatment efficacy of colorectal cancer metastases in a preclinical model

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Background: Majority of the patients with advanced colorectal cancer develop liver metastasis, even after primary tumor resection. Depending on the disease stage, systemic chemotherapy (CT) or radiofrequency ablation (RFA) can be considered. As these two treatments induce DNA damage, their efficacy could be enhanced by DNA damage repair inhibition. Dbait are a new class of molecules that inhibit the complete DNA double-strand break repair machinery. Here, we assess the combination of Dbait and CT or RFA in the treatment of a human colorectal cancer xenograft models.
Materials and Methods: For association with CT, HT29 cells were grafted in the liver of 49 nude mice. Two weeks post graft, mice were administered NaCl (n = 9), CT (oxaliplatin and 5-fluorouracil) (n = 10), systemic treatment with Dbait (n = 10) or a treatment associating Dbait and CT (n = 10). Efficacy was assessed by a blinded pathological study. For association with RFA, 113 mice were flank-grafted with HT29. When tumors reached 500 mm^3, mice were sham treated (n = 18), treated by Dbait (n = 22), RFA using an incomplete ablation scheme (n = 21) or with a combination of Dbait and RFA (n = 52 separated in three Dbait regimens). Subsequently, 39 mice were sacrificed for a blinded pathological study, and 74 were followed for survival analysis.

Treatment	Survival study		Pathological study			
	Median (days)	Complete response	Number of tumor samples	Ki67 (%)	Necrosis (%)	Tumor area (mm^2)
CT*						
Sham treated	N.D.	0/9	9	77±9	35±5	60±29
Dbait	N.D.	0/10	10	80±4	47±7	59±19
CT	N.D.	0/10	10	80±2	29±5	39±21
CT + Dbait	N.D.	0/10	10	4±4	86±7	40±14
RFA**						
Sham treated	28	0/11	7	57±4	26±8	24±22
Dbait	37	1/14	8	50±5	46±18	14±4
RFA	40	1/13	8	52±3	60±17	13±7
RFA + Dbait	87	7/12	8	32±7	83±19	6±4

Histological analyses were performed * 22 days or ** 3 days after the treatment.

Results: Histological studies of tumor sections demonstrate a significant decrease in tumor volume, cancer cell viability and proliferation in the groups treated with CT and RFA in combination with Dbait, compared to the CT or RFA alone groups. Additionally, survival was significantly increased in mice treated with RFA in combination with Dbait compared to RFA alone (median survival: 84 *vs* 40 days, $p < 0.001$). A standalone effect of RFA was also observed compared to controls (median survival: 40 *vs* 28 days, $p < 0.001$).
Conclusions: Our results show that the addition of Dbait to CT or RFA enhances their antitumor activities in this model of colorectal cancer metastases and provide an experimental basis for the use of Dbait as a global adjuvant therapy.
Conflict of interest: *Ownership: M Dutreix and JS Sun are cofunders of DNA Therapeutics. Other substantive relationships: F Devun is employee of DNA Therapeutics*

695 POSTER

Implementation of an individual-level clinical quality audit for community based surgeons and pathologists

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Background: Clinical audits are an important quality assurance tool. Quality data has been sporadically reported as aggregate data to community clinical groups. Our hypothesis was that data consistently reported at the individual level would have a greater impact.
Materials and Methods: Over a 15 month period we identified 'sub optimal' surgical specimens; colorectal cancer excisions which had less than 12 lymph nodes and pT2 prostate cancer which had an R1 margins from a centralized data base at Cancer Care Ontario.
We surveyed the 54 surgeons and pathologists, who removed or evaluated the resected specimens about the usefulness, confidentiality and validity of the data.
The raw data was validated by independent review before scores were created for clinicians. Cases were excluded from the quality scores because of data quality issues, incorrect grossing of the specimen or mitigating clinical situations such as emergency surgery.
Subsequent to 5 quarterly feedback reports to each clinician we surveyed the surgeons and pathologists again.
Results: 23% of suboptimal cases were excluded from surgeons' scores after independent review because they were not handled properly by the pathologists or for mitigating clinical reasons such as emergency or palliative surgery.
With respect to agree/strongly agree responses, two-thirds of clinicians surveyed felt the data provided was valid. both before and after the study.
Prior to receiving the data almost all clinicians agreed that having access to this data was important. That dropped to a 74% positive response after the study period.
Only 53% of respondents believed that the results were useful to them in their practice but paradoxically, almost all believed that access to such data would improve the performance of the healthcare system.
General surgeons and pathologists did well in lymph node retrieval with many clinicians attaining 100% compliance after validation.
Pathologists did less well on handling prostate specimens. 10% of suboptimal specimens were rejected after review.
Urologists had the poorest quality performance as a group at the beginning of the study with over 40% of the resected pT2 prostate specimens having an R1 margin. Only 30% of urologists responded to the surveys.
As of December 2012, a latency of 18 months from the first audit feedback, R1 margins in pT2 to prostate resections have fallen to 26%.
Conclusions: Clinicians have confidence in the process we have established to provide individual clinical audit data in terms of confidentiality and validity but are less inclined to believe the feedback was a benefit to their practice. This observation maybe due to the fact that general surgeons did extremely well on their metric and urologists had a very poor response rate to our surveys.
All clinicians believed that individual level clinical audits would have a positive effect on quality in healthcare.
There has been a positive impact on R1 margin rates in pT2 prostate cancer.
No conflict of interest.

696 POSTER

A potent enantiomer of gossypol, AT-101: Screening of anti-angiogenic protein targets in glioblastoma multiforme cells

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Background: Glioblastoma multiforme (GBM) is the most common malignant glioma in adults with extremely high morbidity and mortality. Angiogenesis in cancer strongly correlates with the risk of invasion and metastasis. Inhibition of angiogenesis by bevacuzimab shows modest activity in highly-vascular GBMs, but more therapeutic options are needed. AT-101, the (−)- enantiomer of gossypol, is a natural polyphenolic compound extracted from the cotton plant with potent cytotoxic effects on various tumor types. In the present study, we investigated the anti-angiogenic protein targets of AT-101 in GBM cell lines (U-87MG and T98G).
Material and Methods: Real time monitoring of cell proliferation was assessed by xCELLigence system in U-87MG and T98G cells after AT-101 (1−40 μM) exposure. Changes in angiogenesis-related protein expressions were investigated by human angiogenesis antibody array. Changes in protein levels were accepted as significant if there was at least a 1.5-fold change in expression when compared to untreated control.
Results: AT-101 inhibited cell proliferation in a dose and time dependent manner in tested cell lines. The IC_{50} values of AT-101 in U-87MG and T98G cells were 2.4 and 2.7 μM, respectively, at 20 h. The exposure of AT-101 in both cell lines resulted in significant inhibition of expression of angiogenesis-related protein levels which are known to have pivotal roles in invasion, angiogenesis and metastasis.
Conclusions: We found out that AT-101 potently inhibited angiogenesis-related cytokines in GBM cells. AT-101 shows preliminary but promising results for the future treatment strategies for GBM.
No conflict of interest.

697 POSTER

The influence of metformin on the breast cancer phenotype

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Background: Metformin is frequently used in the treatment of diabetes mellitus (DM) type 2. To get insight whether the therapy of diabetes or hyperglycemia with metformin might induce the changes in biology of cancer cells, we determined the prevalence of breast cancer patients with enhanced HER-2, estrogen and progesterone receptor expression on tumor cells and compared it with those found in general breast cancer population.
Patients and Methods: In this study 768 patients in the period November 2011-December 2012 with surgically removed tumors were included. From this group 42 patients had DM type 2 or hyperglycemia and were pretreated (not less than one month) with metformin alone or sometimes in combination with other antidiabetic drugs. In 37 out from these 42 patients malignant tumors were found (three of them were with bilateral tumors), while 5 out from 42 patients were with benign breast disease. It needs to be mentioned that 14 of 37 additionally were treated with some sulfonylurea derivatives, while 3 of 37 used additionally insulin as the antidiabetic therapy. Receptor status was assessed analyzing tumor cells obtained at diagnosis by immunohistochemistry. Estrogen and progesterone receptor expression was scored from 0 to 8; scores 3 and above were considered positive. Intensity of HER-2 expression were graded from 0 to 3+; scores 3+ and 2+ (after confirmation of HER-2/neu amplification by additional analysis, chromogenic in situ hybridization) were considered as positive.
Results: In 30 out from 37 patients' tumor enhanced ER/PR positive protein expression was found (81.1%). Score 3+ of HER-2 receptor expression was not found on examined patients tumor cells, even more, tumors with HER-2 expression 2+ (found in five patients) were without HER-2 amplification. Frequency of patients with ER/PR positive tumors in general breast cancer population in Institute of Oncology and Radiology of Serbia (from data obtained analyzing 1410 patients' tumors in the period November 2011-December 2012) was 85.5%. HER-2 expression score 3+ was found in 16.6%. Obtained data show that metformin used alone, or in combination with other antidiabetic drugs could modify biology of breast cancer regarding downregulation of HER-2 amplification and/or expression.
Conclusions: Results from this work show that metformin might influence changes in the biology of malignant breast cancer cells downregulating HER-2 expression.
No conflict of interest.

698 POSTER

Gene expression profiles of circulating tumor cells (CTCs) in patients with metastatic breast cancer (MBC) treated with aromatase inhibitors (AI)

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Background: Enumeration of CTCs can be used to assess prognosis in MBC and to evaluate treatment response. Besides enumeration, molecular characterization of CTCs is a promising tool to develop a more personalized treatment approach. In this study, we evaluated the association between mRNA expression of 96 measurable genes in CTCs and response to first-line AI in MBC patients with estrogen receptor (ER)+ primary tumors.
Materials and Methods: CTCs were isolated and enumerated from the blood of 25 MBC patients prior to start of first-line therapy with an AI. Fourteen patients received a non-steroidal AI (8 letrozole, 6 anastrozole) and 11 patients were treated with exemestane. mRNA expression levels of 96 genes were measured by quantitative RT-PCR as previously described (Sieuwerts et al. Clin Cancer Res. 17:3600–3618, 2011). Expression levels of these genes were studied for their association with time to progression (TTP) after start first-line AI.
Results: Median TTP was 338 (range 14–1239) days and median baseline CTC count for the 25 patients was 14 (range 0–753). In this relatively small cohort, the clinically relevant cut-off level of $\geqslant$5 CTCs in association with TTP did not reach statistical significance (Hazard Ratio [HR] 4.76, 95% Confidence Interval [CI]: 0.59–38.22, $P = 0.14$). For type of AI, when comparing steroidal with non-steroidal AI, the measures in Cox univariate regression analysis were HR 2.54 (95% CI: 0.67–9.64), $P = 0.17$. A 10-gene CTC predictor was constructed based on the Wald statistics of the contribution of the individual genes in univariate Cox regression analysis of TTP. To identify patients with good and poor outcome, the Wald corrected sum of the 10 genes was used to dichotomize the continuous 10-gene predictor (HR 12.87 [95% CI: 1.60–103.56], $P = 0.016$). In multivariate analysis, corrected for the clinically relevant variables type of AI and CTC count, only the 10-gene CTC predictor was an independent factor associated with TTP (HR 12.46 [95% CI: 1.29–120.08], $P = 0.029$).
Conclusions: A 10-gene CTC expression profile was constructed which distinguishes good and poor outcome to first-line AI in MBC patients. This profile is currently being validated in an independent group of patients.
Conflict of interest: *Corporate-sponsored research: Veridex*

699 POSTER

Nanofluidic digital PCR for improved selection of metastatic colorectal cancer patients to anti-EGFR therapies

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Background: Concomitant detection of mutations in downstream signalling molecules of the EGFR pathway (*KRAS*, *BRAF*, *PIK3CA* and *NRAS*) has been suggested to improve the selection of candidate metastatic colorectal cancer (mCRC) patients that will respond to anti-EGFR therapy. In addition, *EGFR*(S492R) point mutation has been associated with acquired resistance to cetuximab. We assessed the feasibility of a nanofluidic digital PCR array platform to simultaneously detect hotspot mutations with high sensitivity.
Methods: 26 primary tumor FFPE tissues from patients (15M/11F; 3 stages I−II; 23 stages III−IV) with chemotherapy-refractory mCRC treated with cetuximab plus chemotherapy in the pre-*KRAS* selection era (between 1997 and 2006) were included in the mutational analysis. Digital PCR was performed using the Digital Array Chip. Conventional genotyping was

performed using LightCycler 480. A panel of 17 hotspot mutations were assessed: all codon 12, G13D, Q61H and A146T9 *KRAS*, V600E *BRAF*, M1043I, H1047R, H1047L and H1047Y in exon 20 of *PIK3CA,* Q61K and Q61R *NRAS* and S492R *EGFR.*
Results: Analytical sensitivity of digital PCR for mutant alleles was 0.05%-0.1% whereas LightCycler detected 1−5%. Eight of 26 (31%) patients were positive for at least one mutation with the Light Cycler. Digital PCR increased this number to 11/26 (42%) confirming all positives. Digital PCR identified multiple mutant alleles in 5 cases. Digital PCR reclassified as mutant 1 of the 5 cases with progressive disease. The case with a G13D mutation identified showed partial response (Table).
Conclusions: Digital PCR provides a robust and highly sensitive detection of EGFR-pathway hotspot mutations that may result in better classification prior to anti-EGFR treatment.
No conflict of interest.

Patient	Stage	FLUIDIGM panel	LightCycler panel	Response
Digital PCR mut only				
7	IV	MUT (G13D)	wt	PR
16	IV	MUT (G12V/G12D)	wt	NE
21	IV	MUT (G12V)	wt	PD
Digital PCR and LC mut				
1	III-B	MUT (G12D/G12S)	MUT (G12D)	SD
4	I	MUT (G12V/H1047Y)	MUT (H1047Y)	SD
9	III-B	MUT (G12D)	MUT (G12D)	SD
11	IV	MUT (A146T)	MUT (A146T)	PD
12	II-A	MUT (G12D)	MUT (G12D)	SD
20	IV	MUT (G12D)	MUT (G12D)	SD
22	IV	MUT (H1047R/H1047Y)	MUT (H1047R)	SD
25	IV	MUT (G12C/Q61H)	MUT (Q61H)	NE
Panel *wild type*				
2	IV	wt	wt	PD
3	IV	wt	wt	SD
5	IV	wt	wt	SD
6	IV	wt	wt	PD
8	II-B	wt	wt	NE
10	III-B	wt	wt	SD*
13	III-B	wt	wt	PD
14	III-C	wt	wt	CR
15	III-B	wt	wt	PD
17	IV	wt	wt	PR
18	IV	wt	wt	PR
19	IV	wt	wt	PR
23	IV	wt	wt	PR
24	III-B	wt	wt	SD
26	II-A	wt	wt	NE

PR: partial response, CR: complete response, PD: progressive disease, SD: stable disease, NE: not evaluable.
*prolongued SD.

700 POSTER

18F-misonidazole positron-emission tomography (FMISO-PET) as an early biomarker of vascular normalization in response to antiangiogenic therapy

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Background: Vascular normalization (VN) is a mechanism by which antiangiogenic drugs (AD) improve vessel function and oxigenation in tumors, enhancing chemotherapy effect. A non-invasive VN marker would allow clinical decisions in patients receiving AD. We evaluated 18F-misonidazole (FMISO) positron-emission tomography (PET) imaging of tumor hypoxia as an early marker of VN, using the AD dovitinib (DOV) in pancreas tumografts (TG).
Methods: Two pancreas TG with characterized gemcitabine (GEM) response (Panc286-resistant; Panc215-sensitive) were implanted in nude mice. Tumor perfusion, hypoxia and glucose uptake before/after 4-day DOV course were explored as potential VN parameters using perfusion computed tomography (P-CT) (HU in 4 ROIs/mice), FMISO-PET (tumor SUV mean), and fluorodeoxyglucose (FDG)-PET (tumor SUV max). Tumor samples at the same timepoints were collected for VN microscopical analysis. Microvessel density and tumor hypoxia were quantified with CD31-pimonidazole co-staining. Perfusion was assessed measuring tumor extravasation of a fluorescent 10KDa-dextran. Whether DOV improved GEM efficacy was studied comparing tumor growth in DOV+GEM *vs* GEM treated animals. Stats: t-test for pairwise comparisons, ANOVA for tumor growth comparisons. Minimum number of tumors per conditionant parameter: 10. All shown data $p < 0.05$.
Results: Total animals in study: 194. In GEM-resistant TG Panc286, DOV+GEM caused a tumor growth inhibition (TGI) of 35.1% *vs* GEM alone at 59 days of treatment ($p = 0.044$). 4-day-DOV course significantly lowered FMISO uptake in Panc286 tumors (SUV mean DOV 0.60, Vehicle 1.16 $p < 0.001$) and tumor perfusion by P-CT (HU mean DOV 123, vehicle 249; $p < 0.001$). Microscopical changes mirrored image findings, as tissue hypoxia was 10-fold decreased and 10KDa-dextran clearance in tumors was 5-fold increased *vs* controls after 4-day DOV course in preliminary analysis. In GEM-sensitive TG Panc215, DOV+GEM also caused a TGI of 54.1% *vs* GEM alone at 116 days of treatment ($p = 0.005$). However, no changes in FMISO-PET and P-CT were observed after 4-day DOV course, neither changes in tissue hypoxia and vascular perfusion in microscopical analysis.
Conclusion: FMISO-PET can tract hypoxia evolution after a short course of DOV. In tumors in which AD reverse chemoresistance by means of VN, FMISO-PET could be an early marker of AD efficacy. However, as evidenced by Panc215 results, other mechanisms than VN may play a role in AD response.
No conflict of interest.

701 POSTER

Erlotinib in EGFR wild type platinum resistant NSCLC: now a predictor factor

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Background: Erlotinib (Erl) is effective in first-line treatment in patients affected by metastatic NSCLC harboring an EGFR mutation. Erl is also approved in the subsequent lines of therapy regardless of EGFR mutational status, although its use is debated in patients with NSCLC EGFR WT. In a retrospective clinical study, we previously demonstrated that EGFR overexpression is associated with a remarkable effectiveness of Erl in second line therapy after a platinum-based treatment in patients with NSCLC EGFR wt. The aim of this *in vitro* study is to investigate whether the exposure to Cisplatin (CDDP) may result in EGFR overexpression, thus determining the acquisition of sensitivity to Erl.
Materials and Methods: We used two EGFR-WT cell lines (A549 and H460) and two EGFR-MT cell lines (H1650 and HCC4006). For each cell line we assessed the sensitivity to CDDP and to Erl performing a MTT-test and the expression of EGFR, pEGFR, c-MET, IGF1-R using PCR and Western Blot.
Results: Among the EGFR WT cell lines, H460 resulted sensitive to CDDP and resistant to Erl. This cell line was subsequently made resistant to CDDP by a continuous exposure to increasing concentrations of the cytotoxic agent (CR-H460). A new MTT-test was then performed on CR-H460, confirming the acquisition of resistance to CDDP and sensitivity to Erl (OR: H460-CR vs H460 0.44, 95% CI 0.27–0.71, $p < 0.001$). CR-H460 showed an increased EGFR and pEGFR mRNA and protein expression compared to the parental cell line (OR: H460 vs H460-CR, 95% CI 3.87–9.30, $p < 0.001$). This increased EGFR expression in H460-CR correlated with the increase of sensitivity to Erl ($r -0.957$, r^2 0.916, $p = 0.043$).
Conclusions: Our *in vitro* model suggests that Erl efficacy in patients affected by NCSCLC EGFR wild-type and previously treated with chemotherapy may be related to the induction of EGFR expression subsequent to the exposure to platinum derivatives. Therefore, a new evaluation of EGFR and pEGFR expression after first-line platinum-based therapy could be a predictor of response to Erl in clinical practice.
No conflict of interest.

702 POSTER

Endoxifen and fulvestrant regulate gene expression of estrogen receptor alpha and its co-activators DEADbox5 and 17

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Background: Application of anti-estrogens remains a standard approach as endocrine treatment of erstrogen-receptor alpha (ERα) -positive breast cancer. ERα antagonists trigger a competitive blockade of the receptor. Tamoxifen, with its active metabolite endoxifen, acts as a selective receptor down-modulator (SERM) by inhibition of activating function 1 (AF-1) of ERα. Fulvestrant acts as a selective receptor down-regulator (SERD) via an increased ERα degradation created by inhibition of both ERα activating functions (AF-1, AF-2). In some cases, both active agents show an inefficacy by lack of the expected therapeutic effects or therapy-resistance occurs due to gain of ERα-independency accompanying tumor progression. The two RNA helicases p68 (DEADbox5, DDX5) and p72 (DEADbox17; DDX17) act as co-activators of several tumor-associated proteins, such as ERα. Overexpression of both factors could be demonstrated in various malignant tumors. DDX17 expression correlates to decreased Her2/neu levels, extended relapse-free periods, and an increase in overall survival rates. In contrast, DDX5 expression is associated with increased Her2/neu levels and higher tumor grading, but no correlation with relapse-free or overall survival became significant so far. This study aimed for the investigation of potential regulatory effects of endoxifen and fulvestrant on the expression of ERα and its co-activators DDX5 and 17.
Material and Methods: Four ERα-positive and one ERα-negative breast cancer cell line underwent 24 hrs treatment with endoxifen or fulvestrant, respectively, mimicking therapeutic concentrations. In parallel, a negative control, treated with solvent DMSO only, was included in analysis. mRNA and protein levels of ERα, DDX5 and DDX17 were analyzed by RT-PCR and Western blot.
Results: Both ERα antagonists created a significant decrease of mRNA and protein expression levels of all target genes. DDX5 and 17 expression levels generally decreased, whereat endoxifen treatment triggered a stronger effect than fulvestrant. While both ERα antagonists caused a uniform decrease in ERα protein levels, DDX protein levels were differentially affected. Fulvestrant triggered a uniform downregulation of DDX5 and 17. In contrast, endoxifen stimulation resulted in an up-regulation of DDX5 and 17 protein levels in some ERα-positive cell lines.
Conclusion: Both ERα antagonists show regulatory effects on ERα, DDX5 and 17 mRNA and protein expression. However, differing effects could be observed on protein levels in different cell lines. The obtained *in vitro* data might explain individual therapeutic efficacy or the occurrence of resistance against endocrine therapy dependent on cellular context. Furthermore, the elucidation of DDX status might serve as a useful prognostic tool to estimate efficacy of anti-estrogen treatment in breast cancer therapy.
No conflict of interest.

703 POSTER

Monitoring cancer treatment responses using cancer-testis antigen microarrays

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Background: There is increasing evidence that the aberrant expression of cancer-testis (CT) antigens − a family of approximately 150 proteins that are both (auto)immunogenic and overexpressed in tumours in various types of human cancers − makes them potentially attractive immunotherapy targets, as well as possible cancer diagnostic markers. More specifically, since none of the CT antigens appear to be cell surface antigens, they are currently considered potential cancer vaccine targets rather than targets for antibody-based therapy. The underlying hypothesis of our study is that there are measurable differences in autoantibody repertoires between pre- and post-vaccinated cancer patient samples, potentially augmented by prior chemo- or radiotherapy, which will correlate with likelihood of response of individual patients to a given therapeutic treatment.
Material and Methods: A novel protein microarray platform containing 123 cancer antigens of interest was developed, optimised and tested, with the intent of allowing the quantification of broad cancer-related autoantibody profiles of cancer patient serum samples collected pre- and post-vaccination, chemotherapy or radiotherapy, and to correlate that data with patient responder phenotypes (Ethical consent: LICR HREC number 2003/01660, UCT HREC number 240/2011). An efficient bioinformatic pipeline of data extraction, filtering, graphing and analysis was also developed, as a means to facilitate and automate processing and analysis of the large volumes of generated microarray data.
Results: Using our CT antigen microarray platform, we have developed a robust, sensitive, high-throughput and highly multiplexed means to assay patient autoimmune responses to an experimental treatment. Our data suggests a limit of detection of 10–100pg/ml − which is competitive with Luminex assays − as well as linearity over 3 orders of magnitude, which is strongly encouraging for future quantitative analyses. Using this platform in preliminary assays on a cohort of melanoma patient sera, we have observed robust, reproducible and relevant patient autoimmune profiles.
Conclusions: A glimpse of the clinical utility of our new array tool is evident, with possible applications in monitoring therapeutic responses to an experimental treatment. However, studies involving larger patient cohorts are necessary to explore these preliminary results in more depth.
No conflict of interest.

704 POSTER

Predictive efficacy of low burden EGFR mutation detected by next-generation sequencing on response to EGFR TKIs in non-small-cell lung carcinoma

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Background: Direct sequencing is the standard method for the detection of epidermal growth factor receptor (EGFR) mutations in lung cancer; however, its relatively low sensitivity limits its clinical use. Therefore, this study was conducted to investigate sensitivity of PNA-LNA PCR clamp and Ion Torrent PGM compared to direct sequencing and predictive value of those sequencing techniques for EGFR-TKI efficacy.
Material and Methods: EGFR mutational status were assessed by direct sequencing, PNA-LNA PCR clamp and Ion Torrent PGM in 57 NSCLC patients who undergone lung resection. We evaluated predictive efficacy of PNA-LNA PCR clamp on the EGFR-TKI treatment in 36 patients with advanced NSCLC retrospectively.
Results: Compared to direct sequencing (16/57, 28.1%), PNA LNA PCR clamp (27/57, 47.4%) and Ion Torrent PGM (26/57, 45.6%) detected more EGFR mutations. Among the EGFR mutant patients from PNA-LNA PCR clamp, EGFR mutant patients had significantly longer PFS (14.31 vs. 21.61 months, P = 0.003) than EGFR wild patients. However, there was no difference in response rate (75.0% vs. 82.4%, P = 0.195), overall survival (34.39 vs. 44.10 months, P = 0.422) between EGFR mutant by direct sequencing and PNA-LNA PCR clamp.
Conclusions: Our results demonstrate firstly that patients with EGFR mutations were detected more sensitively by PNA-LNA PCR clamp and Ion Torrent PGM than direct sequencing. EGFR mutations detected by PNA-LNA PCR clamp may be as a predicative factor for EGFR TKI response in NSCLC patients.
No conflict of interest.

705 POSTER

Angiogenic marker associated with resistance to neoadjuvant chemoradiotherapy in rectal cancer

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Purposes: The ability to achieve pathologic down staging after neoadjuvant chemoradiotherapy (CRT) is correlated with improved survival. However, there is no effective method of predicting which patients will response to neoadjuvant CRT. Neoadjuvant CRT can change the expression of angiogenic factors. However, little is known about its possible changes in response to preoperative CRT. We examined the expression of angiogenic factors in rectal cancer tissues before preoperative CRT and after surgery.
Materials and Method: Fifty five patients with locally advanced rectal cancer were studied. All patients were given preoperative CRT of 5040 cGy for 5−6 weeks with concurrent administration of 5-fluorouracil and leucovorin. Surgical resection was performed 6−8 weeks later in all patients. Immunohistochemical staining for angiogenenic markers (vascular endothelial growth factor [VEGF], placenta growth factor [PLGF], hypoxia inducible factor 1α [HIF 1α], stromal cell derived factor [SDF 1α]) were performed on specimens obtained before preoperative CRT and after surgery. A semiquantitative-immunohistochemical score established from the extension and intensity of the angiogenic factors was used for analysis.
Results: The positive expression rate of VEGF, PLGF, SDF 1α, and HIF 1α was 56.4% (31/55), 65.5% (36/55), 70.9% (39/55), and 47.3% (26/55), respectively. The expression rate of VEGF, PLGF, SDF 1α, and HIF 1α was increased by 3.6% (2/55), 7.3% (4/55), 30.9% (17/55), and 1.8% (1/55)

after neoadjuvant CRT, respectively. Expression of VEGF, PLGF, and HIF 1α protein was downregulated after neoadjuvant CRT in the rectal cancer tissues (P <0.001, P = 0.001, P = 0.044, respectively). However, SDF 1α was upregulated after neoadjuvant CRT (P <0.001). And also, upregulated expression of SDF 1α after neoadjuvant CRT was significantly associated with resistance to CRT (P = 0.035). However, SDF 1α showed no correlation with other clinical factors (age, sex, clinical stage).
Conclusion: Expression of SDF-1α was increased in the rectal cancer tissue after neoadjuvant CRT, as well as has been associated with CRT resistance. Our data suggests that SDF 1α should be evaluated as new target for antiangiogenic therapy.
No conflict of interest.

706 POSTER

Differential molecular analysis of non small cell lung cancer by laser capture microdissection of formalin-fixed, paraffin-embedded tissue

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Background: The introduction of molecular analysis and targeted therapy significantly improved the therapy of lung cancer. In the targeted treatment of lung cancer, monoclonal antibodies such as cetuximab and small molecules such as iressa have shown to be effective subtypes of lung cancer harboring certain molecular characteristics. The predictive biomarkers for the effectiveness of these therapies are mutations in the corresponding targets or in pathway related molecules. In order to accurately determine the molecular signatures of a histological heterogeneous cancer such as lung cancer, microdissection of tumor tissue compartments is mandatory to reveal tumor specific alterations. However, the recovery of good quality RNA from FFPE sections can be challenging due to fixation processes.
Material and Methods: The protocol for Laser Capture Microdissection was implemented on an Axiovert 200/PALM R MICROBEAM IV instrument. Slides were deparaffinized and stained with cresyl violet to enable a betterevaluation of cell morphology. Tumor areas of a homogenous cell type as well as stromal areas were microdissected. RNA as well as DNA was isolated from these different compartments using the Qiagen Allprep Kit and quality control was performed using the Agilent 2100 bioanalyzer. Isolated DNA was used for mutation analysis of hot spot regions of three clinical relevant genes: KRAS, BRAF, and EGFR.
Results: In this study, we have successfully isolated tumor and stromal compartments from five formalin fixed and paraffin embedded NSCLC biospecimen. Total RNA was extracted with overall yields ranging from 1.0 to 279 ng. Extracted RNA was suitable for subsequent RT-PCR. Furthermore, hot spots regions of three genes KRAS, BRAF, and EGFR have been successfully sequenced even with very small amounts of extracted DNA of less than 1 ng. Therein, an EGFR mutation was detected in case 2 and a KRAS mutation in case 3. Mutations were only found in microdissected tumor samples and not in stromal samples, confirming the accuracy of microdissection.
Conclusion: Human tissues, in particular, tumor tissues, are complex structures composed of heterogeneous mixtures of morphologically and functionally distinct cell types. The described workflow is suitable for preparing RNA and DNA from very small amounts of microdissected FFPE tissue samples of <2 mm^2 in sufficient quality and quantity for further applications such as mutation analyses and RT-PCR for gene expression analysis.
No conflict of interest.

707 POSTER

HPV16 detection in HNSCC and correlation with p16 expression and overall survival

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Background: We sought to determine the presence of Human papillomavirus type 16 (HPV16) in tumor samples from patients (pts) with locally advanced HNSCC through E1, E6 and L1 viral fragments detection.
Our aim was to establish their prognostic role in oropharynx tumors (OT) and in non-OT, then to correlate positive (pos) or negative (neg) samples for each fragment with p16 expression.
Materials and Methods: We analyzed 206 samples (OT/non-OT: 66/140) from pts treated with CRT between 1997 and 2011 (175M/31F; median age 59.6, range 20.6–85.6).
E1, E6 and L1 fragments were detected by PCR on DNA extracted from PFFE tissues using specific primer pairs; DNA of pos and neg control cell lines was added at each session. Amplicons were visualized on 2% agarose gel. p16 expression was analysed by IHC.
Results: Although we found a different % of pos samples for each fragment studied, OT showed, overall, a significantly higher % of pos samples vs non-OT: E1 pos was 19.7% in OT and 4.3% in non-OT (p < 0.001), while E6 pos was 68.2% in OT and 50.7% in non-OT (p = 0.02) and L1 was pos 45.5% in OT and 20.7% in non-OT (P < 0.001).
When PCR positivity was correlated to OS, we observed a significant correlation in the OT population with E1 (p = 0.016; median OS = 161.8 in pos *vs* 15 months in neg).
Neither E1 in non-OT (p = 0.145) nor E6 nor L1 in OT and non-OT (p = 0.189 in OT and p = 0.242 in non-OT for E6; p = 0.426 in OT and p = 0.97 in non-OT for L1) reached any difference in overall survival (OS).
p16 pos was 68% in OT and 50% in non-OT (p < 0.007). We have previously demonstrated that p16 high positivity (>50%) confers a survival advantage in patients with OT, while in the non-OT the same pos values correlate with a non significant negative prognostic effect.
A significant correlation between E1 pos samples and p16 high expression was found in OT (p < 0.001). This correlation was not seen in non-OT with E1 neither with E6 nor L1 in the whole population. We identified 3 OT pts E1 pos but p16 neg and 35 pts E1 neg but p16 pos. Analysis of OS suggested E1 pos to be a stronger prognostic marker in OT then p16 pos (p = 0.005).
Conclusions:
1. E1 positivity by PCR may be of clinical relevance in OT. Discrepancies seen with E6 and L1 should be further investigated considering the biological cycle of HPV16.
2. E1 positivity has an even stronger effect as p16 high pos (>50%) in OT. Moreover, where both determinations were not consistent, E1 positivity seems to correlate with OS better than p16.

No conflict of interest.

708 POSTER

Wiskott-Aldrich Syndrome protein (WASP) and WASP interacting protein (WIP) are tumor suppressor in ALK-mediated lymphomagenesis

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Background: Anaplastic Large Cell Lymphoma (ALCL) is a T-cell lymphoma that frequently carries the t(2;5) translocation that fuses the ALK gene to Nucleophosmin (NPM1) gene. NPM-ALK transforms lymphocytes by inducing different signaling pathways that control cell proliferation and survival.
Material and Methods: We performed gene expression profiling (GEP) analysis on different lymphomas samples and immunohistochemistry with WASP and WIP antibodies on human samples of ALK+ALCL. To investigate signaling, we infected ALK+ ALCL cell lines (TS and SU-DHL1) with a specific shRNA against ALK and against Stat3 or CEBP/β. To measure WIP and WASP mRNA and protein levels, we used qRT-PCR and western blot analysis, respectively. Finally, we crossed mice deficient for WASP or WIP gene ($WASP^{-/-}$ or $WIP^{-/-}$) or conditionally deficient for Cdc42 (Cdc42f/f) with NPM-ALK Tg mice to check for lymphoma development and overall survival.
Results: ALK+ ALCL had significantly lower expression of WIP and WASP proteins than normal T cells or other T cell lymphomas, as determined by GEP, immunohistochemistry and WB on cell lines and primary tumor samples. In ALK+ ALCL cell lines, we demonstrated that ALK inhibition resulted in up-regulation of WIP and WASP, thus indicating that ALK directly repressed WIP and WASP expression. Such regulation was dependent on a Stat3 and CEBP/β-mediated transcriptional repression.
In mouse models, we showed that WASP protein levels were strongly reduced in lymphomas from NPM-ALK Tg/$WIP^{-/-}$ mice. Remarkably, WIP and WASP worked as tumor suppressors, as either $WASP^{-/-}$ or $WIP^{-/-}$ backgrounds significantly accelerated NPM-ALK lymphomagenesis. Haploinsufficiency of Cdc42 in NPM-ALK Tg/ $WASP^{-/-}$/$Cdc42^{f/-}$ mice restored normal lymphoma incidence, thus suggesting that WASP deficiency accelerated lymphomagenesis by deregulating downstream Cdc42 activity.
Conclusions: In the present study we demonstrated that the expression levels of WASP and WIP are down-regulated by oncogenic ALK in lymphoma. Remarkably, reduced levels of WASP and WIP have key roles in lymphomagenesis as they accelerate NPM-ALK lymphoma progression in *in vivo* mouse models. Thus, for the first time we demonstrate WASP and WIP as tumor suppressors in lymphoma. Our data implicate that lymphoma arising in Wiskott-Aldrich syndrome (WAS) patients, where WASP function

is impaired, could be better explained by an intrinsic tumor suppressor function of WASP rather than a general immunosuppression of the patients.
No conflict of interest.

709 POSTER

Bevacizumab exposure is accompanied by EGFR activation in colorectal cancer (CRC) models providing a rationale for combinations of bevacizumab and erlotinib in the GERCOR DREAM phase III trial

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Background: Combinations of EGFR and VEGF(R)-targeted agents have consistently shown at least additive activity in preclinical CRC models when the targeted agents were administered alone (*Larsen et al., Pharmacol Therap 131:80, 2011; Poindessous et al., Clin Cancer Res 17:6522, 2011*) paving the way for the GERCOR DREAM-OPTIMOX3 phase III trial, an optimized chemotherapy + bevacizumab strategy ± erlotinib in metastatic CRC patients (*Tournigand et al., ASCO 2012, A 3500*). Currently, the mechanistic basis for the additive activities of the two types of targeted agents is not well understood. Although use of EGFR-directed mAbs are counter-indicated in CRC patients with mutant *KRAS*, the situation is less clear for EGFR-targeted TKIs like erlotinib.
Material and Methods: Three human CRC xenograft models expressing wt *KRAS*/*BRAF*, mutant *KRAS* or mutant *BRAF* were established in nude mice. Animals were treated with bevacizumab and erlotinib, alone or in combination, and the influence on tumor growth, viability and the presence of phosphorylated ErbB/HER family members was determined. Treatment-related toxicity was estimated by weight loss.
Results: Combinations of bevacizumab and erlotinib were significantly more active than either agent alone for all three xenograft models although the advantage of combining the two agents was particularly striking for the *KRAS*/*BRAF* wt xenograft model. Unexpectedly, erlotinib alone showed strong antitumor activity in the *BRAF* mutant HT-29 xenograft model. The bevacizumab plus erlotinib combination was less toxic, as determined by weight loss, compared to erlotinib alone. Interestingly, IHC analysis showed that bevacizumab activates EGFR in all three xenograft models which is attenuated in the presence of erlotinib. Erlotinib also attenuates the active phosphorylated form of HER3/ErbB3, in particular when combined with bevacizumab.
Conclusions: We here report that bevacizumab and erlotinib combinations are significantly more active than either agent alone in CRC models with different *KRAS* and *BRAF* status. We further demonstrate that bevacizumab activates EGFR signaling similar to what has been described for irinotecan and ionizing radiation. Although bevacizumab selectively recognizes human VEGF, this is unlikely to influence our findings, since murine VEGF is believed to play a relatively minor role in CRC xenograft models. Taken together, our findings suggest that mutant *KRAS* and *BRAF* have lesser influence on the sensitivity to EGFR-targeted TKIs than is the case for the anti-EGFR mAbs and provide a mechanistic basis for the increased activity of the bevacizumab and erlotinib combination.
Conflict of interest: *Advisory board: AdG. Corporate-sponsored research: AKL, CT, TA, AdG. Other substantive relationships: AS*

710 POSTER

DOK7 expression in colorectal cancer cells and association with patient survival

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Background: The downstream of tyrosine kinase (DOK) protein family is presently known to have seven members, so called DOK1−7. The precise role of the DOK proteins is not entirely clear; some authors have suggested a potential tumour suppressor role for these proteins whilst others have shown an association between expression of these proteins and cell migration. Our study aimed to determine the expression profile of DOK7 in human colorectal cancer cell lines and its association with clinical and prognostic outcome.
Material and Methods: Three human colorectal cancer cell lines (HRT18, HT115 and RKO) were analysed using polymerase chain reaction (PCR) to determine DOK7 expression. Primary colorectal cancer tissue collected at operation from 94 patients was examined by a consultant pathologist. Anti-DOK7 transgenes and expression constructs for human DOK7 were prepared and used for transfection and creation of sublines with differential expression of DOK7. Frozen sections of each tissue sample were used to extract RNA and this was used to generate cDNA which was analysed using quantitative transcript analysis to determine DOK7 expression. Patients were routinely followed up clinically and radiologically after surgery and the median follow up period was 65 months. The expression profile was then analysed against the clinical, pathological and outcome data.
Results: DOK7 transcript expression was highly positive in HRT18 cells. HT115 and RKO cells on the other hand were negative for DOK7 expression. Knockdown in HRT18 cells (HRT18$^{\Delta DOK7}$) resulted in reduced expression of DOK7. The reduction of DOK7 in the cells resulted in a reduced rate of growth compared to wild-type cells and those transfected with control vector. Analysis of clinical data revealed that DOK7 expression was significantly negatively correlated with grade of tumour differentiation, TNM stage and Dukes stage. Furthermore, DOK7 expression was inversely correlated with patient survival ($p = 0.011$).
Conclusions: DOK7 expression was higher in non-aggressive tumour cells (HRT18) compared with aggressive tumour cells (HT115). However, DOK7 expression was also found to be negatively associated with patient survival suggesting a diverse role for this protein in malignant tumours. Further work is necessary to further elucidate the effect of DOK7 expression on cell function and cell migration response to mitogens and motogens.
No conflict of interest.

711 POSTER

In vitro studies on irradiation and Akt inhibition in human malignant glioma

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Background: Glioblastoma multiforme (GBM) is the most common, invasive and deadly primary type of malignant brain tumor. The Phosphatidylinositol-3-Kinase-Akt pathway is commonly overexpressed in GBM and has been associated with resistance to therapy. The aim of the study was to investigate the cytotoxic and radiosensitizing effects of the Akt inhibitor MK-2206 on human malignant glioma cells and spheroids in vitro.
Materials and Methods: Experiments were performed on a panel of five GBM cell lines (U251, T98, D384, U87, VU122). Cells were treated with the allosteric Akt inhibitor MK-2206 alone and in combination with irradiation (0−8 Gy). Endpoints: cell survival (clonogenic assay), cell invasion (transwell Boyden chamber technique) and expression of the proteins PTEN, Akt and pAkt (Western blot). U87 multicellular spheroids were analysed in a growth − volume − assay following the combination treatment of MK-2206 (1microM), fractionated irradiation (5 x 2 Gy) and repeated administration of temozolomide (TMZ; 5 x 5microM).
Results: MK-2206 reduced the expression of the phospho-Akt key protein of the PI3Kinase-Akt pathway. The drug was cytotoxic for all glioma cells in the dose range between 1 and 10mM for 24 hours, but no radiosensitizing effect was found on clonogenic cell survival. The invasion capacity was assessed at doses between 1 and 10 microM MK-2206 for 16 hours. A dose-dependent inhibition of invasion was observed for all but one of the cell lines. Irradiation (4 Gy) alone increased the expression of pAkt, which was inhibited (30min, 1 h, 2 h and 4 h) following pre-incubation with MK-2206 (1microM and 10microM for 1 h). When the drug was administered additional to irradiation, a further inhibition of cell migration and invasion was observed, which was not found after irradiation alone. The radio-enhancing effect of MK-2206 was most pronounced in inhibition of the growth of glioma spheroids in the fractionated irradiation regimen.
Conclusion: Targeting of the PI3K-Akt pathway enhanced the effect of radiation and TMZ in a series of *in vitro* assays, in particular regarding cell invasion and migration, and on spheroid growth. Taken together, Akt pathway inhibition yields promising perspective in the therapy of GBM patients.
No conflict of interest.

712 POSTER

Smads expression is changed following receptor-like protein tyrosine phosphatase kappa (PTPRK) knockdown in prostate cancer cell

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Background: Smad-dependent pathway is part of TGF-β pathway which regulates different cell function such as proliferation, adhesion and migration. Recently, it has been reported that PTPRK is up-regulated by TGF-β and is probably involved in TGF-β dependent anti-proliferation and migration effects in keratinocyte. Furthermore, PTPRK has been indicated as a potential tumour suppressor in primary central nervous system lymphomas. Our recent works have shown certain implications of PTPRK in both breast cancer and prostate cancer. However, the role played by PTPRK in the Smad dependent signalling and the influence on epithelial mesenchymal transition (EMT) of prostate cancer cells remains largely unknown. Present study aimed to study the effect of PTPRK knockdown on Smad signalling and EMT of prostate cancer cells.
Material and Methods: Ribozyme transgenes were constructed to knock-down PTPRK expression in PC3 cells, following verification of the knockdown was carried out using RT-PCR, real time q-PCR and Western blot. The expression of Smads and relevant EMT markers have been assessed using both PCR and Western blots.
Results: Knockdown of PTPRK resulted in alterations of SMADs expression. SMAD1 and SMAD3 expression were significant decreased at both mRNA and protein levels following PTPRK knockdown; nevertheless, SMAD4 expression was increased at both mRNA and protein levels. Other Smads expression was not affected by the PTPRK knockdown. Furthermore, expression of Snail and Slug were reduced in PTPRK knockdown cells; however, there were no effects on other EMT markers including uPA and Vimentin.
Conclusions: Knockdown of PTPRK can reciprocally regulate the expression of certain Smads in prostate cancer cells and may be involved in the EMT triggered by Smad signaling. However, the underlying mechanism is yet to be investigated.
No conflict of interest.

713 POSTER

Association between c-Met and lymphangiogenic factors in patients with colorectal cancer

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Background: Lymphangiogenesis plays an important role in cancer metastasis. Although animal models show a strong relationship between lymphangiogenesis and lymph node metastasis and survival, the clinical significance of lymphangiogenesis in colorectal cancer (CRC) remains uncertain. The goal of this study was to evaluate the association between c-Met and lymphangiogenic factors and to elucidate their prognostic significance for patients with CRC.
Methods: A total of 379 tissue samples were obtained from surgically resected specimens from patients with CRC in Soonchunhyang University Cheonan Hospital between January 2002 and December 2010. The expressions of c-Met, vascular endothelial growth factor (VEGF)-C, VEGF-D, VEGF receptor (VEGFR)-3, and podoplanin were examined by immunohistochemistry. The expression of each marker and clinical factors were analyzed.
Results: Three hundred and one of 379 (79.4%) tissues had c-Met expression. High expression of c-Met in tumor cells was significantly associated with high expression of VEGF-C ($P < 0.01$) and VEGFR-3 ($P = 0.01$). But, there was no statistically significant association with podoplanin (P =. 587) and VEGF-D ($P = 0.96$). Of the 103 evaluable patients, expression of c-Met in tumor cells was significantly associated with advanced clinical stage ($P = 0.20$), positive lymph node status ($P = 0.38$), and high expression of VEGF-C ($P = 0.20$). But, there was no statistically significant association with podoplanin (P =. 518), VEGFR-3 ($P = 0.85$), VEGF-D (P =. 203), and overall survival (P =. 360).
Conclusion: Our results provide indirect evidence for an association and possible regulatory link of c-Met with the lymphangiogenic factors. But, c-Met expression in patients with CRC are not prognostic indicator for overall survival in this retrospective study.
No conflict of interest.

714 POSTER

Improving cell based models through viral vector technology − chances for target research and screening approaches

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Overexpression (Oex) and knockdown (KD) studies are indispensable tools for basic and clinical research in functional genomics and target research. Here, we demonstrate a systematic method for generation of cell models with near perfect inducible KD rates.
Commercially available and in-house platforms for inducible RNAi were compared and a screening platform for highly active shRNAs developed. The screening platform was adapted to both, RNA Polymerase III- and RNA Polymerase II-dependent shRNA expression. Our fine-tuned combination of shRNA validation and viral vector design enable us to translate high knockdown rates (near 100%) into stable cell lines as well as primary cells, even in inducible systems.
These novel cell systems are likely to leverage cell-based models for target research and screening applications. As a case study we present the potent, inducible knockdown of a G-protein coupled receptor in HEK293 cells.
No conflict of interest.

715 POSTER

MAPK and PI3K activation in esophageal carcinomas

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Background: MAPK (Mitogen-Activated Protein Kinase) and PI3K (Phosphatidyloinositol 3- kinase) pathways play significant role in cell survival and have been implicated in various types of cancer including esophageal carcinomas (EC). The aim of our study was to investigate the possible prognostic significance of MAPK and PI3K pathways in EC in the Greek population.
Material and Methods: Forty four samples from patients with EC were screened for the presence of activating mutations at exons 18, 19, 20, 21 of EGFR gene, codons 12 and 13 of K-RAS gene, exon 15 of B-RAF gene, exons 9 and 20 of PIK3CA gene as well as exon 4 of AKT1 gene by High Resolution Melting Analysis and Pyrosequencing. In 29 cases immunohistochemistry was performed in order to evaluate expression levels of pERK (Extracellular − signal Regulated Kinase) and pAKT.
Results: The analysis of genomic DNA from 44 esophageal samples revealed no mutation in the examined genes except of a somatic K-RAS mutation at codon 12, which was detected in one laser microdissected squamous cell carcinoma. Elevated nuclear as well as cytoplasmic pERK (100% and 62% of cases) and pAKT (90.5% and 52% of cases) expressions were observed. Increasing pERK nuclear and cytoplasmic expression along with the intensity of nuclear staining was found to be significantly correlated with tumor grade in univariate and multivariate statistical analysis. In adenocarcinomas subgroup pAKT cytoplasmic expression was negatively correlated with stage.
Conclusions: Our current study demonstrates the presence of activated ERK and AKT despite the absence of upstream alterations (except one K-RAS mutation). ERK activation is a rather late event, contributing to the acquisition of a more aggressive phenotype in esophageal cancer while AKT activation appears more crucial during early stages in esophageal adenocarcinomas.
No conflict of interest.

716 POSTER

Tumor infiltrating B cells in primary cutaneous T-cell lymphomas correlate with disease progression and might represent a potential target for therapy

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B cells have been recently described to mediate tumor biology but so far their role as tumor promoting or tumor repressing lymphocyte population remains controversial. Mycosis fungoides (MF) and other primary cutaneous T cell lymphomas (CTCL) are characterized by an indolent course in early stages. However, advanced stage MF (⩾ EORTC Stage IIB) and the follicular MF subtype (FMF) as well as Sézary syndrome

(SS) show a more aggressive pattern with a median survival of less than two years. The pathogenesis of these more aggressive courses is still incompletely understood. Anecdotal reports have previously described CD20 positive cells in CTCL but further characterization of these cells have not been performed. We systematically analyzed the B cell infiltrate in paraffin samples of CTCL patients by immunohistochemistry (CD20 and CD79a) and correlated these data with the stage, subtype and clinical course. Advanced stage MF, FMF and SS samples contained significantly increased numbers of infiltrating B cells per lymphoma infiltrate. Moreover, time to progression showed a significant inverse relationship with the density of the B cell infiltrate. Based on our results, we hypothesized that infiltrating B cells might be a therapeutic target. In a 77-year old patient suffering from advanced stage FMF with a significant B-cell infiltration and progression after standard treatments, intralesional B-cell depletion with the anti-CD20 monoclonal antibody rituximab resulted in a sustained local tumor regression. In summary, we present first evidence on the potential tumor promoting role of infiltrating B cells in CTCL which warrants further study as a potential therapeutic strategy.
No conflict of interest.

717 POSTER

Spontaneous canine mast cell tumour as a model to study the correlations between infiltrating c-Kit positive cells and angiogenesis: possible translation for human cancer

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Background: Canine cutaneous mast cell tumour (CMCT) is a c-Kit driven tumour that share similar c-Kit mutations found in human Gastro-Intestinal Stromal Tumour (GIST) and other human malignancies. CMCT is a common cutaneous tumour in dog, with an higher incidence than in human. It is classified in three subgroups, well and intermediately differentiated (G1 and G2), corresponding to a benign disease, and poorly differentiated (G3), corresponding to a malignant disease which metastasize to lymph nodes, liver, spleen and bone marrow.
Materials and Methods: In this study, we have evaluated c-Kit expression status, microvascular density (MVD), mast cell granulated and degranulated status density (MCGD and MCDD) and in a series of 97 CMCTs and we have correlated these parameters each to other, by means of histochemistry, immunohistochemistry double staining and image analysis system.
Results: Date show that diffuse cytoplasmic and focal paranuclear (Golgi-like) immunostaining c-Kit expression correlates with high MVD, G3 histopathological grade and MCDD. On the other hand, cell membrane c-Kit expression status correlates with low MVD, G1-G2 histopathological grade and MCGD.
Conclusion: We suggest that these findings may play a role as highlight the key role of c-Kit in the biopathology of canine MCTs indicating a link between aberrant c-Kit expression, increased angiogenesis and higher histopathological grade. Finally CMCT seems to be a useful model to study the role of c-Kit activated MCs in tumour angiogenesis and inhibition of MCs degranulation or activation by mean of novel c-Kit tyrosine kinase inhibitors might be a useful anti-tumour and anti-angiogenic strategy worthy to further investigations.
No conflict of interest.

718 POSTER

Continuous low-dose topotecan treatment selectively induces premature senescence in MYCN-amplified neuroblastoma cells in vitro and in vivo

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Recurrent disease is a major challenge in high-risk neuroblastoma (NB), demanding new strategies for consolidation treatment. Previous reports have indicated that DNA-damage inducing drugs trigger a cellular program called premature senescence, a state of proliferative arrest, assumed to limit tumor growth *in vitro* and *in vivo*. We have shown that continuous, low-dose treatment with the chemotherapeutic drug hydroxyurea (HU) leads to senescence in primary NB-cell lines *in vitro*. In this study, we have explored, whether senescence can be induced by other low-dose chemotherapeutic drugs in primary *MYCN*-amplified NB-cell lines and in a xenograft mouse model and whether this will limit tumor growth and aggressiveness.
We found that camptothecin (CPT), a topoisomerase I-inhibitor, triggered apoptosis and senescence within 2−3 weeks when added to cultured primary NB-cells at a low concentration of 3−5 nM. CPT-treated NB-cells were G1/0-arrested and stained positive for the senescence-associated-beta-galactosidase. Importantly, HU- and CPT-treated senescent cells secreted less angiogenesis-, metastasis- and inflammation-associated factors, such as VEGF, MMP-9 and MCP-3, compared to the positive control, BrdU-treated NB-cells. However, HU- and CPT-treated cells expressed the favorable CD44, MHCI and activating NK/NKT-cell receptor ligands, which are absent on non-treated cells. For confirmation *in vivo*, topotecan (TPT), a CPT derivative, was injected i.p. at a clinically low dose of 0.1 mg/kg/d over 2 weeks daily in xeno-transplanted nude mice. Preliminary data suggest a higher frequency of senescent tumor cells, a reduction of tumor size and vascularization in TPT-treated mice. Furthermore, analysis of the gene expression profile of 3 CTRL and 3 TPT-treated tumors, revealed up-regulation of p21, CD44 − both up-regulated in senescent NB-cells *in vitro* - and ATRX, which has been associated with favorable outcome in NB patients. These *in vitro* and *in vivo* studies shall enable future clinical application of tumor cell senescence as therapeutic strategy.
No conflict of interest.

Proffered Papers Session (Mon, 30 Sep)
Drug Development

800 ORAL

A phase 1 study of S-222611, an oral reversible dual tyrosine kinase inhibitor of EGFR and HER2, in patients with solid tumours

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Background: S-222611 is a novel, oral, reversible tyrosine kinase inhibitor of EGFR, HER2 and HER4 with potent and long lasting *in vitro* and *in vivo* pre-clinical activity. A dose-escalation study in patients (pts) has been completed and an expansion phase is on-going.
Material and Methods: Doses from 100 to 1600 mg daily were tested in the dose escalation in previously treated pts with solid tumours expressing EGFR or HER2 with expansion in selected tumours at 800 mg. Pharmacokinetics (PK) and pharmacodynamic assessment of serial tumour biopsies, were included. Responses (RECIST) were assessed by imaging at 8-week intervals.
Results: A total of 33 patients (24 male; aged 25−80 y) were included in the dose-escalation. S-222611 was generally well tolerated with two dose-limiting toxicities (rash at 1200 mg; diarrhoea at 1600 mg). A maximum tolerated dose was not defined. To date 17 patients (6 male; aged 32−75 y) have been included in the expansion phase. Diarrhoea was the most frequent toxicity in the 50 pts, but was rarely worse than grade 1/2. Nausea, rash, anorexia, vomiting and fatigue were also seen. Bilirubin rises with normal transaminases were observed.
Plasma concentrations increased with dose up to 800 mg, which was selected for the expansion. Steady state values of C_{max} and AUC_{0-24} at this dose are in the effective range of concentrations in mouse models. Average $t_{1/2}$ of 33 h is consistent with once daily dosing.
Tumour responses were seen over the full dose range tested (100–1600 mg). Of the 50 treated pts, there were 10 tumour responses, of which one was a clinical complete response (a pt with HER2 positive breast carcinoma previously treated with trastuzumab and lapatinib), 3 were partial responses (PRs) confirmed on repeat scans 2 months later, and 6 were unconfirmed PRs. The confirmed PRs were in HER2 positive breast and EGFR positive renal and oesophageal tumours and the 6 unconfirmed PRs were in breast and oesophageal tumours. An additional 3 pts with vaginal, pancreatic and gastric tumours showed stable disease for $\geqslant$26 weeks. Four pts have received treatment for more than 80 weeks.
Conflict of interest: *Other substantive relationships: Donaldson, Posner and Kawabata are all employees of Shionogi Ltd. Other authors have received funding to cover clinical trials costs only*

Table (abstract 801).

	CAP	TAB		TAB			
	400 mg BID (cont)	400 mg BID (cont)	300 mg BID (cont)	200 mg TID (cont)	250 mg TID (int)	400 mg BID (int)	400 mg QD (cont)
Evaluable for safety, n	18*	17*	18*	16	15	16	15
Grade ⩾3 events, n (%)							
Anaemia	4 (22)	5 (29)	4 (22)	1 (6)	1 (7)	0	1 (7)
Vomiting	1 (6)	0	0	2 (13)	0	1 (6)	0
Dose modifications, n (%)							
Reductions	3 (17)	11 (65)	4 (22)	2 (13)	2 (13)	4 (27)	2 (13)
Interruptions	6 (33)	10 (59)	8 (44)	10 (63)	8 (53)	10 (67)	5 (33)
Evaluable for antitumour effect, n	20[†]		13	15	14	16	15
Least-squares mean change in tumour size at wk 8,[‡] %	−19.0	NA[§]	−19.9	−14.4	−5.4	−14.7	−3.3

*Includes ovarian and breast cancer pts with a germline *BRCA1/2* mutation.
[†]Includes pts from a second previously reported group.
[‡]Adjusted for baseline characteristics; [§]Dose not considered tolerable in a prior data review so analysis of antitumour effect not performed

801 ORAL

Administration of continuous/intermittent olaparib in ovarian cancer patients with a germline BRCA1/2 mutation to determine an optimal dosing schedule for the tablet formulation

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Background: Initial studies with the oral PARP inhibitor olaparib identified 400 mg BID as a tolerable and efficacious dose requiring 16 capsules (CAP)/day. We report final results of a study aimed at identifying an optimal dose of the more practical tablet (TAB) formulation, for which we previously reported a dose-response relationship. An expansion cohort was recruited to this multistage Phase I trial to evaluate alternative administration schedules (NCT00777582; sponsor, AstraZeneca).
Materials and Methods: In this expansion cohort, patients (pts) with *BRCA1/2* mutation and relapsed ovarian or primary peritoneal cancer were randomized 1:1:1:1 to one of two continuous (cont; 200 mg TID, 400 mg QD) or two intermittent (int; 250 mg TID: 2 wks on/1 wk off; 400 mg BID: 1 wk on/1 wk off) schedules. Primary objective was safety and tolerability. Secondary objectives included antitumour effect. Results were compared with previously reported groups receiving 400 mg CAP BID, 400 mg TAB BID or 300 mg TAB BID (all cont; Molife *et al* ASCO 2010, 2012).
Results: 62 patients were randomized. Median lines of prior chemotherapy was 3 (range: 1−11). 6 pts (10%) discontinued treatment due to toxicity. The table shows key safety and antitumour effect data.
Conclusions: 400 mg BID TAB (int and cont) were not considered tolerable for long-term use. 250 mg TID (int) and 400 mg QD (cont) failed to match the efficacy seen in prior cohorts. 200 mg TID did not improve tolerability vs 300 mg BID, so 300 mg BID (cont) is the recommended tablet dose for Phase III studies in *BRCA1/2*-mutant ovarian cancer, including the maintenance therapy setting. These findings simplify olaparib administration from 16 CAP to 4 TAB per day.
Conflict of interest: *Ownership: A. Fielding & K. Bowen are employees of AstraZeneca and own AstraZeneca stock. Advisory board: C. Gourley has been a consultant for Roche, Boehringer-Ingelheim, Schering-Plough, GlaxoSmithKline and Chugai. Corporate-sponsored research: C. Gourley has received research funding from AstraZeneca. Other substantive relationships: C. Gourley has received honoraria and other remuneration from Roche, Boehringer-Ingelheim, Schering-Plough, GlaxoSmithKline,Chugai and Pharma-Mar*

802 ORAL

MEDI4736, an anti-PD-L1 antibody with modified Fc domain: Preclinical evaluation and early clinical results from a phase 1 study in patients with advanced solid tumors

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Background: Tumors can evade immune detection by expressing the programmed cell death ligand 1 (PD-L1). Blockade of PD-L1 may help overcome immunosuppressive effects and restore T-cell activity against tumors. In nonclinical experiments, inhibition of PD-L1 was shown to produce durable antitumor activity as a single agent and in combination with other therapies. MEDI4736, a human monoclonal antibody that binds specifically to PD-L1, was engineered with a triple mutation in the Fc domain to abrogate Fc-mediated effector function, and is currently being evaluated in Phase 1 studies.
Materials and Methods: The properties of MEDI4736 were determined via *in vitro* assays, and anti-mouse PD-L1 was used in murine models of cancer to explore pharmacodynamic markers and combinations with other therapies. An ongoing Phase 1, multicenter, open-label study is evaluating the safety profile, pharmacokinetics, biomarkers, and antitumor activity of MEDI4736 administered IV in subjects with advanced solid tumors.
Results: MEDI4736 demonstrated potent and specific binding to PD-L1 with picomolar affinity. It blocks the interaction of PD-L1 with PD-1 and CD80 resulting in increased T-cell activation *in vitro*, but does not trigger cytokine release in whole blood assays. Three point mutations in the Fc domain have abrogated Fc-mediated effector function *in vitro*. Treatment of tumor-bearing mice with anti-mouse PD-L1 resulted in changes in peripheral immune markers and antitumor responses in a subset of mice. The combination of anti-mouse PD-L1 and CTLA-4 antibodies significantly enhanced this activity, leading to tumor regression in all mice treated.
As of 15 April, preliminary results from the Phase 1 study include 8 subjects (med. age 65 yrs, range 46−71), ECOG 0−1, with a median of 4 (3−10) prior treatments, received a median of 6 doses (1−13) of MEDI4736. No dose limiting toxicitites or drug-related grade ⩾3 adverse events were reported (no pneumonitis or colitis of any grade). An early signal of clinical activity was observed as evidenced by RECIST-based responses and prolonged disease stabilization in different tumor types, including patients with extensive disease. Tumor shrinkage was observed as early as 7 weeks and was sustained at subsequent time points.
Conclusions: Preliminary safety and clinical activity data for MEDI4736 are encouraging at the initial dose levels explored and warrant further investigation of this molecule alone and in combination with other therapies.
Conflict of interest: *Corporate-sponsored research: MedImmune sponsored the study. SK, JL, NS, SA, JW are investigators and received research funding for the conduct of the study. ABH, RS, PR, AS, RI are employees of MedImmune. Other substantive relationships: ABH, RS, PR, AS, RI own stock/stock options in Astrazeneca*

803 ORAL

Evaluation of tolerability and anti-tumor activity of GDC-0980, an oral PI3K/mTOR inhibitor, administered to patients with advanced solid tumors or non-Hodgkin's lymphoma (NHL)

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Background: The PI3K-AKT-mTOR signaling pathway is dysregulated in a wide variety of cancers. GDC-0980 is a potent and selective oral dual inhibitor of class I PI3K and mTOR kinases that demonstrates broad activity in various xenograft cancer models.
Materials and Methods: A phase I dose-escalation study, PIM4604g, was conducted in 2 Stages: Stage 1 evaluated oral, daily (QD) doses of 2−70 mg GDC-0980 in a 3+3 design. Stage 2 evaluated 30 mg and 40 mg GDC-0980 QD. Safety and tolerability of GDC-0980 was assessed, as well as pharmacokinetics (including proton pump inhibitor (PPI) interaction), pharmacodynamic (PD) assessment of PI3K pathway inhibition and PIK3CA mutations, and anti-tumor activity.
Results: 113 patients were enrolled, 57 in Stage 1 and 56 in Stage 2. The MTD was 50 mg QD. DLTs were Grade 3 rash and symptomatic Grade 3 hyperglycemia at 70 mg QD. Grade $\geqslant$3 pneumonitis was observed in 3 patients in Stage 1 at doses of $\geqslant$40 mg, including 1 mesothelioma patient with Grade 5 pneumonitis. Based on Stage 1 tolerability data, a recommended phase 2 dose of 40 mg QD was evaluated in Stage 2 for all tumor types, with the exception of malignant pleural mesothelioma (MPM) where the recommended dose was 30 mg QD. The most frequent Grade $\geqslant$3 drug-related adverse events (AEs) at 30 mg and 40 mg GDC-0980 were hyperglycemia (15%), rash (12%), diarrhea (8%) fatigue and abnormal LFTs (7%), and pneumonitis (6%), and 17% of the patients discontinued due to an AE (4% at 30 mg, 24% at 40 mg). The exposure of GDC-0980 was dose-proportional and no interaction with the PPI rabeprazole was detected at 40 mg GDC-0980. RECIST anti-tumor activity was observed in Stage 1 at GDC-0980 doses of 8−50 mg, with 2 PRs (MPM patients, 1 at 50 mg and 1 with a PIK3CA mutation at 8 mg). At the recommended phase 2 dose, 2 PRs for MPM patients at 30 mg and 1 PR for a head and neck cancer patient with a PIK3CA mutation at 40 mg were observed. GDC-0980 doses of $\geqslant$16 mg demonstrated significant PI3K pathway inhibition (pAKT and insulin/glucose levels). Additionally, pathway inhibition by FDG-PET responses was observed in 50% of the patients.
Conclusions: GDC-0980 was generally well-tolerated at the recommended phase 2 doses of 30 mg and 40 mg. Significant PI3K pathway inhibition was observed in PD assays at doses of $\geqslant$16 mg. Anti-tumor activity has been observed at the recommended phase 2 doses. Updated data on clinical outcomes and biomarker correlates will be presented.
Conflict of interest: *Ownership: Genentech, Roche. Advisory board: Genentech, Roche. Board of directors: none. Corporate-sponsored research: Genentech, Roche. Other substantive relationships: Advisor: GSK, AstraZeneca, Pfizer, Exelixis, Merck, Novartis, Arno Therapeutics*

804 ORAL

Phase Ib study of oral pan-PI3K BKM120 in combination with the oral MEK1/2 inhibitor GSK120212 in patients with selected advanced solid tumors and RAS / BRAF mutations

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Background: MAPK and PI3K/AKT/mTOR pathways regulate proliferation, differentiation and cell death in different human cancers. A cross-talk interaction between these two pathways provides the rationale for combining PI3K and MEK inhibitors.
Methods: Primary objective of this phase Ib trial is to determine the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) for daily oral administration of the PI3K inhibitor BKM120 with the MEK inhibitor GSK1120212. Secondary objectives include safety, tolerability, pharmacokinetics and efficacy.
In dose escalation part, patients (pts) with *RAS*/*BRAF* mutated (mt) solid tumors, pancreatic cancer or triple negative breast cancers were enrolled. A Bayesian logistic regression model with overdose control guided dose escalation was utilized. In dose expansion part, pts with RAS/BRAF mt ovarian, pancreatic and non-small cell lung cancer (NSCLC) were enrolled.
Results: As of June 2012, 75 pts were treated with BKM120 + GSK1120212 and have been evaluated for safety, 66 in dose escalation and 9 in dose expansion part. The MTD was reached at 70 mg BKM120 + 1.5 mg GSK1120212. The dose was later reduced due to adverse events (AEs) to 60 mg BKM120 + 1.5 mg GSK1120212, the RP2D. Most frequent AEs (>25%) irrespective of relationship, were diarrhea (60%), dermatitis acneiform (57%), nausea (42%), vomiting, CK elevation (39% each), asthenia (33%), reduced appetite (31%), pyrexia, stomatitis (29% each), maculopapular rash (27%), hyperglycemia and rash (25% each). The most common grade 3/4 AEs (>5%) irrespective of relationship were CK elevation, maculo-papular rash (12% each), ALT increase (9%), AST increase, thrombocytopenia (8% each), stomatitis (7%), diarrhea, acneiform rash, macular rash and acute renal failure (5% each). No deaths were related to treatment. 28 (37%) pts had treatment discontinuation and 48 (64%) dose reductions/delays dues to AEs. As of February 2013, 21 KRAS/ BRAF mt ovarian cancer pts have been treated and 19 were evaluable ($\geqslant$1 post-treatment tumor assessment) for response. 7/19 (37%) evaluable pts achieved a best overall response (BOR) of partial response (confirmed in 6 of them) and 9 had a stable disease (SD). 19/24 pancreatic pts were evaluable for efficacy and 12/19 achieved a BOR of SD. For the 17 NSCLC pats, 11 pts were evaluable and 7 had a BOR of SD.
Conclusions: BKM120 and GSK1120212 can be safely combined. Promising clinical activity has been observed in pts with KRAS/BRAF mt ovarian cancer.
Conflict of interest: *Ownership: GlaxoSmithKline (Le). Advisory board: Trovagene (Janku), Novartis (Bedard). Corporate-sponsored research: Novartis (Janku), Roche (Janku), Transgenomic (Janku), Biocartis (Janku) Trovagene (Janku), Novartis (Bedard), GlaxoSmithKline (Bedard) Research funding paid by novartis to institution (Van Cutsem). Other substantive relationships: Speaker at ECC 2013 * travel covered by meeting organizers (Bedard) Novartis employee and stock owner (Zubel)GSK employee and a GSK stock owner (Le)*

805 ORAL

Final results of a first-in-human clinical trial of OSI-027, a small molecule dual mTORC1/mTORC2 inhibitor in patients with advanced malignancies

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Background: OSI-027 is an orally available selective inhibitor of mTORC1 and mTORC2. We report a phase I trial to evaluate its safety, tolerability, pharmacokinetics (PK), maximum tolerated dose (MTD) and pharmacodynamics (PD) in tumor and surrogate tissues. (NCT00698243; sponsor Astellas Pharma Inc).
Material and Methods: Patients (pts) with refractory malignancies, ECOG performance status $\leqslant$2 and adequate organ function were enrolled in one of 3 administration schedules (S); S1: once daily for 3 of every 7 days (qd 3/7d), S2: once weekly (qwk) or S3: continuous qd, in 21-day cycles. Dose limiting toxicities (DLT) were assessed in cycle 1 (CTCAE v3). Dose escalation was pursued for each schedule with a 3+3 design. Safety and PK were studied after single and multiple dosing. PD analyses were performed in expansion cohorts using paired pre/post-dose tumor biopsies.
Results: 123 pts were treated (S1−54pts, S2−39pts, S3−30pts). Main tumor types were colorectal (n = 32), melanoma (12) and renal (11). Doses ranged from 10–480 mg per week (S1:10–160 mg qd 3/7d; S2:10–240 mg qwk; S3:5−50 mg qd). DLTs were grade (G) 3 fatigue (n = 4), G2 elevated

serum creatinine (2), G3 cardiomyopathy (1), G2 decreased left ventricular ejection fraction (1), G3 hyperglycemia (1), G3 rash (1) and G3 bone pain (1). The MTD for S1 is 120 mg qd 3/7d. Dose escalation in S2 was limited due to high burden of capsules required; no MTD was identified. The MTD for continuous dosing (S3) is 35 mg qd; however, schedule was halted due to renal toxicity, showing insufficient PD inhibition at tolerable dose-levels. G $\geqslant$3 adverse events (AE) included G3 fatigue (n = 6), G3 diarrhea (2), G3 nausea/vomiting (2), G4 myocardial infarction (1) and G5 acute renal failure (1). Expansion cohorts were initiated for S1 at 90 mg and 120 mg based on safety data. 5/13 (38%) pts in S1–120 mg required a dose-reduction or discontinuation due to AE. C_{max} and AUC were dose-linear. PD inhibition was associated with drug exposure, with the most substantial inhibition in tumor biopsies seen at the highest doses. Stable disease (RECIST 1.0) after 24 weeks was seen in 5 pts, including 1 pt with GIST (exons 11 and 17 KIT mut) who was on treatment 45 weeks.
Conclusions: OSI-027 inhibits mTORC1/2 in a dose-dependent manner. The most significant AEs were fatigue, renal and cardiac events. Intermittent schedules were better tolerated. S1–120 mg qd 3/7d achieved substantial target inhibition but was not tolerated by a proportion of patients.
No conflict of interest.

Poster Session (Sun, 29 Sep)
Drug Development

806 POSTER

A new approach to integrate the grade of toxicity and later cycles in the analysis and reporting of phase I dose finding trials

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Background: In oncology, the maximum tolerated dose (MTD) is commonly defined as the dose of a given treatment associated with a certain level of dose limiting toxicities (DLT), evaluated during a predefined time window, typically one or two cycles of treatment. Adverse events (AE) are usually assessed sequentially, using NCI-CTCAE grading criteria. Our working hypothesis is that the longitudinal assessment of AEs can provide relevant additional information for defining the optimal dose and schedule of a new treatment. To illustrate our approach, we retrospectively reanalysed three phase I clinical trials of anticancer agents.
Material and Methods: We developed a new dose-finding method that uses all the data collected at the end of the trials. A mixed effect proportional odds model was used to account for repeated measurements. We collected individual patient data from two continual reassessment method phase I clinical trials (aviscumine in solid tumours and erlotinib with radiotherapy in brainstem gliomas). A third trial was included (classical 3+3 design of DoxLipeg + cyclophosphamide in ovarian carcinoma). The outcome of interest was the worst grade (G) of toxicity in each cycle, using three grading categories (G0−1/G2/G3−5). We estimated the probability of G2−5 and G3−5 toxicity per cycle for each evaluated dose level. We defined the dose associated with a per cycle probability of severe toxicity close to 20% as the recommended phase II dose. The risk of toxicity over time was also investigated.
Results: In the three trials a total of 83 patients were included and treated at 14, 3 and 5 dose levels, respectively. In the first two trials, four and two DLT occurred respectively; 94 and 96 cycles were administered (worst grade: 38 G2, 22 G3 AEs; 19 G2, 7 G3−5 AEs, respectively). No increased risk of toxicity was detected with time for the first two trials. We could not disentangle late toxic AEs from cumulative AEs as time is confounded with cumulative dose. The per cycle risk of G3−5 toxicity was slightly lower with the mixed effect proportional odds model analysis, as compared to an analysis restricted to the first cycle. Analysis of the third trial is in process.
Conclusions: Dedicated methods, whose operating characteristics were evaluated elsewhere, allows for analysing toxic adverse events from all cycles of treatment. They should be integrated in recommended phase II dose assessment.
No conflict of interest.

807 POSTER

Investigating the antiproliferative activity of high affinity DNA aptamer on cancer cells

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Background: The purpose of the study is to investigate the antiproliferative activity of SL_2-B aptamer on cancer cells.
Materials and Methods: *Surface plasmon resonance (SPR)*: The binding affinity of SL_2-B aptamer sequence was investigated using SPR, where $VEGF_{165}$ acted as ligand. The binding analysis was carried out with aptamers at different concentrations and sensorgrams were analysed in BIAevaluation software to calculate the equilibrium dissociation constant K_d.
Antiproliferative activity: SL_2-B aptamer was incubated with Hep G2 cells for 3 days in hypoxia conditions. The antiproliferative effect was determined using MTT assay. For flow cytometry, after 3 days of aptamer treatment, the cells were incubated with anti-human Jagged-1 fluorescein antibody for 1 hr and analysed using flow cytometry.
Results: *Binding analysis by SPR*: Due to presence of nucleases, the unmodified aptamer exhibits low structural stability in the cellular conditions. To alleviate this problem, the SL_2-B aptamer was chemically modified with phosphorothioate (PS) linkages at 5′ and 3′-terminus. The K_d value for the PS-modified SL_2-B was found to be 0.56nM, which is similar to K_d for unmodified. Introducing PS-modification does not appear to affect the binding affinity of the aptamer.
Antiproliferative activity: Lower cell proliferation was observed at 15μM modified SL_2-B concentration after 72 hrs of aptamer treatment (52±2.1%). On the contrary, the unmodified sequence did not exhibit significant inhibitory activity on cellular proliferation. This could be due to the degradation of the unmodified sequence by nuclease enzymes in the media before pronouncing its effect. The incubation of cells with scrambled sequence showed minimal decrease on the cell proliferation, confirming that the inhibitory effect by modified SL_2-B was sequence specific. Due to the crosstalk between VEGF and notch signalling pathways in tumour progression, the effect of PS-modified SL_2-B aptamer was tested on Jagged-1, which is one of the notch ligands via flow cytometry. Compared to the untreated sample, modified SL_2-B exhibited decrease in the fluorescent signal indicating the downregulation of Jagged-1 expression in Hep G2 cells. In western blotting, the modified aptamer appears to induce lower expression of the Jagged-1 protein in Hep G2 cells as compared to the scrambled sequence. This confirms the sequence specific inhibition of the aptamer. Based on these results, it can be concluded that the binding of modified SL_2-B to VEGF exhibits its antiproliferative activity in Hep G2 cells not only by inhibiting VEGF pathway but also the interconnected notch signalling pathway.
Conclusions: From the data, we conclude that post-modification, the PS-modified SL_2-B aptamer retained its binding affinity and exhibited sequence specific antiproliferative activity on Hep G2 cancer cells. Hence, it appears that chemical modification can be a useful approach in prolonging the half-life of SL_2-B aptamer in the *in vitro* conditions.
No conflict of interest.

808 POSTER

Capillary morphogenesis gene 2 is a potential target for anti-angiogenic therapy

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Background: Capillary morphogenesis gene 2 (CMG2) was identified as a gene being up-regulated in capillary morphogenesis. It is also known as a receptor of anthrax toxin. It has been shown to be involved in the cell adhesion and motility of various cell types, including epithelia and endothelia. Present study aims to examine to investigate the therapeutic potential of targeting CMG2 to prevent tumour related new vasculature.
Materials and Methods: Full-length of human CMG2 gene and different fragments of the same gene were amplified and constructed into a mammalian expression plasmid vector. The effect of CMG2 and its different fragmented protein products on functions of vascular endothelial cells was examined using various *in vitro* and *ex vivo* angiogenesis models, and *in*

vivo tumour growth which including tubule formation of endothelial cells, aorta ring assay and xenograft mouse model.
Results: The overexpression of CMG2 enhanced the adhesion of endothelial cells to extracellular matrix, but was negatively associated with cell migration. Over-expression of certain fragments (extracellular domains) inhibited the tubule formation and migration of endothelial cells. Small peptides mimicking the amino acid sequence of the fragments potently inhibit the *in vitro* tubule formation and *ex vivo* angiogenesis. Tests of certain small peptides showed an inhibitory effect on in vivo tumour growth of cancer cells which we have examined.
Conclusion: CMG2 is a potential target for treating tumour related angiogenesis. Small peptides mimicking the extracellular domain of CMG2 can potently inhibit the in vitro and ex vivo angiogenesis, which may contribute to its inhibitory effect on in vivo tumour growth. The mechanisms underlying require further investigation.
No conflict of interest.

809 POSTER

Safety and efficacy of bevacizumab as front-line treatment of brain metastases from solid tumors

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Background: B is approved for the treatment of advanced colorectal, lung, kidney, breast cancers and high-grade gliomas. Despite the large employment of B in the treatment of brain primitive tumors, there is only a very limited experience with BM and none in the treatment of previously untreated secondary brain lesions.
Material and Methods: We have treated the patients (PTS) with BM not suitable for local treatment with a B-based therapy associated with chemotherapy or INF-alfa as indicated for the primary cancer type.
Results: From March 2010 to June 2012 we collected 18 PTS with BM mostly from lung and renal adenocarcinoma and the majority of patients had a treatment-naive brain disease (see table). B has proved to be safe and effective: RR was 82% of PR with 18% of SD. PFS was 14 months (95% CI: 3.0–25.0) and OS was 15 months (95% CI: 3.7–26.3). Moreover, B has a high capability to give clinical benefit in PTS with BM, mostly reducing perilesional edema, sometimes with a long lasting effect. The general toxicity we detected was the same as known in clinical practice: no cerebral hemorrhagic events were reported, even if two cases of cerebral ischemia and 1 of gastric perforation were recorded.
Conclusion: B for BM is feasible and safe and the efficacy data are very promising.
No conflict of interest.

Pt no.	Gender/Age/ Primary tumor	Prior therapy for brain mts	Treatment	CNS response	Extra-CNS response	PFS	OS
1	Fe/62/NSCLC	None	Bev+Cis+Gem	Near CR	PR	31.1+	31.1+
2	Ma/41/NSCLC	None	Bev+Cis+Gem	SD	SD	11.4	15.9
3	Ma/70/kidney	NSurg	Beva+Inf-alfa	CR	PD	18.4+	18.4+
4	Fe/58/lung	None	Bev+Cis+Gem	PR	PR	0.9+	3.6
5	Ma/56/kidney	None	Beva+Inf-alfa	PR	PR	20.3	33.2
6	Ma/73/kidney	SRS	Beva+Inf-alfa	PR	PR	20.7+	20.7+
7	Ma/71/Kidney	None	Beva+Inf-alfa	SD	SD	6.5	12.3
8	Ma/69/NSCLC	None	Bev+Cis+Gem	SD	PD	7.6+	8.2
9	Ma/65/NSCLC	None	Bev+Cis+Gem	SD	PD	1.9	3
10	Ma/70/lung	WBRT	Bev+Cis+Gem	SD	PD	6.8	9.6
11	Ma/50/NSCLC	None	Bev+Cis+Gem	SD	PR	7.2+	9.9
12	Ma/67/NSCLC	None	Bev+Cis+Gem	PR	PR	14.6+	14.6+
13	Fe/75/NSCLC	None	Bev+Cis+Gem	PR	PR	9.6+	9.6+
14	Ma/67/NSCLC	None	Bev+Cis+Gem	PR	PR	8.2+	8.2+
15	Fe/67/endometrial ca	None	Bev+Cis+Gem	PR	PR	17.7+	17.7+

SRS: sereotactic surgery; WBRT: whole brain radiotherapy; NSurg: neurosurgery; Bev: bevacizumab; Cis: cisplatin; Gem: gemcitabine; Inf-alfa: interferon-alfa.

810 POSTER

Phase 1b study of multiple dosing schedules of pazopanib in combination with epirubicin or doxorubicin in patients with advanced solid tumors

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Background: Pazopanib (PAZ) is an oral, multitargeted inhibitor of VEGFR-1/2/3, PDGFR-α/β, and c-Kit. Optimal dose and schedule for combining PAZ with epirubicin (EPI) and doxorubicin (DOX) need to be established.
Methods: Part 1 of the VEG109603 trial explored PAZ+EPI in dose-escalation cohorts to define the optimally tolerated regimen (OTR) for 3 concomitant dosing schedules (21-day [d] cycles): Arm A (PAZ d1−21, EPI d3); Arm B (PAZ d1−8, EPI d3); Arm C (PAZ d14−21, EPI d1). The OTR of each schedule was further evaluated in 3 concomitant cohorts of up to 12 patients (pts) to select the regimen for Part 2, which combined PAZ+DOX (Arm D) based on safety and tolerability results. Blood samples were obtained for pharmacokinetic and pharmacodynamic analysis.
Results: Overall, 111 pts were treated, including 65 pts in the OTR cohorts. The OTRs were PAZ 400 mg/EPI 75 mg/m^2 (Arm A), PAZ 800 mg/EPI 90 mg/m^2 (Arms B and C). Dose-limiting toxicities (DLTs) were evaluated during the first and subsequent cycles to assess prolonged feasibility. In the dose-escalation cohorts, DLTs included grade (Gr)4 neutropenia, Gr3 nausea/vomiting/dehydration, and Gr3 deep vein thrombosis. In the PAZ+EPI OTR cohorts, DLTs included Gr4 neutropenia, Gr4 pulmonary thrombosis, and Gr4 febrile neutropenia. The most common adverse events (AEs; any Gr) in all cohorts were neutropenia, nausea, and asthenia, and the most common Gr⩾3 AEs were neutropenia and leukopenia. Tolerability of PAZ+EPI worsened with repeated doses. Based on the safety profile of Part 1, the Arm B dosing schedule was selected for PAZ+DOX in Part 2, which defined the OTR as PAZ 800 mg/DOX 60 mg/m^2. DLTs in Arm D included Gr4 neutropenia, Gr5 febrile neutropenia, and Gr1 LVEF decrease. Neutropenia and leukopenia were the most common Gr⩾3 AEs.
Pharmacokinetic analysis showed that EPI may increase exposure to PAZ ($AUC_{(0-24)}$ and C_{max} were ~18% greater when PAZ was administered concomitantly with EPI in Arm A). PAZ did not significantly interfere with EPI disposition. In the PAZ+EPI OTR cohorts, 11 evaluable pts had best response as partial response: 2 (13%) in Arm A; 3 (16%) in Arm B; and 6 (38%) in Arm C. In the PAZ+DOX OTR cohort (Arm D), there was 1 complete (7%) and 1 partial response (7%).
Conclusions: The OTRs of PAZ+EPI and PAZ+DOX were PAZ 800 mg d1−8 plus EPI 90 mg/m^2 or DOX 60 mg/m^2 d3 of a 21-d cycle. These regimens showed an acceptable safety profile and should be considered for further evaluation.
Sponsor: GlaxoSmithKline.
Conflict of interest: *Ownership: (BS + HT) GlaxoSmithKline stock ownership. Advisory board: (LG) Roche, Genentech, GSK, Novartis, Pfizer, Boehringer Ingelheim, Astra Zeneca, Celgene, BioScience, Tahio (KH) Stemergie Biotechnology. Board of directors: (LG) Roche, Genentech, GSK, Novartis, Pfizer, Boehringer Ingelheim, Astra Zeneca, Celgene, BioScience, Tahio. Corporate-sponsored research: (LG) Roche, Genentech, GSK, Novartis, Pfizer, Boehringer Ingelheim, Astra Zeneca, Celgene, BioScience, Tahio (KH) will have in the second half of 2013 by Servier. Other substantive relationships: (BS + HT) Employed by GlaxoSmithKline*

811 POSTER

Omega-3 polyunsaturated fatty acids-derived drugs as potential anti-angiogenic treatment for solid tumours

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Background: Polyunsaturated fatty acids (PUFA) can be divided into n-6 and n-3 PUFA depending on the position of the first double bond. Although n-3 PUFAs are found to be cancer-suppressing, n-6 PUFAs are disease-promoting. Mechanisms of such effects are still unknown. Both n-3 and n-6 PUFA undergo bio-conversion by two major enzymes: cyclooxygenases and cytochrome P-450s. Potential reason for different activity of n-3 and n-6 PUFA-derived metabolites could be related to the observed conformational differences between these two fatty acid types and mediators derived from them.
Angiogenesis (creation of new blood vessels from the existing vasculature) is very important process in tumour growth. In this work we have assessed effects of two major classes of n-3 PUFA metabolites: a) cyclooxygenase-2 (COX-2)-derived and b) cytochrome P-450, subgroup 2J2 (CYP2J2)-derived products. PUFA products of these two enzymes have been implicated in regulation of angiogenesis.
Material and Methods: Four types of MDA-MB-468 (human breast cancer cells) clones were constructed by permanent transfection with either control or plasmids expressing COX-2, CYP2J2 or both. These clones were incubated with n-3 PUFA (Eicosapentaenoic acid) and medium or extract from these cells was tested for suppression of two angiogenic processes *in vitro* using human umbilical vein endothelial cells (HUVEC): 1) Tube formation assay and 2) Migration assay. Tube formation assay consisted of observing formation of vascular precursors or 'tubes' after plating HUVEC on the layer of artificial extracellular matrix (Matrigel). HUVEC migration was investigated using our unique 'Matrigel droplet' assay.
Results: Our findings suggest that both types of mediators derived from n-3 PUFA inhibit angiogenesis. COX-derived metabolites suppress both EC

migration and tube formation whereas CYP2J2-derived mediators suppress only tube formation.
Conclusions: Our results provide evidence that both COX-2 and CYP2J2 derived n-3 PUFA metabolites suppress angiogenesis *in vitro* and new molecules derived from them could serve as future anti-cancer therapeutics.
No conflict of interest.

812 POSTER

Phase 1 dose-escalation study of E7820, a novel anti-angiogenic agent, administered orally twice-daily to patients with advanced, refractory solid tumors

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Background: E7820 is a novel sulfonamide derivative with potent anti-angiogenic activity based on the inhibition of endothelial cell proliferation and tube formation. The antitumor effects of E7820 were associated with inhibition of integrin alpha2 expression in endothelial cells *in vitro*. E7820 MTD for single daily administration was achieved at 100 mg. PK/PD analysis integrating preclinical and clinical data showed that twice-daily (BID) dosing results in a greater reduction of integrin alpha2 expression. BID dosing may also ameliorate toxicity associated with high maximum plasma concentration (Cmax) and may allow a greater total daily dose and drug exposure. This Phase 1 study was performed to determine MTD, safety and PK of E7820 following BID dosing.
Patients and Methods: Patients (pts) with advanced solid tumors, ECOG 0−1, ⩾18 years (yrs) and adequate organ function were eligible. E7820 was administered orally, BID continuously in 28 day cycles. Blood samples for PK analysis were collected on Day 1 and Day 8 over 12 hr post dose.
Results: 24 pts (M/F: 18/6; median age 57 yrs (range 38−77) were treated at 50 and 60 mg. Tumor types were colorectal (n = 8), renal (n = 3), GIST (n = 2), and others (n = 11). DLTs were observed in 2 pts at 60 mg BID and included Gr 3−4 leukopenia, Gr 3 neutropenia and neutropenic sepsis and Gr 3 fatigue. MTD was determined to be 50 mg BID. Frequently occurring adverse events ([AEs] all grades with ⩾10% incidence) were fatigue (42%), constipation (33%), diarrhea, nausea and vomiting (29% each), abdominal pain (25%) and dyspepsia (17%). E7820 exposure was dose-related with Cmax observed 0.5−5 hr post-dose. BID E7820 dosing resulted in 1.6−3.8 fold accumulation on multiple dosing. The highest E7820 exposure and highest accumulation (R=3.31, 3.38) was observed on day 8 in subjects who experienced DLTs. Cmax values in patients who had DLTs were comparable to those in other subjects in this dose cohort. The best overall response observed was stable disease.
Conclusions: E7820 at an MTD of 50 mg BID has manageable toxicity. DLTs were associated with high E7820 exposure, but not with Cmax. Twice-daily dosing of E7820 does not appear to offer a better toxicity profile compared to daily administration.
Conflict of interest: *Other substantive relationships: Eisai employees: L. Reyderman, B. de las Heras, D. Verbel, B Ink.*

813 POSTER

Allosteric inhibition of FGFR2 affects angiogenesis and cancer cell proliferation

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Background: The recent identification of fibroblast growth factor receptor 2 (FGFR2) overexpression or mutations in different cancer types has generated an opportunity for a novel target-based therapy. Here we explore the effects of allosteric inhibition of FGFR2 on angiogenesis and cancer cell proliferation.
Material and Methods: To assess the efficacy of RPT835, novel extracellular allosteric inhibitor of FGFR2 (RusPharmTech, LLC) on FGF-mediated cell proliferation, endothelial cells (SVEC-4−10), human umbilical vein endothelial cells (HUVEC), and breast cancer (T47D), gastric cancer (Kato III), lung cancer (A549) FGFR-expressing cells were incubated in a 96-well microculture plate and were treated with serially diluted RPT835. Brivanib was used as a control. Basic FGF was added at a concentration of 25 ng/ml. Control wells were left untreated. Cell growth inhibition was determined using Promega's Cell Titer-Glo® assay. SVEC-4−10 cell migration was evaluated in the Boyden Chamber assay. In vivo angiogenesis was measured with subcutaneously implanted Matrigel plugs containing bFGF (100 ng/ml) or bFGF (100 ng/ml) + RPT835 (15 mg/kg). Negative control group was without stimulation and treatment. Number of endothelial cells/vessels was calculated.
Results: Basic FGF significantly increased proliferation of the HUVEC, SVEC-4−10 and cancer cells in untreated control group (P = 0.001). RPT835 significantly inhibited FGF-triggered endothelial cell proliferation when compared with control (P<0.001) or brivanib (P<0.001, IC50=289 nmol/L) with IC50 of 11 nmol/L (HUVEC) and 10 nmol/L (SVEC-4−10). RPT835 significantly decreased proliferation of A549 (IC50=10 nmol/L) as well as T47D (IC50=0.97 umol/L) cells. There was no impact on Kato III cells (IC50 >10 umol/L). In Boyden Chamber assay, RPT835 reduced endothelial cell migration up to 60%. In vivo, bFGF induced proliferation of endotheliocytes and mature vessels formation (P<0.001). There were no vessels in FGFR2 inhibitor and negative control groups.
Conclusions: Allosteric inhibition of FGFR2 affects endothelial and cancer cell proliferation, migration as well as mature vessel formation.
No conflict of interest.

814 POSTER

The pterocarpanquinone LQB118 alters the subcellular localization of Nrf2 and reduces XIAP expression sensitizing acute myeloid leukemia cells to apoptosis

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Background: Despite advances in chemotherapy, the five-year survival rate for patients with acute myeloid leukemia (AML) is about 20%. There have been efforts in recent years to establish new antileukemic drugs with decreased side effects and lower toxicity to healthy cells of AML patients. Pterocarpanquinone LQB118 [2-hydroxy-3-(3-methyl-2-butenyl)-1,4-naphthoquinone] has emerged as a promising molecule for therapeutic applications. Recently, we have shown that LQB118 is effective in inducing apoptosis in cells from patients with AML and chronic myeloid leukemia (CML). Our partner group has shown that LQB118 increases the reactive oxygen species (ROS) levels in a leukemia cell line, suggesting a possible role of this pathway in its mechanism of action. Nrf2 is a transcription factor that controls the expression of various genes that encode proteins involved in detoxification, transport of xenobiotics, apoptosis inhibition, which are all involved in the response to oxidative/electrophilic stress to preserve cell life. XIAP is a member of the inhibitor of apoptosis family of proteins (IAP) which, in addition to being a caspase inhibitor, may be up-regulated under oxidative/electrophilic stress. Our objective is to elucidate the molecular mechanism of LQB118.
Material and Methods: The effect of LQB118 (3 and 6 μM) and idarubicin (0.01 μM), a chemotherapeutic agent used in AML therapy, on XIAP gene expression by real-time PCR and subcellular localization of Nrf2 transcription factor by immunofluorescence was evaluated in the AML cell line, Kasumi-1.
Results: In previously published reports, we have shown that LQB118 sensitizes Kasumi-1 cells to apoptosis and induces DNA fragmentation. XIAP mRNA expression was decreased by LQB118, whereas idarubicin increased said expression. Thus, after incubation with both concentrations of LQB118 for 24 and 48 h, the subcellular localization of Nrf2 was cytosolic as compared to untreated and also with idarubicin-treated Kasumi-1 cells, where Nrf2 localization was predominately nuclear.
Conclusions: In agreement with literature data, we found that a decrease in XIAP expression may contribute to sensitization of AML cells to ROS, after treatment with LQB118. In addition, Nrf2 cytosolic localization is a mechanism of maintenance of oxidative homeostasis, guaranteed by an efficient molecular complex. However, in AML there is constitutive nuclear activation of Nrf2, which contributes to the resistance to chemotherapy. Together, these findings may contribute to understand chemotherapy resistance in AML. Further investigation is currently in progress.
Financial support: Programa de Oncobiologia, INCT, FAPERJ, CNPq, Ministério da Saúde.
No conflict of interest.

815 POSTER

Antitumor activities and drug resistance overcoming of novel nogalamycins

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Background: *Streptomyces nogalater* Lv65 is a producer of an anticancer antibiotic nogalamycin. Its derivatives are used in chemotherapy of tumors. Certain aspects of the regulation of nogalamycin production have been characterized. However, most enzymatic reactions of nogalamycin biosynthesis have not been studied. The mechanisms controlling formation of the sugar moieties of nogalamycin and their enzymatic modification, particularly methylation, are not known.
Material and Methods: The anticancer activity of modificated nogalamicine was compared with doxorubicine after 72 h treatment in 12 cancer cell lines. To identify the alterations in cell cycle distribution induced by the nogalamicine, PI staining was performed. Changes in the expression levels of diverse cell regulatory proteins were investigated by Western Blotting.
Results: Bioinformatic analysis of the *snogM,* gene revealed that the product of these gene was involved in methylation of the nogalose moiety of nogalamycin. Disruption of the *snogM* gene in the chromosome of *S. nogalater* Lv65 resulted in *S. nogalater* strains ΔsnogM. The fact of gene disruption was confirmed by DNA−DNA hybridization. Inactivation of the *O*-methyltransferase genes had no affect on morphological features of the recombinant strains. One of the main goals of our work was also verify activity of this new modification of nogalamicine against several tumor cell lines. We have found that IC50 all used cell lines is between 4.3 nM (SW1573 lung adenocarcinoma cell line) and 15.21 nM (MCF-7 brest cancer cell line). By the way, the IC50 of famous anticancer drug doxorubicin is between 31.74 nM (SW1573 lung adenocarcinoma cell line) and 79.31 nM HCT116 p53 −/− human colorectal carcinoma cell line). Also nogalamicine was very efectiv against MRP1-overexpressing sublines HL60/adr and SW1573/2R120, which are srong resitence to the action of doxorubicine. Interesting, HCT116 cells with deleted p53 gene are almost 2 times more sensitive to the new nogalamicine as its wild type cell line. And in case of doxorubicine, human colorectal carcinoma HCT116 cells with deleted p53 −/− gene are more resistance, as its wild type cell line. This data show that such kind of modification of nogalamicine can be a new word in overcoming of p53 dependent drug resistance.
Conclusions: Genetic manipulations with the *snogM* gene of the nogalamycin biosynthetic gene cluster is a potentially valuable tool for generation of novel anthracycline antibiotics which can permit overcoming resistance of various human tumor cells.
This work was supported by WUBMRC grant (to D. Klymyshin and Y. Senkiv).
No conflict of interest.

816 POSTER

Trichosanthin, a type I ribosome-inactivating protein, inhibits lymphoma cell growth by promotion of apoptosis

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Background: Trichosanthin (TCS) is a 27 kDa type I ribosome-inactivating protein purified from the root tuber of a traditional Chinese medicine herb *Trichosanthes kirilowii*, which has been reported to have an anti-tumor activity. The aim of this study was to explore the growth inhibition effect of TCS on lymphoma cells and its possible mechanism. A total of 9 non-Hodgkin's lymphoma (NHL) cell lines were included in the experiment, including 5 diffuse large cell lymphoma (DLBCL) and 3 Burkkit lymphoma and one T cell lymphoma cell lines.
Methods: After different doses of TCS were added to the cultured cells, MTT assay, flow cytometry and Western blotting methods were used to investigate the effects and mechanism of TCS on the growth of lymphoma cells.
Results: The results showed that TCS could inhibit the proliferation of all NHL cells especially DLBCL cells. And the growth inhibition activity was associated with the expression levels of Mcl-1, Bcl-2 and Puma. Higher expression of Bcl-2 and Puma and lower expression of Mcl-2 were associated with higher efficacy. Flow cytometric analysis disclosed that TCS mainly induced apoptosis in those cell lines. Furthermore, the TCS-induced apoptosis was attributed to the activations of caspased-3 and PARP-1.
Conclusions: Therefore, TCS can inhibit NHL cell growth through inducing apoptosis, and the expression of Mcl-1, Bcl-2 and Puma maybe predicts its efficacy (JCYJ 20120613113228732, NSFC 81171154, GJHS 20120621153317134).
No conflict of interest.

817 POSTER

Autophagy modulation with mTOR inhibitor sirolimus and anti-EGFR monoclonal antibody cetuximab: phase I study in patients with advanced cancers

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Background: EGFR kinase activates PI3K/mTOR and MAPK pathways and EGFR nonkinase function is important for SGLT glucose transport. Preclinical data suggest that knocking down EGFR increases autophagy, which in combination with mTOR inhibition can lead to autophagic cell death. In addition, PI3K/mTOR activation can mediate resistance to EGFR targeting therapies, which can be abrogated by simultaneous mTOR inhibition.
Methods: Patients (pts) with refractory advanced cancers received IV cetuximab (day 1, 8, 15, 22) with oral sirolimus (day 1−28) in 28-day cycles. Doses were escalated in a 3+3 schema. Endpoints were maximum tolerated (MTD) or phase 2 recommended dose (RP2D), safety, response, and PD/PK analyses.
Results: To date, 112 pts were treated in 8 dose levels and 4 expansion cohorts at RP2D of sirolimus 6 mg and cetuximab 400 mg/m^2 followed by 250 mg/m^2 since MTD has not been reached. Dose limiting toxicities included grade (G) 3 mucositis (n = 3), and grade 4 thrombocytopenia with bleeding (n = 1). Other significant drug related toxicities included G3 mucositis (n = 1), G3 acneiform skin rash (n = 4), $\geqslant$ G3 hypersensitivity reaction (n = 3), G3 proteinuria (n = 1), G3 hyperglycemia (n = 1), G3 hyperlipidemia (n = 1), G4 lymphopenia (n = 5) and G4 thrombocytopenia (n = 3). Shrinkage per RECIST of more than 20% tumor was observed in 7 pts (head and neck squamous cell [HNSCC, n = 4], non-small cell lung [NSCLC, n = 2], and parathyroid cancer [n = 1]) including 4 partial responses (5 received prior EGFR therapies). PK data (n = 31) shows dose proportional increase in sirolimus weekly trough levels and the median trough level at RP2D was 15.7 ng/mL. PD data showed adequate mTOR inhibition as measured by pS6K activity in PBMC (ELISA) in 25 tested pts ($p < 0.001$) and decreased accumulation of autophagosomes as measured by % of LC3 positive PBMCs (flowcytometry) in 23 tested pts ($p < 0.001$). Some spots are still open in the expansion cohorts. Updated clinical, PK and PD data (including pre- and post-treatment biopsies) will be presented.
Conclusions: Cetuximab and sirolimus is well tolerated and demonstrates early antitumor activity in patients with refractory HNSCC, NSCLC, and parathyroid carcinoma.
Conflict of interest: *Corporate-sponsored research: Filip Janku has research funding from Biocartis, Novartis, Roche, Transgenomic, Trovagene*

818 POSTER

4,4'-dimethoxybenzophenone thiosemicarbazone: Underlying mechanism of action of a compound with selective proapoptotic novel activity in human leukemia cells

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Thiosemicarbazones have shown wide pharmacological versatility and their application as antibacterial, antiviral and anticancer agents make them valuable candidates for the development of new drugs.
In the search for new potential anti-leukemic drugs, a family of benzophenone thiosemicarbazones were synthesized and tested for antiproliferative activity in human acute leukemia U937 cell line. From this initial screening the 4,4'-dimethoxybenzophenone thiosemicarbazone (T44Bf) was identified as the most potent. Based on that, the aim of the present study was to elucidate the mechanisms that mediate the antiproliferative effects of T44Bf over different models of human acute leukemia (KG1a, HL60, U937 and Jurkat cell lines). T44Bf treatment of the cell lines led to a significant reduction in cell growth in a dose/time

dependent manner (IC50=5μM). To evaluate whether this inhibition was due to the induction of apoptosis, we analyzed by western blot, caspase 3 and poly (ADPribose) polymerase (PARP) cleavage. The results obtained in the apoptosis studies correlates in time and concentration with the observed inhibition of proliferation for the four cell lines. Similar results were obtained when we measure caspase-3 activity by a colorimetric assay and phosphatidylserine extrusion by Anexine V staining. On the other hand, peripheral blood monocytes and lymphocytes isolated from healthy blood donors were treated with T44Bf up to 20 μM. Interestingly, T44Bf did not promote death of normal cells indicating selectivity of the compound at the working concentrations.

To elucidate the action mechanism involved in the pro-apoptotic activity of T44Bf we studied by Western blot, the phosphorylation state of MAPKs: ERK, Akt, p38 and JNK, using phospho-specific antibodies. T44Bf treatment increased phosphorylation in a time dependent manner of ERK1/2, while p-Akt, p-p38 and p-JNK levels remained unchanged. To evaluate whether the observed ERK1/2 modulation was involved in the pro-apoptotic activity of T44Bf, we measured caspase 3 and PARP clevage in cells treated with T44Bf in presence of the MEK inhibitor U0126. Inhibition of ERK phosphorylation by U0126 blocked T44Bf induced apoptosis, indicating that phosphorylation of ERK is a necessary step to achieve apoptosis by T44Bf.

Our results shed new light in the mechanism of action of thiosemicarbazones as anticancer agents and postulated T44Bf as a promising compound for the development of novel and selective antileukemic drugs.

No conflict of interest.

819 POSTER

The novel peroxisome proliferator-activated receptor gamma (PPARg) agonists CB11 and CB11d, induced apoptosis through DNA damage by reactive oxygen species (ROS) in a human non-small cell lung cancer (NSCLC) cell line H460

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Background: PPARγ agonists have been shown to induce apoptosis a variety of cancer cells. Lung cancer is the most common cause of cancer death in the world and the second most common cancer in the Republic of Korea. PPARγ is known to be highly expressed in human lung cancer cell lines. In this study we investigated effects of novel PPARγ agonists CB11 (8-(2-aminophenyl)-3-butyl-1,6,7-trimethyl-1H-imidazo[2,1-f]purine-2,4(3H,8H)-di-
one) and its derivative, CB11d1(8-(2-aminophenyl)-3-butyl-1,7-dimethyl-1H-imidazo[2,1-f]purine-2,4(3H,8H)-dione) on a human lung cancer cell line H460.

Material and Methods: CB11 was selected using chemical library (ChemBridge, USA) screening and its derivative CB11d1 was purchased from the same company. These chemicals as PPARγ agonists were confirmed by Oil Red O staining or effect of specific antagonist GW9662 in differentiated 3T3L1 cells. Cell viability was measured by WST assay. The subdiploid cellular DNA fraction, mitochondrial membrane potential (MMP) collapse and ROS were analyzed by flow cytometry. Activation of the caspase pathway by PPARγ agonist treatment was detected by Western blot analysis and caspase activity assay.

Results: Both CB11 and CB11d1 dose-dependently inhibited cell growth and induced apoptosis in H460 cells. Pretreatment of H460 cells with GW9662, a PPARγ specific antagonist did not recover cell viability showing that both CB11 and CB11d1 induced apoptosis in a PPARγ-independent pathway. These agonists increased activation of caspase −3, −8 and −9 as well as cleavage of poly (ADP-ribose) polymerase (PARP). Moreover, MMP collapse was increased by these agonists and blocked by pretreatment of cell with cyclosporin A, MMP inhibitor, suggesting that these agonists induced apoptosis via a mitochondria-dependent pathway. Concomitantly, both CB11 and CB11d1 increased ROS generation and DNA damage in H460 cells. ROS inhibitors such as N-acetyl-cystein (NAC) suppressed ROS generation, apoptosis and DNA damage suggesting that apoptosis by CB11 and CB11d1 is involved in ROS generation.

Conclusions: Our results suggest that novel PPARγ agonists, CB11 and CB11d1, may be used for the treatment of NSCLC.

No conflict of interest.

820 POSTER

Niclosamide radiosensitizes non-small cell lung cancer cells through activation of c-Jun

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Background: Radiotherapy is one of the effective modalities in the clinical treatment of cancers, and currently has been tried to combine with chemotherapy to improve therapeutic efficacy. Therefore, we aimed to develop small molecules that enhance the cytotoxic effects of radiotherapy. In this study, we provide evidence that Niclosamide can be an effective radiosensitizer in non-small cell lung cancer cells.

Material and Methods: To identify small molecules that increase cell death following radiotherapy in H1299 lung cancer cells, we screened a chemical library (a US-Drug Collection) containing 1,040 compounds using a cell viability assay system with Cell Counting Kit-8 in a 96-well plate format. A potent radiosensitizer among hits was validated by clonogenic survival assay, annexin V/PI staining and immunoblotting.

Results: Using a cell-based high-throughput screening with the 1,040 compounds in combination with irradiation, we found Niclosamide, an FDA-approved antihelminthic agent, exhibited radiosensitizing effect on H1299 human lung cancer cells. Combination treatment with Niclosamide and IR significantly reduced clonogenic survival of H1299 lung cancer cells in a dose-dependent manner and induced more apoptotic cell death than IR or Niclosamide alone, determined by increased level of PARP cleavages via caspase-3 activation and annexin V-positive cells. Given that IR induced apoptosis through generation of reactive oxygen species (ROS), we next examined ROS-induced molecular target signaling by the combination treatment of Niclosamide with IR. The combined treatment significantly induced phosphorylation of c-Jun in H1299 cells. Moreover, Niclosamide combined with H_2O_2 which was employed another ROS generator also induced c-Jun and its phosphorylation, leading to more increased apoptosis. N-acetyl-L-cysteine (NAC) treatment abolished c-Jun activation as well as apoptosis. Inhibition of c-Jun by siRNA also decreased PARP cleavages and attenuated clonogenic cell death of H1299 cells.

Conclusions: Our findings suggest that Niclosamide could be a promising radiosensitizer in lung cancer patients through activation of c-Jun which plays a pivotal role in ROS-induced apoptosis.

No conflict of interest.

821 POSTER

NFkB subcellular modulation and gene expression profile of chronic myeloid leukemia cell lines after treatment with the new compound LQB-118

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Background: Development of drugs more capable of overcoming tyrosine kinase inhibitors (TKIs) resistance, observed in about 30 % of chronic myeloid leukemia patients (CML), is of great importance nowadays. It was recently demonstrated by our group that treatment of CML cell lines (K562 and Lucena) with the new compound pterocarpanquinone LQB118 reduced the cellular viability and induced high levels of apoptosis. It was also observed a reduction in protein levels of glycoprotein-P (Pgp), and the inhibitor of apoptosis proteins (IAPs), XIAP and survivin. The NFkB transcription factor, which is capable of activating the transcription of Pgp, survivin and XIAP, is related to oncogenesis since regulates the expression of a variety of genes related to apoptosis, cellular proliferation and differentiation. The aim of the study was to evaluate the mechanism of LQB118 in inducing apoptosis and the gene expression profile of CML cell lines K562 and Lucena after treatment with LQB118.

Material and Methods: After treatment with LQB118 the levels of caspase-8 and IkBa, NFkB endogenous inhibitor, were analyzed by Western blotting. For NFkB subcellular localization, an immunofluorescence assay was performed. Proteasome activity was measure using Proteasome-Glo™. DNA microarray was performed to evaluate the differential gene expression profile of the CML cell lines treated with LQB118.

Results: LQB118 induced the activation of caspase-8 in both cell lines and maintained or induced IkBa levels, suggesting that NFkB was inactive in the cytoplasm. These results were confirmed by immunofluorescence, once NFkB was predominantly observed in the cytoplasm of the cell lines treated with LQB118. Further analysis also demonstrated that LQB118 was able to inhibit proteasome activity in both cell lines. DNA microarray results showed that LQB118 altered the expression of 109 and 75 genes, in K562 and Lucena, respectively. *TOB2, TAP2, NCF1* and *IKZF5* genes were differentially expressed after treatment with LQB118.

Conclusions: Our results suggest that LQB118 induced high levels of apoptosis in both CML cell lines through the extrinsec pathway of apoptosis and seems to be able to modulate NFkB activity, preventing its translocation to the nucleus, probably by avoiding IkB degradation by proteasome and, therefore, preventing XIAP and survivin expression. The study of the gene expression profile allowed us evaluate the putative genes involved in LQB118 mechanism.

No conflict of interest.

822 POSTER

Evaluation of tolerability and anti-tumor activity of GDC-0032, a PI3K inhibitor with enhanced activity against PIK3CA mutant tumors, administered to patients with advanced solid tumors

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Background: GDC-0032 is an orally bioavailable, potent, and selective inhibitor of Class I PI3K alpha, delta, and gamma isoforms, with 30-fold less inhibition of the PI3K beta isoform relative to the PI3K alpha isoform. Preclinical data show that GDC-0032 has enhanced activity against PI3K alpha isoform (PIK3CA) mutant cancer cell lines.
Material and Methods: A Phase I dose escalation study was conducted with evaluation of GDC-0032 doses ranging from 3−16 mg QD in a modified 3+3 design. Dose expansion cohorts at 9 mg QD were conducted in patients with solid tumors or with HER2-positive breast cancer. Safety and tolerability of GDC-0032 was assessed, as well as pharmacokinetics (PK), pharmacodynamic (PD) assessment of PI3K pathway inhibition by paired tumor biopsies and by FDG-PET, and anti-tumor activity by RECIST.
Results: Enrollment onto the dose escalation stage has been completed (n = 34). Two DLTs (G4 hyperglycemia and G3 fatigue) were observed at the 16 mg cohort. As of Nov 30, 2012, adverse events (AEs) assessed by the investigator as related to GDC-0032 in ⩾10% of patients, were diarrhea, fatigue, hyperglycemia, decreased appetite, nausea, rash, stomatitis, and vomiting. GDC-0032 has dose-proportional PK and a mean half-life of 40 hours, from 3−16 mg QD. PD inhibition of the PI3K pathway was observed via paired tumor biopsies as assessed by reverse phase protein array. Metabolic partial responses via FDG-PET (⩾20% decrease in $mSUV_{max}$) were observed in 12 out of 17 patients assessed (71%). Confirmed partial responses (PRs) have been observed in 5 patients who were treated at doses ranging from 3−12 mg QD. Of the 6 patients with PIK3CA mutant breast cancer (RECIST −30 to −70%), there have been 4 confirmed PRs observed. One confirmed PR has been observed in a patient with PIK3CA mutant NSCLC. Enrollment onto the solid tumor cohort (n = 13) and the HER2-positive breast cancer cohort (n = 10) has been completed. Preliminary PK and safety data from these expansion cohorts are consistent with those observed in the dose-escalation portion of this study. Updated data on clinical outcomes and biomarker correlates will be presented.
Conclusions: GDC-0032 is a next-generation PI3K inhibitor with promising anti-tumor activity observed in patients with PIK3CA mutant tumors. GDC-0032 is being investigated in combination with endocrine therapies such as letrozole and fulvestrant for patients with hormone receptor-positive breast cancer.
Conflict of interest: *Ownership: Richard Graham, Tim Wilson, Jerry Hsu (Genentech). Advisory board: Ian Krop, Jose Baselga (Genentech)*

823 POSTER

Reactivation of apoptosis in cancer cells with new class of fusion proteins

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Introduction: Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL/Apo2L) was going to be promising, natural therapeutic that selectively targets tumor cells while omitting normal cells. However it occurs that many cancer cell lines have developed a number of resistance mechanisms to TRAIL. Among recently discovered, overexpression of X-linked IAP (XIAP) molecules is considered as the main cause of TRAIL resistance.
There are many strategies, regarding chemo- and radio-sensitization, enhancing TRAIL efficacy, however combining TRAIL with chemotherapy may also sensitize normal cells to TRAIL induced apoptosis.
Here we present a recombinant variant of TRAIL fused with the peptide derived from Smac/DIABLO protein. The peptide we used is responsible for the interaction with BIR domains of IAP molecules. The fusion protein contains membrane transduction motif followed by sequences recognized by tumor-specific proteases (MMPs). General mechanism of action of this protein is considered as specific targeting the tumor by TRAIL, followed by activation (release) and transduction of pro-apoptotic peptide into cancer cells. Delivery of the Smac/DIABLO peptide blocks X-linked IAP (XIAP) proteins activity and reactivates apoptosis in cancer cell.
Methods: TRAIL/APO2L-SMAC/DIABLO fusion protein was expressed in *E.coli* and purified by IEC chromatography. Obtained protein was tested regarding *in vivo* distribution, apoptosis induction, protease cleavage and MTT cell cytotoxicity assays. For *in vivo* potential we examined the efficacy of fusion protein on mice xenograft model of colorectal adenocarcinoma (Colo205) and uterine sarcoma (MES-SA/Dx5) cells in comparison to reference − active TRAIL.
Results: We had obtained molecule and verified its mechanism of action. Our Smac/DIABLO-TRAIL fusion variant showed *in vitro* specific cytotoxic effect on various cancer cell lines at the level of IC50 below 0.1 ng/ml. In contrast to IC50 values obtained for cancer cell lines the fusion molecule showed no or very low activity on normal cells. The fusion protein showed specific targeting into the xenograft tumor and superior effect displaying significant tumor volume regression *in vivo* when compared with TRAIL.
All those results confirm that we had developed very promising molecule with high potential of pro-apoptotic activity that could be considered as a novel anticancer therapeutic agent showing clear synergistic effect of TRAIL and pro-apoptotic peptide.
No conflict of interest.

824 POSTER

A phase 1 study of oral rucaparib in combination with carboplatin

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Background: Targeting poly (ADP-ribose) polymerase (PARP), an enzyme involved in DNA damage repair, may increase efficacy of DNA-damaging agents. This study evaluated the tolerability of oral rucaparib, a potent and selective PARP1/2 inhibitor, in combination with carboplatin (CP).
Methods: Patients (pts) aged ⩾18 with advanced solid tumors were included. Pts received lead-in doses of IV and oral rucaparib on Days −10 and −5, respectively, followed by CP on Day 1 and oral rucaparib on Days 1−14 q21 days. Treatment continued until disease progression. Pts with benefit could continue rucaparib monotherapy once CP dosing was completed. Dose escalation was based on toxicities observed in Cycle 1 in cohorts of n = 3−6. PK was assessed during Cycle 1.
Results: 26 pts (median age 60.5 yrs [range 20−76]; 19 female; 10 ECOG PS=0; 7 ovarian/peritoneal (OC), 6 breast (BC), 2 NSCLC, 11 other tumor) were enrolled. Rucaparib doses of 80, 120, 180, 240, and 360 mg were administered with AUC3 CP, followed by 360 mg rucaparib with AUC4 and AUC5 CP. Two of 5 pts treated with AUC5 CP/360 mg rucaparib experienced dose-limiting toxicity (Gr 3/4 neutropenia & thrombocytopenia). Evaluation of AUC5 CP and 240 mg rucaparib is being completed. Treatment-related adverse events in ⩾5 pts, all grades, include fatigue (n = 11), anemia (n = 10), neutropenia (n = 8), thrombocytopenia (n = 8), nausea (n = 7), lethargy (n = 6), and constipation (n = 5). One pt (OC, $BRCA^{wt}$, AUC3 CP/180 mg rucaparib) had a PR of 5.1 mo duration and 1 pt (BC; $BRCA2^{mut}$, AUC5 CP/360 mg rucaparib) is ongoing in week 10 with confirmation of PR pending. Three pts (1 CRC, 2 OC; 2 $BRCA^{unk}$, 1 $BRCA^{wt}$) discontinued CP (after 4 or 8 cycles) and continued on rucaparib (additional 2, 5, or 10+ cycles). An additional 3 pts (mesothelioma, NSCLC, pseudomyxoma peritoneii; all $BRCA^{unk}$) had stable disease (SD) >12 wks. Overall disease control rate (CR+PR+SD>12 wks) in evaluable OC pts across all dose levels was 50% (3/6). Dose-proportional increase in rucaparib exposure was observed with steady state achieved by Day 14 and mean $t_{1/2}$ of 15 h. Oral bioavailability was 38% and dose-independent. Rucaparib exposure was not changed by CP co-administration.
Conclusions: The combination of oral rucaparib and CP exhibits activity at clinically relevant doses of each agent. Further studies in platinum-sensitive and homologous recombination repair deficient populations are warranted.
Conflict of interest: *Ownership: Heidi Giordano, Dayna Simpson and Sarah Jaw-Tsai are employees/stock holder of Clovis Oncology, Inc. Advisory board: Prof Ruth Plummer is an advisory board member for Clovis Oncology, Inc. Corporate-sponsored research: Institutions for Drs. Roxburgh, Molife, Gupta, Wilson, Evans, and Cresti received research funding for trial from Clovis Oncology, Inc.*

825 POSTER

Magnetic nanoparticle-entrapping liposomes for localized hyperthermia and controlled drug release in solid tumours

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Background: Hyperthermia is a powerful tool to trigger content release from thermosensitive liposomes (TSL) encapsulating chemotherapeutic drugs. A major challenge of nowadays' hyperthermia and TSL-mediated chemotherapy treatment, is the precise heat delivery to only trigger drug release in the tumour area, preventing healthy tissue toxicity. Nanometre scale magnetic iron oxide nanoparticles (MNPs) can, when exposed to an alternating magnetic field (AMF), generate heat and can also be imaged by magnetic resonance imaging (MRI). When MNPs are co-encapsulated with chemotherapeutics into TSL, a drug carrier is obtained, which under imaging-guidance can be heated to release its contents at any desired moment using a non-invasive AMF impulse. The aim of this study is to develop such MNP entrapping thermosensitive liposomes.
Material and Methods: We have applied various liposome preparation methods, to optimize incorporation of hydrophobic MNPs into liposome bilayers or hydrophillic MNPs in the aqueous core. Magnetoliposomes were analysed by dynamic light scattering for size, polydispersity index and zeta potential, followed by transmission electron microscopy. Magnetic properties of these samples were determined by T1, T2 measurements and NMRD profiling.
Results: When using film hydration, hydrophllic MNPs were loaded in aqueous core of 100 nm liposomes. For hydrophobic MNPs, more delicate approaches were required for incorporation into liposomal bilayers. The magnetic properties of MNPs after liposome incorporation remained unaltered.
Conclusions: Hydrophilic and hydrophobic MNP were incorporated in TSL. Current studies focus on optimising MNP loading efficacy and further characterization. After this stage hyperthermia potential and heat triggered drug release will be studied in vitro and in vivo.
No conflict of interest.

826 POSTER

Dual inhibitors of NFkappaB and Akt activation: Synthesis, in vitro anticancer activity and molecular docking studies

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Background: The C-2 arylidene analogs of pentacyclic triterpenoid Lantadene A **(1)** and B **(2)** were synthesized as dual inhibitors of NF-kappaB (NF-κB) and Akt. The compounds were further evaluated for *in vitro* anticancer activity against four human cancer cell lines (HL-60, MCF-7, A549 and HCT-116).
Material and Methods: The cytotoxicity was evaluated by using MTT assay, the NF-κB and Akt inhibition was evaluated by NF-κB luciferase assay and Akt kinase inhibition assay respectively. Automated molecular docking was performed to find out molecular interaction and optimized geometry by using docking software AutoDock 4.2.
Results: Analogs **3, 4, 7** and **8** showed enhanced inhibitory activity as compared with parent compounds **1** and **2**. These analogs were found more active than standard drug cisplatin with selective toxicity towards cancer cells and were inactive against normal cells (VERO). Furthermore, the mechanistic studies to investigate the effects of the new compounds on Akt protein in lung cancer cell line A549 and the NF-κB signalling pathway suggested that the compounds may exert their inhibitory activity on cancer cells through inhibition of both Akt and NF-κB activation. The docking studies of most potent analog **(7)** with 3D crystal structure of the nuclear factor kappa-B (NF-κB) P50 homodimer (PDB ID: 1NFK) revealed that carbonyl group of ester side chain and C-28 carboxylic acid groups were mainly involved in hydrogen bonding interaction. The oleanane frameworks was involved in strong hydrophobic interaction with amino acid phenylalanine and structure of lead compound have the potential to be developed as potent NF-κB inhibitor and anticancer agent.
Conclusions: Novel dual inhibitors of NF-κB and Akt activation inhibitors were synthesized and found to have potent selective anticancer activities in low micro molar range.
No conflict of interest.

827 POSTER

A phase I of study of Everolimus (EVE) in combination with LBH589B (LBH) [HDAC inhibitor] in advanced malignancies with enrichment for EBV driven tumors

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Background: Pre-clinical evidence suggests that combination of HDAC and m-TOR inhibition abrogates multiple EBV-driven oncogenic pathways by increasing expression of EBV lytic genes coupled with immune-modulatory and anti-angiogenic effects.
Material and Methods: Patients with advanced malignancies enriched for EBV-driven cancers were enrolled to determine the safety, tolerability, maximum tolerated dose (MTD), pharmacokinetics, pharmacodynamics and preliminary anti-tumor activities in a 3+3 dose escalation design. LBH was administered 7 days prior to initiation of combination treatment. NPC patients received either acyclovir or val-acyclovir prophylaxis. Serum EBV-DNA levels were measured weekly and plasma cytokines profiled using a 31-plex luminex panel.
Results: 20 patients have been treated [male:female 15:5, median age 52.5 (37−63, 11 nasopharyngeal carcinoma (NPC) and 9 non-NPC] at 4 dose levels − LBH (3x/week)-EVE (daily):10 mg-2.5 mg (3pts), 10 mg-5 mg (6pts), 15 mg-2.5 mg (exploratory) (6pts) and 15 mg-5 mg (5pts). 73 cycles of treatment were administered in total. Two dose limiting toxicities of G4 (grade) thrombocytopenia were observed at LBH 15 mg-EVE 5 mg. Significant adverse events (AE) (G⩾3) were dysphagia (1),diarrhoea (1), epistaxis (1) and thrombocytopenia (3). Common AEs (G1/2) included mucositis (70%), fatigue (65%), anorexia (50%), fever (40%), cough (30%) and diarrhoea (30%). One patient experienced a partial response (lymphoma) and 6 patients (3 NPC, 2 breast and 1 renal cell carcinoma) had prolonged stable disease (>16 weeks). Modulation of EBV DNA titres was seen only in NPC patients, with median fold-change from baseline of 9 (0.9–174). In a limited patient subset (n = 9, 30 timepoints), plasma cytokine profiles were consistent with a T- cell response, specifically, elevated levels of FLT3L, IFN-gamma, IL-13 and IL-17. Target engagement was also observed with increased histone-3 acetylation as early as 4 hours after administration of LBH. Results of the PK studies would be presented during the meeting.
Conclusion: Combination of LBH and EVE resulted in induction of EBV DNA titres with concomitant T-cell host response. The recommended phase 2 dose is LBH 10 mg 3x/week and EVE 5 mg daily in an Asian population comprising of predominantly NPC patients.
No conflict of interest.

828 POSTER

p21Cip1/Waf1-mimetic peptide bound to elastin-like polypeptide carrier enhances bortezomib cytotoxicity in androgen-independent prostate cancer cell lines

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Background: Bortezomib is a proteasomal inhibitor approved for the clinical use in hematological tumors. However, due to a narrow therapeutic window it has a limited potential to be utilized as a treatment for solid tumors. In this work we have investigated the effect that externally delivered $p21^{Cip1/Waf1}$-mimetic peptide (aa 139–164) has on bortezomib cytotoxicity in DU-145 and PC-3 androgen-independent prostate cancer cell lines.
Materials and Methods: In this research elastin-like polypeptide (ELP) was used for the intracellular delivery of the p21-mimetic peptide. ELP is a genetically engineered, thermally responsive macromolecular carrier previously shown to be able to improve the stability of therapeutic peptides as well as to mediate their targeted delivery in response to mild hyperthermia. The effect that ELP-bound p21 peptide has on bortezomib cytotoxicity was measured using MTT test. Flow cytometry was used to quantify ELP-p21 peptide cellular uptake, as well as changes in the cell cycle distribution, apoptosis and autophagy induction after the combination treatment with bortezomib and ELP-p21 peptide. Western blot technique was used to monitor the change in the expression of various proteins involved in cell cycle regulation, while the senescence-associated beta-galactosidase assay was used to assess changes in the senescence activation.

Results: We demonstrated that co-treatment with bortezomib and ELP-bound p21-mimetic peptide carrier enhanced bortezomib cytotoxicity in both androgen-independent prostate cancer cell lines. In our research the ELP-p21 polypeptide led to a 1.5-fold decrease in the bortezomib IC_{50} value in the two cell lines tested. The combination treatment affected the cell cycle distribution and caused an intra-S phase cell cycle arrest. Additionally, the combination treatment augmented autophagy and apoptosis induction. On the protein level, we detected a different pattern in the cyclin D1, E and B1 expression, which we believe is due to the different status of the Rb protein in the two cell lines tested. Moreover, in contrast to PC-3 cell line that possesses wild type Rb protein, DU-145 cells, that contain non-functional Rb protein, did not display increase in the senescence induction upon the combination treatment.
Conclusion: In summary, our results suggest that ELP-bound p21-mimetic peptide may prove to be useful tool in combination therapy with proteasomal inhibitors.
Conflict of interest: *Other substantive relationships: D. Raucher is the president of Thermally Targeted Therapeutics, Inc., Jackson, MS, USA*

829 POSTER

Immunoliposomes with single-domain antibodies targeted against mucin 1 (MUC1)

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In response to the lack of specificity in anti-cancer drugs, we want to use anti-MUC1 antibodies to improve targeting of drug-loaded liposomes to cancer cells. Liposomes can be used as carrier for various molecules, including targeting moieties and chemotherapeutics, to increase specificity or reduce toxicity. After extravasation the drug needs to be targeted to the tumor cells to be most effective. We use MUC1 as target, since it is overexpressed in pancreatic cancer, which is difficult to treat and has a 5-year survival rate of 6%. In this project we will use liposomes targeted with human single domain antibodies, i.e. antibodies containing only the variable domain of the antibody's heavy chain. Due to their small size (10−15 kDa) they are likely to be much less immunogenic than whole antibodies coupled to liposomes, but with all complementary determining regions intact, they can still show high affinity for their targets.
A transgenic mouse has been developed, which enables the production of heavy-chain-only antibodies of human origin. After immunization with MUC1, antibodies have been isolated and expressed to create a clone library. These clones have been screened for affinity on FortéBio Octet and have been used for subcloning of heavy chain variable domains with an additional cysteine. This cysteine will be used for thiol-maleimide conjugation to the polyethylene glycol (PEG) chains of liposomes. Affinity measurements of the single-domain antibodies and the antibody-liposome complex will be performed on MUC1 positive cell lines, such as CFPAC-1, by flowcytometry and immunostaining.
After immunization of several mice, and selection steps against MUC1, twelve related heavy-chain-only-antibodies have been found with dissociation constants (Kd) between 1E-9 to 1E-10 M. These twelve will be tested on MUC1 positive cell lines and a selection will be made into a single-domain format, which can be used for liposome conjugation and further affinity measurements. Liposomal conjugation with other antibodies has been performed, where antibodies are conjugated to micelles, which are post-inserted into preformed liposomes. These liposomes will be optically labeled to enable *in vivo* biodistribution studies.
Research on liposomes equipped with single-domain antibodies will help to identify novel targeted liposomal chemotherapy formulations that combine the liposomal drug encapsulation together with improved cell targeting and intracellular drug delivery.
No conflict of interest.

830 POSTER

Paclitaxel resistance is associated with drug accumulation in intracellular compartments and paclitaxel-binding proteins in human lung cancer cell lines

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Background: Several mechanisms have been suggested for paclitaxel resistance in cancer cells, including overexpression of the multidrug transporter gene, ATP-binding cassette, sub-family B, member 1 (*ABCB1*), and the presence of a point mutation in the β-tubulin gene at the paclitaxel-binding site. However, the mechanisms underlying resistance to this agent have not yet been completely elucidated.
Material and Methods: Three human lung cancer cell lines, II18, A549, and RERF-LC-KJ, were analysed; their 50% inhibitory concentrations of paclitaxel were −8.33, −7.69, and −4.51 logM, respectively. The cell lines did not have any β-tubulin mutation. We evaluated the expression levels of *ABCB1*, intracellular accumulation of paclitaxel, paclitaxel-induced stabilisation of microtubules, and intracellular localisation of Oregon Green® 488-conjugated paclitaxel in these cell lines. Moreover, we prepared paclitaxel conjugated ferriteglycidyl metacrylate (FG) beads to purify paclitaxel-binding proteins from whole cell lysates of these cells.
Results: The *ABCB1* expression level was strongly correlated to intracellular [^{3}H]-paclitaxel accumulation (r^2 = −0.804) but was not related with paclitaxel resistance. The changes in the quantities of polymerized tubulin and acetylated tubulin after paclitaxel exposure were not related to paclitaxel resistance. Differences were observed between the intracellular localisation of paclitaxel in RERF-LC-KJ, the most resistant cell line, and in the other 2 cell lines. The use of Oregon Green® 488-conjugated paclitaxel enabled visualization of not only the normal microtubule formation in the partial cells but also the aggregated vesicle formation in RERF-LC-KJ cells; aggregated vesicle formation was not remarkable in the other cell lines. Affinity purification by paclitaxel immobilised beads revealed several specific bands in RERF-LC-KJ; these bands were not revealed in the other cell lines.
Conclusions: We propose that paclitaxel resistance is associated with intracellular compartments in which paclitaxel accumulates and paclitaxel-binding proteins expressed specifically in resistant cell line.
No conflict of interest.

831 POSTER

Naturally occurring isothiocyanates potentiate doxorubicin cytotoxicity in doxorubicin-resistant colon cancer cells

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Background: Doxorubicin and other anthracyclines are well-known, widely used and very efficient cancer therapeutics agents. Unfortunately, prolonged administration very often causes severe toxic effects and leads to resistance, thereby limiting the usability in chemotherapy. One of potential strategies to lower the toxicity and overcome resistance is to use an additional compound as a sensitizing agent making cancer cells more susceptible to cytostatics. Naturally occurring isothiocyanates (ITC), due to their low toxicity and multi-targeted mechanism of action, have been recently introduces as a potentially effective agents in combined therapy.
Material and Methods: Isothiocyanates, including benzyl, 3,4-dimetoxybenzyl and 6-hydroxyhexyl isothiocyanate were tested in combined therapy with doxorubicin in two colon cancer cell lines − drug-sensitive LoVo and its doxorubicin-resistant subline LoVoDX. Several different schedules of treatment were checked and their outcome was analyzed using MTT assay. Further studies on the combination mechanism of action involved determination of: ROS production, doxorubicin accumulation and caspase-3/7 activity, as well as cell cycle and glutathione level analysis.
Results: Short, 1 hour pretreatment with isothiocyanates (concentration in the range of 10−2.5μM) followed by medium removal and doxorubicin treatment for next 48 hours led to the most pronounced synergistic effect (Combination index CI, calculated using Chou-Talalay method 0.28–0.45). Isothiocyanate concentration proved to be an important factor affecting observed effect − concentrations lower than 2μM used in above mentioned schedule gave additive or even an antagonistic effect. In LoVoDX cell line 3,4-dimetoxybenzyl isothiocyanates almost completely abrogated doxorubicin resistance (resistance index RI calculated as a LoVoDX/LoVo IC_{50} ratio − 9 without isothiocyanate, and 1.6 for combination). Doxorubicin accumulation remained at the same level after isothiocyanates pretreatment, thereby increased drug concentration appears to be not involved in increased cytotoxicity. Further studies showed that glutathione depletion caused by isothiocyanates (30%-45% decrease in glutathione content after 1 hour) led to increased ROS-production in cells treated with combinations. Moreover, isothiocyanates pretreatment induced cell cycle arrest in G2/M phase which might be also associated with increased doxorubicin cytotoxicity. The final outcome of combined treatment was apoptotic cell death indicated by caspase-3/7 increased activity.
Conclusions: Naturally occurring isothiocyanates proved to be a potent sensitizing agents when used along with the doxorubicin in properly designed schedule. Their main mechanism of action in combined treatment appears to be based on the modulation of cell cycle and redox status.
No conflict of interest.

832 POSTER

Gene resilencing following decitabine therapy is initiated by nucleosome reoccupancy and is related to CpG island shore methylation

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Decitabine is a front line therapy for myelogenous leukaemias and is in clinical trials for various solid tumour types. This DNA demethylating agent reactivates genes silenced by promoter hypermethylation in cancer. However upon drug withdrawal reactivated genes undergo resilencing which may underlie drug resistance. While resistance is associated with resilencing of genes, the mechanism underlying this resilencing is unknown. We aimed to decode the ordered sequence of epigenetic events associated with resilencing in order to improve the clinical effectiveness of Decitabine. Using biallelically methylated MLH1 as a model gene, we profiled epigenetic changes at the MLH1 promoter associated with reexpression and resilencing in a colorectal cancer cell line before, during and after Decitabine treatment. In contrast to the closed chromatin structure observed before treatment, Decitabine induced increased MLH1 expression and 54% decreased promoter methylation. Using single molecule analysis at multiple time points, we show that gene resilencing, which occurs 6−8 days following removal of therapy, was initiated by nucleosome reassembly on demethylated DNA and only then was followed by remethylation and stable silencing. Furthermore, long-term monitoring of cells following treatment showed MLH1 resilencing never reverts to pretreatment levels with low-level MLH1 expression and demethylated MLH1 promoter alleles persisting up to 118 days after withdrawal of Decitabine. Genome-wide methylation profiling was used to categorise promoter CpG Islands (CGI) based on their degree of demethylation after treatment. This revealed that CGIs with persistence of demethylated promoter alleles after long-term recovery ($n = 108$) showed significantly lower levels of CGI shore methylation ($p = 0.0231$). Our findings suggest a role for shore methylation in susceptibility to CGI remethylation. The data also establishes the importance of nucleosome positioning in mediating resilencing of drug-induced gene reactivation and suggest a role for therapeutic targeting of nucleosome assembly as a mechanism to overcome drug resistance.

No conflict of interest.

833 POSTER

New pharmacological approaches against human epidermal growth factor receptor 2 (HER2+) resistant breast cancer

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Background: Therapeutic acquired resistance of HER2 positive breast cancer represents a major health care problem given the lack of curative interventions for a large subset of patients bearing this disease. Many efforts are being devoted to find new pharmacological strategies for patients unresponsive to existing treatments. Our group has shown that HER2+ tumors also overexpress fatty acid synthase (FASN+).

The purpose of this study is to test drugs inhibiting different molecular targets to assess the effects in HER2+ breast cancer, even in those resistant to anti-HER2 drugs.

Materials and Methods: We have developed long term HER2+ breast cancer cell lines (SKBr3) resistant to the HER2-monoclonal antibody (trastuzumab, herceptin®) (SK**TR**), the EGFR/HER2-tyrosine kinase inhibitor (lapatinib, tykerb®) (SK**LR**) or both (SK**LTR**). Once established, we have characterized these cells by studying a panel of EGF receptors signaling proteins with western blot analysis, changes in adherence to extracellular matrix proteins and invasion capacity with colorimetric assays. Using MTT assay, we have assessed the effect of a HER2 dimeritzation-inhibitor (pertuzumab, perjeta®), an mTOR-inhibitor (temsirolimus, torisel®) and a new FASN inhibitor developed in our laboratory (G28UCM) on the viability of parental and resistant cells. Currently, we are establishing orthotopic xenograft mice models to test the anti-cancer effect of these drugs, alone or in combination.

Results: Resistant cells maintained downstream HER2 pathway activation by stimulating the expression/activation of alternative EGF family receptors and/or those specific ligands. Moreover, these cells increased adherence to extracellular matrix proteins and invasion capacity.

The HER2-dimerization inhibitor (perjeta®, 50 μg/ml) produced a decrease of approximately 20−40% in cell viability, even in resistant cells non-responding to trastuzumab and lapatinib. Inhibition of mTOR had a potent effect in parental and resistant breast cancer cells, producing a drop of 30% in cell viability with 4.8−6 μM of temsirolimus. The inhibition of 30% in cell proliferation was obtained with 5.5–11.6 μM of G28UCM. Moreover G28UCM improved the cytotoxic effects of other known FASN inhibitors (C75 and EGCG).

Conclusions: FASN inhibition, alone or in combination with other targets (such as mTOR or EGF family receptors) could be a new pharmacological strategy to fight HER2+ breast cancer resistant to trastuzumab and lapatinib. New studies in ortoxenopatients are needed to strengthen this study.

Conflict of interest: *Other substantive relationships: Puigner V. is employed by Roche Farma SA, which kindly yielded us pertuzumab, perjeta™. Viqueira A, Bolos MV are employed by Pfizer, which kindly yielded us temsirolimus, torisel™.*

834 POSTER

Epithelial–mesenchymal transition confers resistance to FGFR inhibitors in gastric cancer cell line

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Background: Targeted therapies based on kinase inhibitors may bring encouraging results but they frequently elicit resistance that makes the therapy ineffective and is often accompanied with cross-resistance to other drugs. Understanding and anticipation of the resistance mechanism for novel targeted drugs provides new approaches to use alternative or combine therapy which would improve patients' chances for recovery.

Fibroblast growth factor receptor (FGFR) comprises a promising target for anticancer therapy as it's amplification, mutation or overexpression is considered to be an oncogenic driver in various types of human neoplasms. Several clinical trials are currently carried out with the use of FGFR inhibitors but there still lacks the information about possible mechanisms of resistance to therapy in treated patients. The aim of the study was to define the mechanisms of acquired resistance to FGFR inhibitors: AZD-4547, BGJ 398 and PD173074 in selected in vitro models.

Material and Methods: To explore the mechanism of acquired resistance to FGFR inhibitors we have applied SNU16 human gastric cancer cell line with FGFR2 amplification. The cells were cultured with increasing concentrations of each inhibitor: AZD-4547, BGJ398 or PD173074 until reaching a concentration exceeding the IC50 value ten times. The mechanism of resistance was verified using immunoblotting techniques.

Results: In the following study we have established three gastric cancer cell lines SNU16R AZD, SNU16R BGJ, SNU16R PD, resistant to selective FGFR inhibitors AZD-4547, BGJ398 or PD173074, respectively. Since we found the loss of FGFR phosphorylation in all three lines we concluded that the resistance results from activation of alternative signaling pathways and is not evoked by mutation in FGFR kinase gene. We found however loss of several cell surface growth factor receptors like cMet or EGFR in these lines. Concurrently, the protein profile of established cell lines indicated epithelial–mesenchymal transition (EMT). We found the decrease in E-cadherin level and an increase of vimentin which are markers of EMT.

Conclusion: Our results reveal that one of the mechanisms of acquired resistance to FGFR selective inhibitors can be epithelial–mesenchymal transition. To our best knowledge it is the first time to show EMT as mechanism of resistance to the therapy targeting at FGFR. This finding indicates that EMT could emerge in patients treated with FGFR inhibitors.

No conflict of interest.

835 POSTER

Molecular mechanisms of resistance to protein kinase B inhibitors of the alkylphosphocholine family

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Background: Resistance of solid tumors to standard chemotherapy and radiotherapy remains challenging to successful treatment. But new hypothesis based on current studies reveal that tumor cells also show resistance to small molecule signal transduction inhibitors, including the membrane-targeted apoptosis modulators of the alkyllysophospholipid drug family (van der Luit A, Biochem J 2007). Drugs of the ALP or alkylphosphocholine (APC) drug families potently induce apoptotic cell death in various cancer cells and enhance radiation-induced cell death as well as radiation induced eradication of clonogenic tumor cells.

Aim of the proposed project was to mimic clinically relevant long-term treatment with the intravenously applicable APC erucylphosphocholine (ErPC) to select for ErPC resistance and to use a proteomics approach

to identify proteins and signaling networks that promote acquired drug resistance in these cells.
Material and Methods: Non-small cell lung cancer cells (A549) were treated in 20 cycles with increasing concentrations of ErPC (10 to 50μM). Drug resistance was confirmed by using standard short term (proliferation, apoptosis) and long-term (clonogenic survival) assays. Potential cross-resistance to treatment with ionizing radiation (IR) was determined accordingly. Proteome analysis was performed by 2D differential gel electrophoresis (DIGE) and subsequent mass spectrometry of altered protein spots. Changes in protein expression ratio were calculated from related spot intensities.
Results: Chronic treatment with rising ErPC concentrations resulted in the selection of A549 with increased resistance to ErPC. Surprisingly, the drug-resistant cells displayed increased susceptibility to IR compared to the non-selected controls. Fluorescence microscope pictures showed morphological changes featuring multiple vesicle-like structures with high auto-fluorescence. Proteome analysis via 2D differential gel electrophoresis and mass spectrometry evidenced changes in expression level of structural proteins and of proteins involved in stress defense.
Conclusions: The role of specific deregulated proteins for cellular sensitivity to ErPC and IR is subject to current investigations. Understanding the mechanisms underlying drug resistance will allow the design of combination strategies that exploit predicted adaptive changes to prevent or overcome drug resistance and improve treatment outcome.
No conflict of interest.

836 POSTER

Curcumin-mediated oxaliplatin resistance reversal in CRC cell lines through modulation of NF-kB, STAT3 and CDK5 signaling pathways

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Background: Oxaliplatin (OXA) is a chemotherapeutic drug widely used in the treatment of colorectal cancer (CRC). Unfortunately, acquired resistance results in a major obstacle for effective treatment. In previous work we observed an up-regulation of Cyclin-dependent kinase 5 (CDK5), pS727-STAT3 and p-P65 (NF-κβ) in the HT29-derived OXA-resistant cell line, HTOXAR3. Curcumin (diferuloylmethane), the major active ingredient of turmeric (*Curcuma longa*), without discernable toxicity, has been shown to inhibit the growth of transformed cells and colon carcinogenesis in rodent models. Curcumin has also been shown to suppress activation of transcription factors NF-κβ and STAT3. The aim of this work was to demonstrate whether the combined treatment of curcumin and OXA could revert the acquired resistance to the latter in HTOXAR3 cells.
Material and Methods: Curcumin IC50 determination and the effect of curcumin and OXA treatment on the proliferation of HT29 and HTOXAR3 cells was determined by a MTT assay and data were analysed by Chou and Talalay method. Curcumin time-dependent phosphorylation status of CDK5 (tyr-15), STAT3 (S727) and P65 (Ser536) was studied by Western Blotting at different times after curcumin treatment.
Results: Curcumin IC50 (μM) was approximately the same for both cell lines (HT29 IC50: 10.2±0.85, HTOXA IC50: 11.2±0.43). HT29 and HTOXAR3 cells were treated with 10μM curcumin for 4, 8, 24 and 48 h. As compared with untreated cells, maximum effect was observed after 48 h. pSTAT3 inhibition was 40% in both HT29 ($p = 0.0036$) and HTOXAR3 ($p = 0.0016$); pCDK5 inhibition was 60% in both HT29 ($p = 0.0006$) and HTOXAR3 ($p = 0.0073$) and pP65 inhibition was 30% in HT29 ($p = 0.0067$) and 40% in HTOXAR3 ($p = 0.0011$). We investigated the effect of sequential and concomitant treatment of OXA and curcumin. Preliminary results indicate that the highest effect is obtained in the concomitant schedule for 24 h as compared with sequential treatments (24 h-treatment with OXA or curcumin followed by an additional 24 h-treatment with OXA or curcumin). Cell viability was 27% (curcumin + OXA), 9% (OXA + curcumin) and 2% (concomitant treatment) as compared with individual exposures.
Conclusions: We demonstrated that curcumin suppressed activation not only of NF-κβ, STAT3 but also CDK5 in HT29 and HTOXAR3 cell lines, providing evidence that curcumin can be used in therapeutic regimes directed against CRC and suggesting that in combination with OXA, it could revert the resistant phenotype to this drug. Further experiments are ongoing in order to elucidate the best combination schedule.
No conflict of interest.

837 POSTER

A novel 3D cell culture system for in vitro evaluation of anticancer compounds

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Background: Traditional method for evaluating chemo-therapeutic drug has generally employed single layer of cells grown on plastic surface (2-dimentional cell (2D) cultures), which is physiologically different from the natural environment of the cells. Screening compounds by using the method therefore has the potential to result in less effective anticancer drugs than anticipated when tested in clinical trial. Recently, a number of approaches have been developed to generate 3D cell culture models for cancer study; e.g. scaffolds, microcarriers, and spheroids. However, many challenges remain, such as applying them into high throughput screening systems and improving the efficiency of anticancer drug discovery.
Material and Methods: In this study, we screened large-molecule compounds for the ability to suspend cancer cells homogeneously in liquid culture medium with keeping the medium low-viscosity, and identified FP001 as the most potent compound. We also established a novel method for the generation of cancer cell spheroids in suspension by using FP001 in ultra-low attachment multiwell plates. The cultured spheroids of cancer cells were characterized in terms of cell growth, apoptosis, cell cycle, and susceptibility to anticancer drugs to demonstrate the competency of the method.
Results: We cultured A549, HCT116, and HeLa cells for 5 days in medium containing FP001 and observed their cellular appearance and growth. The spheroids formed in the 3D culture medium were appropriate in size and suspended homogeneously, which led to easy handling for various assay. The cultures with FP001 exhibited a >10-fold increase in the number of living cells and contained decreased numbers of $BrdU^+$ cells and increased numbers of Annexin V^+ cells as compared to those with vehicle. Furthermore, the cells cultured in the medium were more sensitive to Mitomycin C, and the inhibition concentration obtained by the method was closer to actual blood level than that by 2D cultures. These data suggest that FP001 promotes the proliferation of spheroid forming-cancer cells which allow practical sensitivity to anticancer compounds. We are now investigating the feasibility of the method for development of automated and miniaturised screening systems.
Conclusions: We have identified FP001 as a novel substrate for the 3D culture of cancer cells. The approach using FP001 would facilitate the development of novel models for in vitro evaluation of anticancer compounds.
No conflict of interest.

838 POSTER

High-throughput assay for screening cancer metastasis inhibitors in human cancer cells using adenoviral knock-down

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The de-differentiation from a normal non-invasive epithelial cell into an immortalized, metastatic cell requires deregulation of multiple cellular processes. Our aim was to establish a high-throughput assay in human cancer cell lines to identify novel drug targets that reverse this deregulation by inducing Mesenchymal-to-Epithelial transition (MET).
Invasive mesenchymal cells express vimentin whereas non-invasive epithelial cells express E-cadherin, and the ratio between these markers reflects the identity of the cancer cells. We established an image-based functional high throughput assay measuring these markers in different cancer cell lines. Images were acquired on an INCell2000 Analyzer and an in-house written algorithm was used to calculate vimentin and E-cadherin expression. Using this assay, we screened an adenoviral shRNA knock-down library directed against human drugable genes for their potential to induce MET.
We successfully developed an automated high-throughput MET assay in multiple cancer cell lines which can be used for discovery and validation of novel targets for their potential to inhibit metastasis. Using this approach, we identified new targets as well as known players involved in MET. Knock-down of the transcription factor Snail, known to control epithelial–mesenchymal transitions, induced MET, similar to knock-down of members of the Wnt-signaling pathway.
Discovery of novel targets in metastasis may lead to the development of small molecule compounds or antibody therapeutics in cancer therapy.
No conflict of interest.

839 POSTER

A novel cell assay to screen for wnt pathway inhibiting drugs

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The wnt pathway is one of the most crucial pathways in colon cancerogenesis: In most colorectal cancers (CRC) wnt correlated genes are mutated. Since screening assays for drugs modifying this important pathway are still rare we generated a stable cell line transfected with a new fluorescence-based reporter.
Therefore, we designed a reporter gene construct based on the well-established TOPFLASH reporters coupled with eGFP instead of luciferase and then stably transfected into SW480 cells. As the wnt-state in this cell line is known to be active the new cell line named SW480-SuperTopEGFP can easily be used as a screening tool for new inhibitors the pathway.
In preliminary experiments the known wnt inhibitory compounds acetylsalicylic acid, XAV939 (tankyrase inhibitor; Hollande et al., 2010), PKF118–310 (Tcf4/β-catenin complex inhibitor; Wei et al., 2010) or FH535 (β-catenin inhibitor, Handeli et al., 2008), bleached the fluorescence of the tested well and measured the fluorescence recovery 24 hours after treatment compared to the untreated control. This resulted in a lower fluorescence signal in treated cells than in untreated cells. Following this treatment we used a self-made set-up to bleach cells seeded in a 96-well plate simultaneously. For quantification the fluorescence recovery time can be measured after treatment to have a dimension for the effectiveness for specific wnt inhibitors.
In conclusion we established an assay-set-up capable for use in automated image screening assays. In comparison to already established assays this new approach is much more cost-effective and easy to perform. Therefore this is a further step towards in specific compound research targeting the wnt pathway.
No conflict of interest.

840 POSTER

XenoBase enabled growth rate analysis improves xenograft study design

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Xenograft models are widely used in the oncology drug discovery and development process. However, the lack of available information regarding the Xenograft models, such as growth curves, standard of care treatment results, IHC analysis of biomarkers, as well as target gene expression, mutation and amplification, hampers the selection of suitable models for accurate evaluation of therapeutic molecules. We have created XenoBase™ that combines public cell line profiling data with our own data on >180 xenograft models. A searching engine is also built in the database to search for models based on gene mutation, expression, amplification, as well as SOC information, types (orthotopic, subcutaneous, systemic) of the xenograft models. The XenoBase™ will enable informed decision in selecting the most relevant models for the development of targeted therapeutics.
Armed with hundreds of xenograft studies available in the XenoBase™, we analyzed the tumor growth rate of each study in order to compare the results with traditional T/C analysis. The T/C analysis is the current standard, and a T/C value less than 0.42 is widely accepted as an indication of efficacy in evaluating a test article. However, this T/C analysis is limited in using only the data points on one day, overlooking the fact that tumor growth curves are generated over a long period of time (months) and with many days of data collection. To take advantage of the tumor growth curves, we analyzed tumor growth rate utilizing every data points, and derived growth rate based on slopes. Our analysis with the XenoBase™ data indicated that the growth rate based approach is more powerful in evaluating test articles for efficacy. If adopted by the industry, this approach may save hundreds of millions of dollars spent in excess number of animals and prolonged observations that may not be necessary.
No conflict of interest.

841 POSTER

High-throughput 3D screening reveals differences in drug sensitivities between culture models of JIMT1 breast cancer cells

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Background: Many cellular features are impaired in the traditional 2D cell culture conditions and big alterations in gene expression in comparison to tumors have been reported. Three-dimensional (3D) cell culture models are suggested to be better models than 2D monolayers due to improved cell-to-cell contacts and structures that resemble in vivo architecture.
Materials and Methods: The aim of this study was to develop a simple high-throughput 3D drug screening method and to compare drug responses in JIMT1 breast cancer cells when grown in 2D, in polyHEMA induced anchorage independent 3D models and in Matrigel 3D cell culture models. We screened 102 compounds with multiple concentrations and biological replicates for their effects on cell proliferation. Gene expression patterns of cells in the different culture models were also compared to xenografts.
Results: Big variations in drug responses were observed between the models. We show that, in general, JIMT1 cells grown on Matrigel were significantly more sensitive to drugs than cells grown in 2D cultures, while responses of cells grown in polyHEMA resembled those of 2D. Furthermore, comparison of gene expression profiles of the cell culture models to xenograft tumors indicated that cells cultured in Matrigel and as xenografts most closely resembled each other.
Conclusions: 3D cultures can provide a platform for systematic experimentation of larger compound collections in a high-throughput mode and can be used as alternatives to traditional 2D screens towards better comparability to in vivo state.
No conflict of interest.

842 POSTER

5-FU Monitoring in clinical practice: Pharmacokinetic variability

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Background: Current dosing of 5-Fluorouracil (5-FU) is based on body surface area (BSA). However BSA dosing has been associated with clinically significant pharmacokinetic (PK) variability. Dosing based on BSA has been seen to result in low exposure and loss of efficacy, or high exposure and severe toxicity. The reported target area under the concentration vs. time curve (AUC) for 5-FU is 20−30 mg.h.l^{-1}. 5-FU therapy which achieves this AUC has been shown to improve response rates and minimize toxicity. The aim of this study was to evaluate the practicality of sampling 5-FU for dose management and evaluate the PK variability resulting from BSA dosing in commonly used continuous infusion (CI) regimens for colorectal cancer (CRC).
Material and Methods: Blood samples were obtained from 24 patients with colorectal cancer receiving 5-FU CI: 9 patients received FOLFOX 4, 7 received FOLFIRI, 7 received De Gramont and 1 5FU/LV. The mean dose of 5-FU administered was 1151 mg/m^2 (range 440–1270 mg/m^2). In total 57 EDTA samples were drawn a minimum of 1 hr before the end of the 5-FU CI at 5-FU steady state concentration. The 5-FU concentrations were subsequently quantified on a Roche Cobas® 6000 using a homogeneous immunoassay (MyCARE™ 5-FU, Saladax Biomedical, Inc.). The 5-FU AUC was calculated from the reported plasma concentrations and one result was discarded as it was clearly an outlier.
Results: The 24 patients analyzed demonstrated a wide range of AUCs: ranging from 2.7 to 37 mg.h.l^{-1} with a mean of 12.2 mg.h.l^{-1} and a standard deviation (SD) of 6.19 mg.h.l^{-1}. There was no significant correlation observed between 5-FU dose and AUC for any of the regimens − overall R^2=0.0312; p = 0.576.

Regimen	Patients/ Samples	AUC, mg·h·l^{-1}		Number of patients below range
		Mean	SD	
Folfox 4	9/24	13.7	7.0	8 (89%)
Folfiri	7/18	8.4	2.7	7 (100%)
DeGramont	7/13	14.4	6.2	6 (86%)
5-FU/LV	1/1	15.3	−	1 (100%)

Conclusions: These data support the previous reports that standard BSA dosing of 5-FU leads to a high PK variability. Using the optimal AUC range of 20−30 mg.h.l^{-1}, out of the 24 patients, 22 (92%) were under the target level with only 2 out of the 24 receiving an initial dose resulting in an AUC within the target range. Exposure appeared independent of regimen. Based on the results of this small study it appears that sampling and measuring concentrations of 5-FU during CI to adjust the dose to reach optimal exposure is practical and may be a rational approach to delivering effective treatment.
No conflict of interest.

843 POSTER

Nanostructured silica functionalized with an organotin compound induces differentiation of B16 melanoma cells

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Background: Cancer nanotechnology is a promising area of research in science and medicine that finds application for molecular imaging, molecular diagnosis, and targeted therapy. Using targeted nanoparticles with anti-cancer drugs offers the possibility of destroying tumors with minimal damage to healthy tissue and organs using significantly lower doses of toxic chemotherapy. Nanostructured silica-based materials proved to be an excellent candidates as drug carrier for cancer therapy. Here we evaluated potential of silica nanoparticles SBA-15p grafted with an organotin(IV) compound [$SnPh_3\{(CH_2)_8OH\}$] against B16 melanoma cells.
Material and Methods: Cell viability was estimated by MTT and CV tests. Flow cytometric analysis was done on cells stained by Propidium Iodide, Annexin V-FITC/PI, Apostat, DAF-FM, DHR or CFSE dye. Differentiation of melanoma cells was evaluated by measuring intracellular amount of melanin and activity of key enzyme involved in melanin synthesis − tyrosinase and microscopic analysis of cells stained with hematoxylin dye.
Results: SBA-15pSn as well as [$SnPh_3\{(CH_2)_8OH\}$] strongly suppressed the viability of B16 cells. The amount of [$SnPh_3\{(CH_2)_8OH\}$] in MC_{50} concentration of SBA-15pSn is approximately 100 times lower than IC_{50} dose of free [$SnPh_3\{(CH_2)_8OH\}$]. Carrier alone had no influence on cell viability. Reduced cell viability was the consequence of inhibited cell proliferation. In parallel, small percentage of cells died by caspase dependent apoptosis. The rest of the cells were transformed into large, granulated cells. Observed granules were in fact melanosomes since it was determined that SBA-15pSn strongly enhanced tyrosinase activity and melanin quantity. On the other hand free compound slightly increased tyrosinase activity and production of melanin. Amount of reactive oxygen and nitrogen species was not significantly changed in the presence of SBA-15pSn suggesting that antitumor activity was not associated with their production. Free compound reduced the production of ROS which can be explained as a defense mechanism against toxic stimuli.
Conclusion: Overall results show that packaging of toxic metal-based drug in nanoparticles achieved a stronger antitumor effect with less toxicity.
No conflict of interest.

844 POSTER

Physical and chemical compatibility of fosaprepitant dimeglumine for injection with concomitantly dosed medications

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Background: Fosaprepitant (EMEND IV®, IVEMEND® and PROEMEND®) is a key anti-emetic therapy for highly emetogenic chemotherapies (MASCC/ESMO Antiemetic Guideline 2011). As fosaprepitant is frequently co-administered with other agents, it is important to understand which combinations of drugs will not adversely impact the chemical or physical stability of Fosaprepitant. Therefore, we explored the impact of concomitantly dosed medicines on the physical and chemical stability of fosaprepitant (and only fosaprepitant). Mixtures included combinations of other anti-emetics, corticosteroids, anti-histamines, H2 blockers, anti-spasmodics, B vitamins, Vitamin K, diuretics and infusion solutions (including saline, glucose solution and multiple electrolyte solutions).
Materials and Methods: 172 different combinations of fosaprepitant with up to four other agents were prepared together to simulate simultaneous administration from a single IV bag. The impact on fosaprepitant stability was determined by visual observation and HPLC analysis after storage under ambient conditions for 24 hours.
Results: Fosaprepitant was found to be compatible with many of the admixtures. Degradate growth was determined to the most sensitive predictor of stability. The extent of degradation of fosaprepitant was strongly dependent on the solution pH. These results are consistent with the known chemistry of fosaprepitant. The only degradate observed was the active pharmaceutical ingredient aprepitant, which readily forms via hydrolysis from the prodrug fosaprepitant.
Conclusions: Acceptable in-vitro physical and chemical stability of fosaprepitant was demonstrated with many of the concomitantly dosed medicines. The pH of the admixture was shown to have a significant impact on the stability of fosaprepitant.
Conflict of interest: *Other substantive relationships: BD and MDS are employees of Merck and may own stock/stock ownership in the company.JS and HK are employees of Ono Pharmaceuticals Co., Ltd.*

846 POSTER

Safety results from a Phase I study with a new tablet formulation of olaparib (O) in combination with carboplatin (C) and paclitaxel (Pa)

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Background: This Phase I study evaluated safety/tolerability and preliminary antitumour activity of the PARP inhibitor O with C and Pa in patients (pts) with advanced solid tumours refractory to standard therapies (NCT00516724; sponsor, AstraZeneca). Previously, we reported data from cohorts 1−15 that evaluated the capsule form of O and identified a tolerable schedule with CPa: O 200 mg bid (d1−10) plus CPa AUC4/175 mg/m^2 q 3 weeks (van der Noll *et al* ASCO 2013). Here, we report data from cohorts evaluating a new tablet form of O with higher bioavailability and improved pt convenience vs the capsule.
Materials and Methods: O tablets were introduced at 200 mg bid (days 1−10 per 21-day cycle) with CPa AUC4/175 mg/m^2 q 3 weeks (both on day 1 per cycle); as this proved non-tolerable, other regimens were explored. AEs were graded by CTCAE v3.0. Objective tumour response was evaluated by RECIST.
Results: 102 pts were enrolled in 3 centres. The table shows dose schedules for tablet cohorts.

Cohort (pts, n)	O, mg bid (days)	C, AUC
16 (8)	200 (1−10)	4
17 (6)	100 (1−10)	4
17b (15)	100 (1−10)	4
18 (6)	100 (1−10)*	4
19 (6)	100 (1−5)	4
20 (6)	100 (3−12)	4
21 (13)	50 (1−5)	5
22 (6)	200 (1−2)	5
23 (6)	100 (1−2)	6
24 (6)	100 (1−5)	5
25 (6)	100 (1−2)	5
26 (6)	50 (1−2)	6
27 (6)	50 (1−2)	5
28 (6)	50 od (1−5)	5

Pa dose: 175 mg/m^2 in all cohorts. *100 mg od on day 1 (6 h post-C).

Most common tumour types were breast (53%) and ovarian (33%); 90 (88%) pts had received prior chemotherapy. 40 (39%) pts were known to have a *BRCA1/2* mutation. Common haematological AEs included neutropenia (53%), thrombocytopenia (41%) and anaemia (20%). Other common AEs included fatigue (82%) and nausea (73%). Neutropenia leading to delays in chemotherapy cycles was the main dose-limiting toxicity. Toxicities in tablet cohorts were generally consistent with those in capsule cohorts, but lower O tablet doses and/or treatment durations were needed to manage increased haematological toxicity (neutropenia) and treatment delays. Cohort 19 was tolerable but, due to the low C dose (AUC4), further dosing schedules were assessed leading to identification of a second tolerable schedule with C AUC5 (cohort 27). Preliminary antitumour activity was encouraging with 5 (5%) pts achieving a complete response and 39 (38%) a partial response.
Conclusions: When combined with CPa, a lower dose of the tablet formulation of O (vs capsule) is required to optimize tolerability. O 50 mg

bid plus CPa AUC5/175 mg/m^2 was considered tolerable, but with limited duration of O use (2 days per cycle).
Conflict of interest: *Ownership: I. Tchakov & K. Bowen are employees of AstraZeneca and own AstraZeneca stock*

847 POSTER

Discovery of naturally occurring toll-like receptor-4 signalling inhibitors: Their anticancer effects and mechanisms of action

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Background: Toll-like receptor 4 (TLR-4) plays a key role in pathogen recognition and activation of innate immunity. Very recent studies have suggested aberrant TLR-4 activation by tumour cells promotes their proliferation and survival. To the best of our knowledge, there are no studies on the potential use of TLR-4 signalling inhibitors in cancer treatment. Therefore with the aim of exploring the potential of TLR-4 signalling inhibitors in cancer treatment.
Materials and Methods: We have employed the target- and ligand-based *in silico* screening to discover novel natural products as TLR-4 signalling inhibitors. The best drug-like compounds were selected for *in vitro* studies to measure their efficacy in inhibiting the actions of lipopolysaccharide (LPSEc) in TLR-4/MD-2/CD-14 transfected HEK-293 cells. Their IC_{50} value was determined using dose-response curves. The IC_{50} value is defined as the concentration of these compounds inhibit the 50% of LPSEc's activity. The anticancer effects of these compounds were evaluated in 12 human cancer cells using MTT assay. We also evaluated the apoptotic induction effects of these compounds using fluorescence microscope and enzyme linked immunosorbent assay (ELISA).
Results: The majority of the selected compounds were shown significant inhibition of LPSEc induced TLR-4 activity. The experimental results are in good agreement with virtual screening results suggesting the constructed *in silico* model is a good model and can be used in discovering novel TLR-4 signalling inhibitors. The results suggested the TLR-4 signalling inhibitors are effective in inhibiting cancer progression. The cytotoxic effects exhibited by these compounds were also confirmed to be more selective towards cancer cells rather than non-cancerous cells. Our results suggested the TLR-4 signalling inhibitors induced apoptosis in cancer cells rather than necrosis.
In conclusion, we have discovered a natural product that inhibits TLR-4 signalling and have proven that TLR-4 signalling inhibitors play a a role in preventing cancer progression.
No conflict of interest.

848 POSTER

Targeting Immuno-liposomes using TCR-like antibodies directed against melanoma antigens

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Chemotherapeutic treatment of solid tumors is greatly hampered by factors like toxicity, rapid drug clearance and poor perfusion of the drug to tumor areas. Nanocarriers such as liposomes make an attractive alternative to free cytotoxic drug by reducing toxicity and promoting drug accumulation in tumors. When coupled to a ligand they can be internalized selectively by target tumor cells. Here, we aim to improve liposomal chemotherapy by developing drug-loaded liposomes that specifically target cell surface-expressed peptide-MHC complexes which constitute the natural targets for T-cells and are uniquely or overexpressed on melanoma cells.
Single chain Fv's G8 and Hyb3 against Melanoma Antigen 1 presented by human leukocyte antigen class 1 (MA1/A1) were derived from a phage-display library. scFv for liposome conjugation are cloned in a modified vector pABC4 which holds an additional cysteine at the C′ terminus of scFv during the production. These scFv are produced in periplasmic fractions and extracted by immobilized metal ion affinity chromatography. Purified scFv are validated by flow cytometry on APD cells pulsed with MA1/A1. Liposomes are prepared by film hydration and extrusion method and characterized by size, polydispersity and lipid concentration and then coupled to scFv via a thio-ether bond. Various analytical approaches are applied to validate this immunoconjugate.
scFv with C-terminal cysteins were produced and purified in considerable yield. Purified scFv were tested for target specificity toward MA1/A1 complex and demonstrated desired affinity for the ultimate molecular target. G 8 and Hyb 3 differ with respect to their ligand-binding affinity towards wild type MA1/A1, expressed by native tumor cells: KD's of 250 and 14 nM, respectively. The difference in ligand-binding affinity will allow us to compare the importance of this parameter for multivalent nanoparticles. The process of coupling scFv to liposomes is being optimized with regard to efficiency and antibody density. Produced immunoliposomes demonstrated cell specific targeting using flow cytometry, in vitro. Various cell assays will be done using fluorometry and confocal microscopy to confirm binding and internalization.
TCR like antibodies have been produced in a scFv format ready for coupling to liposomal nanocarriers. Preliminary data suggest cell specific binding of the newly produced immunoliposomes. Final aim is to evaluate these immuno-conjugates in vivo in relevant tumor models.
No conflict of interest.

849 POSTER

First in human phase I study of PankoMab-GEXTM: a novel glyco-optimized anti-TA-MUC1 monoclonal antibody

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Background: PankoMab-GEX is a potent humanized and glyco-optimized IgG1 recognizing the novel carbohydrate-induced conformational TA-MUC1 epitope expressed on the majority of tumor cells in a wide variety of cancers. Its epitope comprises a tumor specific carbohydrate antigen (TF or Tn) together with the immunodominant peptide region of MUC1, is human-specific and virtually only expressed on malignant cells. PankoMab-GEX promotes potent tumor cell killing via ADCC, phagocytosis, apoptosis induction and proliferation inhibition.
Methods: Eligible patients with TA-MUC1 positive (IHC reactivity score $\geqslant$3 on a 12 grade scale) advanced solid tumors, progressing after standard treatments, were enrolled into this first in humans phase I trial. Primary endpoints were safety and tolerability. Pharmacokinetics (PK), immunogenicity and anti-tumor activity were also assessed.
Results: Of the 74 pts included, 73 were treated per protocol: 52 (51) q3w (13 dose levels (DL) from 1–2200 mg), 18 q1w (5 DL from 300–700 mg), 4 q2w (1200 mg + 900 mg start dose one week prior). No MTD was reached. Infusion-related reactions (IRRs), mostly of º1/2 during and after cycles 1 or 2 occurred in ~50 % of the pts starting at the DL of 300 mg q1w. IRR consisted of dyspnea, rash, erythema and flushing, but no cytokine release, and no increases of factor C3a or eosinophilic cationic protein and hence no allergic reactions were observed. Premedication reduced IRRs at 1st inf. from 86% (6/7pts) to 53% (19/36pts) at DL $\geqslant$600 mg. PK was linear and dose-independent with a mean t1/2 =184 h (q3w). In pts with at least one post-baseline CT (62) overall confirmed clinical benefit rate (CBR) was 32% (20/62 pts) across all DL and schedules and 50% (17/34) at DL $\geqslant$600 mg including 1 CR with normalization of CA125 in an ovarian cancer case for 483 days at 1100 mg q3w, and 1 PR for 295 d in a NSCLC case at 600 mg q1w. Confirmed CBR in pts with OvCa was 45% (9/20) over all DL, and for DL $\geqslant$600 mg 60% (9/15). All 5 pts sensitive to their last platinum based therapy experienced CB. Maximum CB duration was in a pseudomyxoma peritonei pt (−21% SLD ongoing for >700 d at 900 mg q3w).
Conclusions: PankoMab-GEX is safe and demonstrated clinical activity in heavily pre-treated pts. The q1w, q2w and q3w administration schedules were feasible and associated with CB.
No conflict of interest.

850 POSTER

S100A4 neutralizing mAbs for the treatment of cancer

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Background: S100A4 belongs to the S100 family of small Ca-binding proteins. Secreted by tumor and stromal activated cells, plays an important role in tumor progression, angiogenesis and metastasis and therefore it turns out into a very compelling target for cancer therapy. S100A4 has gained increasing attention over the last two decades because of its metastasis-promoting properties and its over-expression has been reported to be associated with poor prognosis of cancer correlates. Although extracellular roles of S100A4 are closely associated with tumor invasion and metastasis, the mechanism by which it promotes an invasive phenotype is not fully understood. This study aimed to determine the role of S100A4 in tumor growth, angiogenesis and metastasis and we

addressed the use of a neutralizing monoclonal antibody (5C3) targeting the extracellular activity of S100A4, to inhibit tumor progression.
Materials and Methods: Endothelial cell-based studies were used pointing to the involvement of S100A4 in at least two steps in the angiogenic cascade: remodeling of the extracellular matrix and cell migration.
We have developed the 5C3 neutralizing monoclonal antibody against S100A4 protein. To examine the inhibitory effect of our antibody a panel of *in vitro* and *in vivo* experiments were run. We used several subcutaneous, orthotopic and intrasplenic mouse tumor models to test the efficacy in tumor development.
Results: Boyden chamber migration assay showed that S100A4 synergizes with VEGF on HUVECs migration and the combination of 5C3 mAb with Bevacizumab is more effective than the two drugs separately. In addition, S100A4 induces the secretion of active forms of MMP-9 and 5C3 mAb blocks this effect.
We observed that treatment with 5C3 reduced in vivo angiogenesis on MiaPACA-2, M21 and HT29 subcutaneous tumor model thereby affecting tumor growth ($p < 0.05$).
Treatment with 5C3 revealed a potent decrease in lung and liver metastasis using the 4T1 orthotopic model and the KM12L4luc intrasplenic model respectively.
Finally, we have also observed that extracellular S100A4 induces metastasis formation by building the pre-metastatic niche on the CT26 intrasplenic model.
Conclusions: Our results highlight the relevance of extracellular S100A4 in tumor development and prove it as a novel therapeutic target in cancer.
No conflict of interest.

851 POSTER

Assessing the potential of S100A7 as target for tumor therapy using neutralizing monoclonal antibodies

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Background: S100A7, a member of the S100 calcium-binding protein family, is a low molecular weight protein whose expression have been reported in several cancer types such as breast, lung, bladder, skin, esophageal, gastric and head and neck, correlating in most of them with a poor prognosis. It has been described that extracellular S100A7 can act as a pro-inflammatory, pro-angiogenic and pro-metastatic factor, but its mechanism of action remains poorly understood. In this study, we have developed neutralizing monoclonal antibodies against S100A7 and tested its functionality in different in vitro and in vivo models as therapeutic and diagnostic tools.
Materials and Methods: Cell migration and MTT assays were performed to test the capacity of the obtained specific monoclonal antibodies to neutralize extracellular S100A7 activity. We also studied the downstream signaling pathways and the secretion of pro-inflammatory factors in response to extracellular S100A7 and its blockade by our antibodies. Finally, we assessed the usefulness of the monoclonal antibodies as diagnostic tools for the detection of S100A7 in biofluids and in tumor samples by ELISA and immunohistochemistry respectively.
Results: Extracellular S100A7 induced an increase on MDA-MB-231 breast cancer cell migration and secretion of pro-inflammatory factors possibly by the activation of the MAPK pathway. Furthermore, S100A7 promoted the proliferation of HT1080 fibrosarcoma cells. Our anti-S100A7 specific monoclonal antibodies were effective in neutralizing the *in vitro* activity of S100A7 protein. Finally, we have demonstrated that our antibodies can be used in diagnosis and prognosis by determining the presence of S100A7 in tissue samples and in plasma from tumor bearing mice. A positive correlation between the S100A7 plasma levels and the tumor presence and tumor burden was found.
Conclusions: We have elucidated the extracellular action of S100A7 in tumor cells and obtained useful tools for cancer diagnosis and therapy by the blockade of this protein as a therapeutic target.
No conflict of interest.

852 POSTER

Targeting extracellular S100P: therapeutic potential of monoclonal antibodies

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Background: S100P has gained increasing attention over the last two decades because of its cancer-promoting properties, via its specific roles in survival, cell proliferation, angiogenesis, metastasis and drug resistance. Furthermore, high S100P expression has been identified as a significant marker for poor prognosis in several cancer types (such as pancreatic, breast, colon, prostate and lung) when compared with their matched normal tissues and associated to an increased incidence of metastasis. S100P have also shown to be a potential marker with diagnosis and prognosis value for several cancers. The purpose of this study was to validate S100P as a promising target for therapeutic and diagnostic applications by using neutralizing monoclonal antibodies.
Materials and Methods: Specific monoclonal antibodies able to neutralize the extracellular activity of S100P were obtained.
To better understand the role of S100P in tumor cell proliferation and survival, we used two cell lines; one expressing S100P (human pancreatic BxPC3) and one no-expressing (fibrosarcoma HT1080). Proliferation, drug resistance and migration properties were studied *in vitro*. *In vivo* tumor models (subcutaneous, orthotopic and intrasplenic) were developed to assess the efficacy of anti-S100P mAbs on tumor growth and metastasis.
Results: Here we have clearly demonstrated the inhibitory effect of our mAbs on S100P-induced tumor cell proliferation. Additionally, S100P protected BxPC3 and HT1080 cell lines to the cytotoxic effect induced by chemotherapeutic drugs by increasing their survival while anti-S100P mAbs reversed this effect.
Moreover, anti-S100P mAbs blocked tumor growth *in vivo* on a BxPC3 subcutaneous model either by i.t or i.p. route. Moreover, a clear reduction on liver metastasis formation and in the final staging of the disease was observed in an orthotopic and an intrasplenic tumor model when treated with anti-S100P mAbs.
Finally, we have demonstrated a positive correlation between S100P plasma levels and tumor incidence.
Conclusion: These results have shown the importance of S100P in tumor progression and aggressiveness. Therefore, blocking S100P is a valid therapeutic approach and it might improve the response to other therapeutic treatments as well as to decrease the metastatic capacity of the tumor.
No conflict of interest.

853 POSTER

Immunogenicity assessment of PF-05280014, a potential biosimilar to trastuzumab, in healthy subjects (REFLECTIONS B327−01)

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Background: PF-05280014, a proposed biosimilar to trastuzumab, was evaluated for immunogenicity in a phase 1 pharmacokinetic (PK) similarity study.
Methods: In this double-blind trial (NCT01603264), 105 healthy male subjects with no known prior biologics exposure, were randomized to receive a single 6 mg/kg IV dose of PF-05280014, or trastuzumab sourced from the US (trastuzumab-US) or the EU (trastuzumab-EU) and followed for 10 weeks for PK, safety, and immunogenicity assessments. Serum samples for detecting anti-drug antibodies (ADA) and neutralizing antibodies (Nab) were collected at 0, 336, 672, 1008, and 1680 hours post-dosing. ADA was detected using two validated electrochemiluminescent immunoassays, one each to detect antibodies against PF-05280014 and reference drugs. Samples were first tested for antibodies against the dosed product. Confirmed positive samples were further tested for Nab using a validated semi-quantitative competitive ligand binding assay, and for ADA cross-reactivity. All subjects provided informed consent.
Results: Samples for immunogenicity assessment were collected from all 105 subjects. Only 2 samples tested positive; the rest (99.6%) tested negative in the ADA assay specific for the dosed product. One positive sample was collected at 1680 hours after dosing from a subject who received trastuzumab-EU (Subject 1). This sample had a low titer of ADA and tested negative against PF-05280014. There were no adverse events attributable to the ADA finding for this subject. The other sample testing positive was collected before dosing from a subject who subsequently received PF-05280014 (Subject 2). This low false-positive rate (1/105) of ADA at baseline was consistent with assay validation requirements to ensure high probability of identifying all subjects who develop ADA. The 2 ADA-positive samples were negative for Nab. The 3 study agents were well-tolerated and adverse events were similar. The PK profile of Subject 1 was similar to other subjects in the trastuzumab-EU group. The PK of the 3 study agents were shown to be similar based on C_{max}, AUC_t, and AUC_{inf} and the standard bioequivalence criteria of 80–125%.
Conclusions: Consistent with reported data for trastuzumab in patients with cancer, PF-05280014 appears to have low immunogenic potential

when given as a single IV infusion to healthy subjects. Overall, PF-05280014 demonstrated PK similarity and comparable safety and immunogenicity profiles to trastuzumab in healthy subjects.
Conflict of interest: *Ownership: Stock in Pfizer (DY, CTT, KBB, XM, DR, RL, ADR, CZ). Advisory board: None. Board of directors: None. Corporate-sponsored research: None. Other substantive relationships: All authors are current employees (DY, CHC, CZ, DR, KBB, RL, XM), former employees (ADR), or contract employees (CTT, SDR) of Pfizer Inc*

854 POSTER

Neoadjuvant-adjuvant treatment of breast cancer: A model for extrapolation of clinical data for trastuzumab biosimilar candidates

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Background: Trastuzumab (Herceptin®) is approved for HER2-positive EBC, MBC and MGC. Trastuzumab biosimilars raise questions about how best to conduct mandatory, head-to-head clinical equivalence studies, to show similarity in efficacy, safety and immunogenicity and mitigate risks associated with extrapolation to indications not investigated by the biosimilar mAb. EMA mAb biosimilar guidelines recommend sensitive and homogenous populations and sensitive endpoints for such studies. MBC patient (pt) populations are generally heterogenous, and pts may have a compromised immune response. Establishing clinical similarity in the neoadjuvant–adjuvant setting may be the better risk mitigation strategy for extrapolating clinical data to MBC and may be more acceptable to regulators than the reverse.
Materials and Methods: Data from NOAH (neoadjuvant–adjuvant trastuzumab + CTx vs. CTx, N = 231) were used to retrospectively assess treatment effect size (difference between arms) and identify a sensitive, homogenous population, as per the EMA guidelines. tpCR treatment effect differences were evaluated as a sensitive endpoint for investigation of clinical benefit. This can then allow assessment of equivalence only based on tpCR endpoint.
Results: tpCR treatment effect size was 19%. Based on the study results, a 15−20% difference in tpCR rate may translate to a clinically meaningful difference in disease-free survival. If biosimilars were evaluated using an equivalence design and margins of 10% based on the tpCR endpoint (40% response), the sample size would be 500 pts per arm (80% power, 18% drop-out rate). In trials of this sort, similarity in immunogenicity could be assessed when pts are given trastuzumab monotherapy excluding bias or immunosuppressive effects due to concomitant CTx.

	tpCR %
Trastuzumab + CTx (n = 115)	40
CTx alone (n = 116)	21
Effect size	**19**

Conclusions: Sensitive populations as defined by EMA regulations are those that are homogenous, often the most responsive to therapy and are treatment naive. If equivalence in efficacy, safety and immunogenicity of trastuzumab (reference product) and a trastuzumab biosimilar candidate is demonstrated in the neoadjuvant–adjuvant setting, this may provide a reasonable basis for extrapolation to other indications not specifically studied during biosimilar development. This may be a more sensitive approach than one based on ORR in MBC, as ORR is less sensitive to treatment differences and only weakly correlated with clinical endpoints.
Conflict of interest: *Other substantive relationships: All authors are employees of Genentech or F. Hoffmann-La Roche Ltd*

855 POSTER

Anti-FGFR1 humanized monoclonal antibody OM-RCA-01 inhibits FGF-induced angiogenesis

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Background: The growth of new blood vessels is regulated by several proangiogenic factors. We believe that the angiogenesis induced by basic fibroblast growth factor (bFGF) is resistant to anti-VEGF/R therapy and can be targeted by anti-FGFR1 monoclonal antibody.
Methods: In our in vivo study, angiogenesis was measured with subcutaneously implanted Matrigel plugs containing: 1) bFGF; 2) VEGF; 3) bFGF+bevacizumab; 4) VEGF+bevacizumab; 5) bFGF+anti-FGFR1 monoclonal antibody OM-RCA-01 (Tsimafeyeu et al. 2012 ASCO meeting); 6) VEGF+OM-RCA-01. Control group was without stimulation or treatment. Doses of bFGF, VEGF-A (R&D Systems), bevacizumab (Roche), OM-RCA-01 (OncoMax) were 100 ng, 200 ng, 10 mg/kg, and 10 mg/kg per animal, respectively. Number of endothelial cells/vessels was calculated.
Results: There was no neovascularization in bFGF negative, VEGF negative group (mean, 0). bFGF and VEGF strongly induced angiogenesis ($P<0.001$). There were no vessels and endothelial cells in anti-FGFR1 antibody FGF-stimulated group (mean, 0). In bFGF-induced angiogenesis, bevacizumab did not impact on neovascularization in comparison with bFGF positive control ($P = 0.5$). The angiogenic effect of VEGF was significantly inhibited by bevacizumab in comparison with VEGF positive control ($P<0.0001$). OM-RCA-01 not significantly inhibited growth of vessels in VEGF positive group ($P = 0.064$).
Conclusion: Anti-FGFR1 monoclonal antibody OM-RCA-01 inhibited FGF-induced angiogenesis. Targeting VEGF(R) by bevacizumab significantly impacted on VEGF-induced angiogenesis and not on bFGF-induced neovascularization.
Conflict of interest: *Other substantive relationships: N. Golub, E. Zaveleva are employers of OncoMax LLC*

856 POSTER

Eudesmol isomers induce caspase-mediated apoptosis in human hepatocellular carcinoma HepG2 cells

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Background: Eudesmols are naturally occurring sesquiterpenoid alcohols that present cytotoxic effect to cancer cells. In this work, we studied the mechanisms of cytotoxic action of eudesmol isomers (α-, β- and γ-eudesmol) in human hepatocellular carcinoma HepG2 cells.
Material and Methods: In first, Three tumour cell lines (HepG2, K562 and B16-F10) were treated with increasing concentrations of eudesmol isomers for 72 h and analysed by methyl-[^{3}H]-thymidine incorporation assay. The pro-apoptotic affect of these compounds was assessed in HepG2 cells by morphological analysis (using hematoxylin/eosin staining and acridine orange/ethidium bromide staining), flow cytometry (cell membrane integrity, mitochondrial transmembrane potential, cell cycle distribution and internucleosomal DNA fragmentation analysis) and caspase-3 activation assay after 24 h incubation.
Results: All eudesmol isomers displayed cytotoxicity to different tumour cell lines. α-Eudesmol showed IC_{50} values ranging from 5.38 to 10.60 μg/mL for B16-F10 and K562 cell lines, β-eudesmol showed IC_{50} values ranging from 16.51 to 24.57 μg/mL for B16-F10 and HepG2 cell lines and γ-eudesmol showed IC_{50} values ranging from 8.86 to 15.15 μg/mL for B16-F10 and K562 cell lines, respectively. After 24 h incubation, HepG2 cells treated with eudesmol isomers presented typical hallmarks of apoptosis, as observed by morphological analysis in cells stained with hematoxylin–eosin and acridine orange/ethidium bromide. Significant increases in internucleosomal DNA fragmentation without affecting membrane integrity were also found. In addition, eudesmol isomers induced loss of mitochondrial membrane potential and an increase of caspase-3 activation in HepG2 cells, suggesting that this apoptotic cell death was caspase-dependent.
Conclusions: In conclusion, the eudesmol isomers herein investigated are able to reduce cell proliferation and to induce tumour cell death through apoptotic pathways.
No conflict of interest.

857 POSTER

Eusynstyelamide B: a novel topoisomerase II inhibitor isolated from an ascidian from the Great Barrier Reef

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Researchers have shown that marine ascidians are an excellent source of new anticancer compounds that can exhibit new mechanisms of action. The Great Barrier Reef is a rich environment harbouring a prolific ascidian biodiversity, and many of the species have never been explored for bioactive natural products. The aim of this project was to isolate and characterize

anticancer compounds from ascidians belonging to the family Didemnidae. We tested a total of 143 ascidian specimens from the Eskitis Biota Library for anti-proliferative effects in the prostate cancer cell line LNCaP using the real-time cell analyser xCELLigence System. Twenty-one hit extracts were identified, and the most interesting extracts were selected for bioassay-guided fractionation in order to purify the bioactive compound(s). From these studies we identified a previously reported modified tryptophan-arginine dipeptide dimer, named eusynstyelamide B (EB). We found that EB inhibited proliferation of LNCaP cells with an IC_{50} of 5 μM. Cell cycle studies and analysis of histone H3 phosphorylation showed that EB arrested LNCaP cells in the G2 phase. RNA expression profiling by micro array and qRT-PCR suggested that the EB-induced G2 arrest was caused through DNA damage pathways. Western blotting experiments confirmed phosphorylation of ChK2, but not of p53 or ChK1, and down-regulation of CDC2 protein expression. EB-induced DNA damage was confirmed by neutral comet assay and the formation of γH2AX foci. Intercalation displacement assays and melting curve analysis demonstrated that EB did not interact with DNA. Importantly, when incubated with kDNA and topoisomerase II EB strongly inhibited the decatenation of kDNA. These data indicate that EB is a novel topoisomerase II inhibitor which causes DNA damage in LNCaP cells. Studies are ongoing to further characterize the potential anti-cancer properties of this compound and validate the findings in additional cancer cell lines.
No conflict of interest.

858 POSTER

Allylbenzenes as potential chemosensitizers and P-glycoprotein inhibitors

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Background: Allylbenzenes are a family of compounds found essentially in spices. Some of them can induce apoptosis in tumour cells. In our previous studies we determined that eugenol can inhibit topoisomerase II and induce apoptosis in mammalian cells, while myristicin can also induce apoptosis in human leukaemia K562 cells. Eugenol was genotoxic while myristicin was non-genotoxic. The apoptotic activity of the allylbenzenes raised the possibility of them potentiating the activity of standard chemotherapeutic drugs, particularly in cases of multidrug resistance, a major cause of failure of cancer chemotherapy. Multidrug resistance can also occur as the result of drug extrusion due to up-regulation of membrane efflux pumps (EP) such as P-glycoprotein (P-gp, ABCB1). Much research has been performed to identify EP inhibitors, and a large number of natural compounds have shown promise in inhibiting EP.
Material and Methods: We analysed five allylbenzenes for their ability to inhibit the function of P-gp by using a Semi-automated Fluorimetric Method that monitors ethidium bromide (EB) uptake and extrusion, on a real-time basis by L5178 mouse T-cell lymphoma cells expressing the human ABCB1 (P-gp) gene. Monitoring of uptake and extrusion of EB was assessed using the Rotor-gene™ 3000 (Corbett Research). MDA-MB-231 breast metastatic cancer cells were used to analyse synergy with doxorubicin using the MTT assay.
Results: We observed that eugenol, α and β-asarone potentiated the cytotoxicity mediated by doxorubicin in MDA-MB-231 breast metastatic cancer cells. Extrusion of EB took place readily in control cells expressing ABCB1. In cells exposed to known inhibitors of efflux pumps (verapamil and cyclosporine A) there was marked EB accumulation. The allylbenzenes α and β-asarone strongly inhibited EB efflux, followed by myristicin and eugenol. The allylbenzene trans-anethole did not present significant inhibitory activity.
Conclusions: In conclusion, α and β-asarone can potentiate the cytotoxicity of doxorubicin and also inhibit P-gp efflux pumps and can be regarded as promising candidates, in co-treatments, to increase cell death and overcome resistance to known chemotherapeutics.
No conflict of interest.

859 POSTER

Population pharmacokinetics (PPK) of eribulin in cancer patients

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Background: Eribulin mesylate (Halaven®) is a non-taxane microtubule dynamics inhibitor, approved for the treatment of certain patients with breast cancer. A combined population PK analysis was conducted using data from seven Phase 1 studies, one Phase 2 study and one Phase 3 study in cancer patients to characterise eribulin PK profile and identify covariates that affect eribulin exposure. Eribulin mesylate was administered intravenously at doses between of 0.25 and 2 mg/m^2.
Materials and Methods: Data from 69 males and 444 females (389 with breast cancer), aged 27 to 81 years and weighing 39 to 161 kg were available for PPK analysis. The pooled dataset comprised of 4093 eribulin concentrations. PPK was conducted using NONMEM with first-order conditional estimation method with interaction (FOCEI). Stepwise covariate building was performed and the final model was evaluated using bootstrap analysis and predictive check simulations. Covariates tested were age, weight (WGT), hepatic function markers (albumin (ALB), alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate trasnferase (AST), bilirubin (BILI)), renal function (creatinine clearance (CLCr)), gender, race, ECOG status and tumor type (breast vs. other).
Results: Eribulin PK was characterised by a three-compartment model where both volume (V_1, V_2, V_3) and clearance (CL, Q_2, Q_3) parameters were proportional to WGT according to an allometric model. Other covariates were related to hepatic function with effects of ALB, ALP and BILI levels significantly affecting CL. Population estimates were: CL = 3.11 L/h, $V_{1=}$ 4.06 L, Q_2 = 2.64 L/h, $V_{1=}$ 4.06 L, V_2 = 2.42 L, Q_2 = 6.60 L/h and V_2 = 121 L. Eribulin CL increased proportionally with ALB levels (exponent: 0.946) and decreased proportionally with ALP (exponent: −0.209) and BILI levels (exponent: −0.180). Inter-individual variability was moderate ranging between 37 % for V3 and 52 % for CL. Proportional residual variability in eribulin concentrations was moderate (24 %). Evaluation from bootstrap and predictive checks suggested robustness of the final model for all patients. Eribulin PK was unaffected by age, renal function, gender, race, ECOG status and tumor type.
Conclusions: The population model adequately described eribulin PK in breast and other cancer patients. WGT, ALB, ALP and BILI were significant predictors of eribulin CL. The current model can be utilised to characterise eribulin PK and predict eribulin exposure in cancer patients.
Conflict of interest: *Corporate-sponsored research: All authors are employees of Eisai Europe Ltd, or Eisai Inc.*

860 POSTER

Lurbinectedin (PM01183) in combination with doxorubicin (DOX): Preliminary results of a phase Ib study

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Background: PM01183 has wide antitumour activity through minor groove DNA-binding. Synergism with DOX was observed preclinically. PM01183 monotherapy is undergoing clinical evaluation in pancreatic, ovarian and breast cancer patients (pts). Reversible neutropenia and high emetogenic potential are its main side effects.
Methods: Pts were included in successive cohorts aiming to define the recommended dose (RD) of PM01183 combined with 50 mg/m^2 of DOX (fixed dose) q3wk, with or without colony-stimulating factors (CSF) prophylaxis. Less than 1/3 of at least 9 pts had to have dose-limiting toxicities (DLTs) in Cycle 1, at the RD. Pharmacokinetics (PK) were assessed. Consenting adults ⩽75 years, ECOG PS 0−1, adequate organ function and up to 2 prior chemotherapy lines were included. Prior adjuvant DOX was allowed. DOX had to be withdrawn before exceeding 450 mg/m^2 of cumulative dose. PM01183 could be continued alone if clinical benefit.
Results: As of March 2013, 43 pts were treated: 53.5% were males, median age was 61 years (r: 22−78). SCLC (30%), STS (21%) bladder (12%), and gynaecological, stomach and NET (9%, each) were the most frequent locations. DLTs occurring at the MTD, 5.0 mg flat dose (FD) of PM01183, with or without CSF, were febrile neutropenia (FN=3), sepsis, grade 4 thrombocytopenia and grade 3 diarrhoea (1 each). PM01183 at 4.0 mg FD combined with DOX, 50 mg/m^2 without CSF is the RD; 1 pts out of 9 had a DLT (FN). Toxicities in ⩾10% of pts, in addition to myelosuppression, were generally mild, including anaemia, ALT/AST increases, fatigue, alopecia, mucositis, nausea/vomiting, diarrhoea, anorexia and constipation. One pt had >10% asymptomatic decrease in left ventricular ejection fraction (LVEF). Out of 41 evaluable pts, 14 responded, for an ORR = 34% (95% CI: 20−51%), including 3 radiological CRs (7%). Of note, 5 out of 12 evaluable SCLC pts had PRs (42%). Over 1/3 of pts received ⩾6 cycles. There are ongoing pts at cut-off. DOX and PM01183 clearance (CL) were not affected, whereas doxol CL decreased with PM01183 dose.
Conclusions: The RD is PM01183 4.0 mg + DOX 50 mg/m^2. Toxicity is manageable and predictable. CSF prophylaxis is not required. This combination showed impressive response rates, including CRs

in relapsed/refractory solid tumour pts. This activity warrants further investigation in specific disease-settings, including SCLC.
Conflict of interest: *Advisory board: PharmaMar. Corporate-sponsored research: PharmaMar*

861 POSTER

Ruta chalpensis: a promising phytotherapeutic candidate against multiple forms of cancer

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Background: Studies on medicinal plants are mostly based on information provided by traditional healers in ethno botanical surveys. The treatment of cancer is mainly based on the use of Doxorubicin as chemotherapeutic agent, despite its potential to elicit serious cardiotoxicity often leading to degenerative cardio-myopathy/heart failure. The proposed mechanism of DOX-toxicity is complex and involves increased oxidative/nitrosative stress. Thus, inflammatory responses could be in the top of induction of cancer and hence treatment target. Based on Tunisian traditional medicine, *Ruta chalpensis* was explored for its anti-cancer activities and modulation of immune responses.
Material and Methods: The activity of *Ruta chalpensis* methanolic extract was tested against different cancerous cells; human carcinoma of bladder (RT112), of laryngeal (Hep2) and myelogenous leukemia (K562). Cellular viability was evaluated by MTT assay and microscopic count of nucleus upon extract treatment. In addition, annexinV staining and [^{3}H]Thymidine incorporation assays were used to control the viability within K562 cells. Furthermore, the release of free radicals was analyzed within the lipid peroxidation by AAPH assay and iNOS mRNA and NO production.
Results: In this study, biological activities of *Ruta chalpensis* methanolic extract related probably to its high tenor in phenolic compounds were investigated. This extract showed high antioxidant activity, and inhibited the production of NO, in murine macrophages, *via* transcriptional regulation indicating appreciable anti-inflammatory activities. Cytotoxicity assay results indicate a specific anticancer therapeutic property while there was no effect on healthy PBMC.
The observed decrease of viability was not due to cellular death but to an anti-proliferative effect of *Ruta chalpensis* methanolic extracts with ERK-dependent growth inhibition.
Conclusion: The use of plant compounds of *Ruta chalpensis* may be a novel approach for specifically inhibiting cancer cells' growth, which will lead to the development of new anti-cancer agents. Interestingly, our findings show, in opposite to the doxorubicin treatment, that *Ruta chalpensis* inhibits nitrosative stress. These results demonstrate the remarkable potential of traditional medicinal plants as valuable source of anti-oxidants exhibiting anti-inflammatory and anticancer properties.
No conflict of interest.

863 POSTER

Phase I study of U3-1565, a fully human anti-HB-EGF monoclonal antibody, in Japanese patients with advanced solid tumors

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Background: Human heparin-binding epidermal growth factor-like growth factor (HB-EGF) is a member of an EGF family and a ligand that binds to and activates the EGF receptor and human epidermal growth factor receptor 4 (HER4). U3-1565 is a fully human monoclonal antibody directed against HB-EGF that has demonstrated anti-tumor activity in preclinical models. This phase I study explored safety, tolerability, pharmacokinetics (PK) and potential anti-tumor activity of U3-1565 in Japanese patients with solid tumors.
Material and Methods: This study was conducted using a 3+3 design and tested U3-1565 at 2, 8, 16, and 24 mg/kg once every two weeks (with the second dose given three weeks after the first), and at 24 mg/kg weekly.
Results: Fifteen patients (6 females) were enrolled, 3 in each dose level cohort, and median age of 62 (range 52−73) years. Tumor types were colorectal (10), ovarian (2) and others (3). No dose-limiting toxicities and no treatment-related serious adverse events were observed; the MTD was not reached. PK data indicated serum U3-1565 concentration was dose-proportional, similar to US phase I study in parallel, though slightly lower exposure was observed. The highest administered dose of 24 mg/kg weekly generated Ctrough above the predetermined target concentration resulting in 90% tumor growth inhibition in preclinical study. Drug related AEs included malaise(20.0%), dermatitis acneiform(13.3%), and decreased appetite(13.3%), which were G1 or G2. Of 15 patients enrolled, 3 patients(20.0%) had stable disease and 12 patients had progressive disease as best response based on RECIST, and the median duration of stable disease was 15 (range 13−20) weeks with no decrease in tumor volume.
Conclusions: U3-1565 was well tolerated without DLT up to the dose level of 24 mg/kg weekly in Japanese patients. The dose of 24 mg/kg weekly was considered to be appropriate for the following phase. Biomarker evaluation in serum and tumor biopsy specimens and exploratory anti-tumor activity are ongoing in the additional study at the dose level of 24 mg/kg weekly as dose expansion part of this phase I study. (Trial Registry Number: JapicCTI-111484.)
Conflict of interest: *Ownership: This study was funded by DAIICHI SANKYO CO.,LTD.(JapicCTI-111484). Advisory board: A.Ohtsu: DAIICHI SANKYON.Fuse: DAIICHI SANKYO. Corporate-sponsored research: T.Yoshino: DAIICHI SANKYON.Fuse: DAIICHI SANKYO. Other substantive relationships: A.Ohtsu: Honoraria: DAIICHI SANKYOS.Fujitani, Y.Aramaki: Employed by DAIICHI SANKYO CO.,LTD.All other authors have declared no conflicts of interest.*

864 POSTER

Phase I study of LOR-253, a novel inducer of Kruppel-like factor 4, in patients with advanced solid tumors

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Background: LOR-253 is a novel small molecule inducer of tumor suppressor Kruppel-like factor 4 (KLF4) that has shown potent antitumor activity in NSCLC and colon tumor xenograft models. Objectives are to determine the maximum tolerable dose (MTD) or target-appropriate dose (TAD), and to characterize safety.
Materials and Methods: Patients with advanced solid tumors who progressed on standard therapies received LOR-253 by i.v. infusion on Days 1, 2, 15, and 16 of each 28 day cycle. The study design consisted of a brief run-in (Stage I) with 100% dose escalation until 2 patients with grade 2 toxicity or 1 patient with grade 3 toxicity, followed by a standard 3+3 design with escalating doses (Stage II). Dose limiting toxicity (DLT) was defined as $\geqslant$ grade3 other than reversible electrolyte abnormalities. RECIST 1.1 assessments were performed every 2 cycles (8 weeks). Serum samples for PK were collected in Cycle 1 pre-treatment, 0, 0.5, 1, 2, 4 and 7 hours (hr.) after end of infusion on Day 1 & on Day 2 omitting the 7 hr. sample and adding 24, 48 and 144 hr. samples.
Results: Twenty seven patients have been enrolled, with a mean age of 59 (range, 39−75), 67% male, and a mean of 4 (range, 1−7) prior regimens. Primary tumors included 16 colorectal, 3 appendiceal, 2 non small cell lung, 2 esophageal and, 4 others. Of 24 patients dosed only 1 patient experienced a $\geqslant$ grade 3 toxicity at least possibly related to drug (grade 3 hypophosphatemia). The most frequent grade 2 toxicity was hypersensitivity (2 patients) preventable by pre-treatment. Dosing was at 20, 40, and 80 mg/m^2 in Stage I until a DLT of grade3 hypophosphatemia, and at 80, 104, 135, 176, and 229 mg/m^2 in Stage 2. Of 17 pts evaluable for RECIST assessment, 7 (41%) had stable disease as best response. Stable disease of $\geqslant$4 cycles (4 Pts; mean 154 days) was seen exclusively at the higher dose levels from 176 to 229 mg/m^2 which corresponds to a preclinically efficacious KLF4 inducing dose. PK elimination appeared biphasic with mean $T\frac{1}{2}$ at doses $\geqslant$80 mg/m^2 ranging from 48−61 hr. AUC(0-t) was dose proportional with a median accumulation ratio of 4 on Day 2 vs. Day 1.

Conclusions: LOR-253, a first-in-class molecule, is well tolerated to a TAD of 229 mg/m^2 without significant toxicity. A biomarker investigation has therefore been initiated with continued evaluation of PK and expansion for pre- and post-dose biopsies and correlative tissue analyses.
Conflict of interest: *Other substantive relationships: P. Murray, S. Zhou and Y. Lee work are employed by Lorus Therapeutics, the manufacturer of the drug LOR-253.*

865 POSTER

Evaluation of the interaction of copper(II) and ruthenium(II) compounds with fibronectin and tubulin proteins: two potential chemotherapeutic targets

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Most current research efforts with respect to the quest for novel metal-based drugs are devoted to investigating their interaction with the DNA double helix, considering the accepted mechanism of action for the well-established anticancer drug cisplatin. However, this approach neglects the fact that other cellular components may be targeted by metal complexes. In the present study, fibronectin and tubulin, two proteins involved in fundamental cellular processes that are cell division and cell migration, have been chosen as (cytotoxic) targets for copper(II) and a ruthenium(II) compounds.
The potential interaction of a series of metal-based molecules with these two proteins was first assessed by circular dichroism (CD) and atomic-force microscopy (AFM). MTT assays were subsequently used to determine the cell-growth inhibitory activities (IC_{50}) of the compounds in HeLa and HL60 cell lines. Immunofluorescence assays were then carried out with the two most cytotoxic metal complexes, with HeLa cells, using anti-α-, anti-β-tubulin and anti-fibronectin antibodies to investigate their effect on microtubules and the extracellular matrix. The microtubule-depolymerizing agent Nocodazole was used as positive control. Cell cycle analyses by flow cytometry and annexin V-FITC + PI apoptosis assays (with cisplatin as positive control) were performed with both cell lines to better understand the mechanisms of action of the two compounds.
The AFM and CD experiments clearly evidenced the interaction of the Cu(II) and Ru(II) compounds with both proteins, the most efficient being the copper molecule. IC_{50} values lower than those of the reference compound cisplatin® were obtained for both the Ru(II) (13.01 μM HeLa; 2.48 μM HL60) and the Cu(II) (3.63 μM HeLa; 14.50 μM HL60) complexes. The immunofluorescence assays revealed a microtubule-depolymerizing behaviour for the copper molecule and the formation of apoptotic nuclei with both compounds. The cell cycle tests did not show an arrest at the G2 phase, which would have indicated microtubule stabilization (that prevents cell division), therefore suggesting that the cells had died by apoptosis, as confirmed by the annexin assays.
In summary, fibronectin and tubulin are legitimate target proteins for potential metal-based anticancer drugs such as the two compounds evaluated herein, which showed apoptotic cytotoxic activities.
No conflict of interest.

866 POSTER

Factors predisposing to development of hyperglycaemia in phase 1 studies involving PI3K, mTOR, AKT and mTORC1 and mTORC2 inhibitors

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Background: Dysregulation of the PI3K/AKT/mTOR pathway is implicated in human cancer growth and progression. Agents targeting this pathway can be associated with on target effects of hyperglycaemia due to partial compensation of the insulin-glucose regulatory axis. Identifying those factors predictive of developing hyperglycaemia in patients (pt) treated with these agents may help direct future management.
Materials and Methods: Clinical characteristics and outcomes of pts treated consecutively with PI3K, AKT or mTOR inhibitors in the Drug Development Unit, The Royal Marsden between 2007 and 2012 were recorded. Baseline variables and their association with grade (G) 3 hyperglycaemia (CTCAE version 3.0) were analysed, using chi-square test and significant values were further analysed by multivariate regression analysis (MVA).
Results: 341 pts were identified and treated on 12 phase I trials of PI3K/AKT/mTOR inhibitors, during the study period. Clinical, laboratory and demographic data including personal and family history of diabetes, use of steroids, body mass index (BMI), and baseline blood sugar levels (BSL), biochemistry, treatment and outcomes of hyperglycaemia were recorded. 81.5% of pts developed hyperglycaemia during treatment. Majority had G1 (n = 217, 63.6%) and G2 hyperglycaemia (n = 61, 17.9%). Development of G $\geqslant$3 (n = 20, 5.9%) hyperglycaemia was associated with age <65 (p = 0.03), previous history of diabetes (p = 0.003) and treatment with AKT and mTOR inhibitors (p = 0.00). On MVA, maximum BSL at Cycle (C) 1 [inter quartile range (IQR) =6.3−8.5 mmol/l; odds ratio (OR) =2.4(1.66–3.46)] and fasting BSL at C2 [IQR=4.9−5.9 mmol/l; OR=2.07(1.09–3.95)] were associated with development of G $\geqslant$3 hyperglycaemia. BMI>30, history of steroid use, tumour type or histology, fasting BSL and HbA1C were not predictive of the risk of developing G3 hyperglycaemia. The majority of patients did not require intervention for hyperglycaemia [n = 316; 92.7%]; however, metformin [n = 20; 5.9%] and/or insulin [n = 2; 0.6%] were the most common pharmacological agents used, where required. One pt required a dose reduction and there were no permanent drug discontinuations.
Conclusion: Pts aged <65 y, with a history of diabetes, treated with AKT/mTOR inhibitors are more likely to develop significant hyperglycaemia on study. These predictive factors may warrant further validation in a prospective setting, and may help in the future management of pts treated with this important class of agents.
No conflict of interest.

867 POSTER

Fatty acid synthase inhibition as a potential therapeutic target in triple-negative breast cancer

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Background: Triple-negative breast cancer (TNBC) are defined by the lack of detectable expression of estrogen receptor, progesterone receptor and do not have amplification of HER2. There is no clinically validated molecularly targeted therapy for TNBC and patients have a poor prognosis due in part to the high probability of relapse after chemotherapy. Thus, the identification of novel targeted therapies for TNBC patients is needed.
The expression levels of FASN, a multi-enzyme protein that catalyses de novo synthesis of fatty acids, are low or undetectable in normal tissues. In contrast, high levels of FASN expression have been detected in several human carcinomas. Some reports highlight that FASN over expression correlates with progression, aggressiveness and metastatic potential of the disease.
The aim of our study is determine the FASN tumor expression levels in TNBC patients and in parallel evaluate the therapeutic effect of FASN inhibition (alone or in combination with current treatments) in a panel of TNBC cells sensitive and resistant to conventional therapies (such as doxorubicin and paclitaxel).
Methods: FASN and EGFR expression was retrospectively evaluated in 29 paraffin-embedded core-biopsies of patients with TNBC by Immunohistochemistry (IHC).
TNBC cell lines were long-exposed to increasing doses of doxorubicin (DR), paclitaxel (PR) or both (DPR) to establish long-term chemoresistant cells. Western-Blot (WB) analysis were performed to evaluate the main signaling pathways in both sensible and resistance cells. The cytotoxic effect of the anti-FASN compounds were determined by an MTT assay. Quantitative Real-Time PCR (qRT-PCR) was used to analyze the expression of basal and mesenchymal markers to determine the molecular subtypes and for the study of cell population changes under chemotherapy.
Results: FASN staining was positive in all 29 TNBC tumor samples, with low (69%) and moderate (31%) levels. EGFR were positive in 76% of the tumors respectively. Analysis by WB and qRT-PCR showed higher levels of FASN in TN CK5/6$^+$ and EGFR$^+$ cells than in TN VIM$^+$ cells. FASN pharmacological inhibition (alone and in combination) was cytotoxic and induced apoptosis in all TNBC cells treated.
Conclusions: FASN is expressed in TNBC tumors and *in vitro* FASN inhibition (alone and in combination) induces apoptosis in TN cells. The absence of target therapies for this breast cancer subtype and its poor prognosis lead to the exploration of FASN as a therapeutic target for TNBC patients.
No conflict of interest.

868 POSTER

Phase 1 dose escalation study of the investigational drug TAK-960, an oral polo-like kinase 1 (PLK1) inhibitor, in patients (pts) with advanced solid tumors

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Background: PLK1 is involved in mitosis and DNA integrity and is over-expressed in various tumor types, presenting a target for cancer therapy. This first-in-human study evaluated TAK-960 in pts with advanced solid tumors to determine safety, tolerability, MTD/RP2D, pharmacokinetics (PK), anti-tumor activity and pharmacodynamics (PD) (NCT01179399; sponsored by Millennium: The Takeda Oncology Company).
Materials and Methods: Key eligibility: ⩾18 y with metastatic solid tumor unresponsive to current treatment, ECOG status of 0−1. TAK-960 PO QD in a 3+3 design for 21-d in a 28-d cycle. Samples for plasma PK assessment were taken pre-dose and at time points post-dose on d 1 and 21 of cycle 1. 25 pts provided skin biopsies at screening, pre-dose and 6 hr post-dose on day 7 of cycle 1. Average mitotic index and phosphorylated keratin (pKeratin) intensity were determined by immunohistochemistry.
Results: 32 pts (median age 65 y [range 47−84]) received 1−28 mg TAK-960 (median 2 cycles, range 1−12; 7 pts ⩾6 cycles). Safety population was 32 pts, 1 dose limiting toxicity reported (grade 4 neutropenia). 20 pts (63%) had a drug-related AE, fatigue (34%), decreased appetite (25%), nausea (19%). 6 pts (19%) had a grade ⩾3 drug-related AE; 1 pt (3%) had a drug-related serious AE and discontinued (grade 4 neutropenia); 3 (9%) unrelated on-study deaths. The study was terminated due to business reasons before the MTD or RP2D were established, a further 21-d cycle was considered (7-d QD then 14-d rest period). In 31 PK evaluable pts, TAK-960 was characterized by a median T_{max} of 6 hr, low fluctuation at steady-state (overall mean peak-to-trough ratio of 1.4), and moderately long mean $t_{1/2}$ of 48 hr. Overall mean accumulation ratio was 3.8-fold following repeated QD dosing for 21 d. Steady-state exposures (d 21 AUC, Time 0 to end of dosing interval $AUC_{(0-tau)}$,) increased in an approximately dose proportional manner over 1 to 28 mg. Average mitotic indices were <1 at screening, with indices >2 in 2 pts (1, 20 mg; 1, 28 mg) on day 7 of cycle 1. No trends in pKeratin intensity were observed. Best response was stable disease (14 pts, 3 pts >3 months, 3 pts >6 months: pancreas, CRC, breast, ovarian, H and N x2, squamous, bladder, thyroid, colon x2, prostate, rectal, unknown). Progressive disease observed in 17 pts.
Conclusions: TAK-960 was generally well tolerated, exhibiting linear PK and characteristics that support QD dosing. Stable disease in 14 pts with a range of tumor types.
Conflict of interest: *Corporate-sponsored research: Research funding: Emiliano Calvo, Kyriakos P Papadopoulos, Antonio Cubillo, Drew Rasco (Millennium: The Takeda Oncology Company). Sunil Sharma (Millennium: The Takeda Oncology Company Beta Cat Pharmaceuticals Salarius ConverGene). Other substantive relationships: Employment: Hongliang Shi, Stephanie Faucette, Xiaofei Zhou, Keisuke Kuida, Cristina Oliva (Millennium: The Takeda Oncology Company).*

869 POSTER

Rapid validation of a novel kinase target FAM20C through integration of large scale genomic databases and matched patient derived tumor models

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Background: Target discovery and validation in oncology has largely relied on molecular and functional studies performed in cell lines. Recent advances in genomics have now created large databases based on well-characterized tumor tissue, which has enabled direct investigation of patient tumors for novel targets.
Material and Methods: We have developed a target validation platform based on a large scale genomic database matched to patient-derived tumor models. The platform relies on Molecular Response's proprietary bank of more than 144,000 patient derived tumor cells, of which nearly 400 tumors have been genomically characterized and databased for target discovery studies. The database is growing, but currently features the following cancer indications: colon carcinoma, NSCLC, melanoma, ovarian carcinoma, prostate cancer and Non-Hodgkins Lymphoma. Upon discovery of a novel target, tumors of interest are immediately implanted into mice to perform functional studies in direct patient derived models–either in vivo or ex vivo.
Results: Through use of this platform, we have identified the novel kinase target FAM20C for therapeutic development. We investigated prevalence of target overexpression across 7 cancer indications, and identified melanoma as a clinical indication of high interest. We examined growth characteristics from patient tumors featuring high kinase gene expression vs. low expression to help characterize the role of this target in oncology disease progression. Finally, we performed functional knockdown studies in patient derived models to further validate this novel kinase as a druggable target of pharmaceutical interest. Studies are ongoing to develop small molecule and antibody-based therapeutics which will serve as drug candidates for further development.
Conclusions: FAM20C represents a novel molecular target for development of targeted therapeutics in the treatment of melanoma, and potentially other cancers.
No conflict of interest.

870 POSTER

Novel receptor-mediated transport of the anticancer agent Dp44mT

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Background: Defective iron homeostasis in cancer cells, owing to the perturbed expression of iron-related proteins, may confer a survival advantage to neoplastic cells and poorer patient prognosis (*Cancer Res* 2011;71:1511–1514). Iron chelators have emerged as anti-tumour agents that disrupt vital iron and copper trafficking of cancer cells. Several *in vitro* and *in vivo* studies have demonstrated the potent anti-cancer and anti-metastatic activity of the chelator, di-2-pyridylketone 4,4-dimethyl-3-thiosemicarbazone (Dp44mT; *PNAS* 2006;103:14901−6; *EMBO Mol Med* 2012;4:93–108). Recent investigations have shown that Dp44mT accumulates within the lysosome, disrupting lysosomal membrane integrity and resulting in apoptosis (*Cancer Res* 2011;71(17):5871−80). However, the mechanism by which this drug is transported into cells to induce cytotoxicity is unknown.
Materials and Methods: ^{14}C-Dp44mT was employed to assess membrane transport mechanisms using 3 tumour cell lines, namely: SK-N-MC neuroepithelioma, SK-Mel-28 melanoma and DMS-53 lung carcinoma and mortal MRC-5 fibroblasts.
Results: The cellular uptake of ^{14}C-Dp44mT as a function of concentration was saturable in SK-N-MC cells (B_{max} 4.28 x 10^7 molecules of chelator/cell and K_d 2.45 μM), suggesting it enters cells *via* a receptor-mediated process. Saturable uptake was also observed in DMS-53 and SK-Mel-28 cells as well as MRC-5 fibroblasts. The uptake of ^{14}C-Dp44mT was examined in the presence of its unlabelled precursors, namely dipyridyl ketone (Dp) and 4,4-dimethyl-3-thiosemicarbazide (44mT), in order to decipher the stereospecificity of the transport mechanism involved. ^{14}C-Dp44mT uptake was significantly (p<0.01) decreased in the presence of unlabelled Dp44mT, while its unlabelled precursors, Dp or 44mT, had no significant effect (p>0.05) on ^{14}C-Dp44mT transport in SK-N-MC cells. A range of structurally similar and diverse thiosemicarbazones were also screened to determine the specificity of the receptor, including the DpT series (DpT, Dp4mT, Dp4eT, Dp4aT, Dp4pT and DpC); the BpT series (BpT, Bp4mT, Bp44mT, Bp4eT and Bp4aT); the ApT series (ApT, Ap4mT, Ap44mT, Ap4eT and Ap4pT); as well as the well know chelators, Triapine® and PIH. All unlabelled ligands of the DpT series and unlabelled Bp44mT, Bp4mT and Ap44mT significantly (p<0.01) inhibited the uptake of ^{14}C-Dp44mT in comparison to the control (^{14}C-Dp44mT alone). The other members of the BpT and ApT series as well as Triapine® and PIH had no significant (p>0.05) effect on ^{14}C-Dp44mT uptake. As may be expected, unlabelled Dp44mT appeared to most markedly (p<0.001) decrease the cellular uptake of ^{14}C-Dp44mT.
Conclusion: The receptor involved in the uptake of Dp44mT by cells shows high affinity for Dp44mT. Our studies highlight the importance of the saturated N4 structural moiety in the receptor-mediated transport of our ligands. The uptake of Dp44mT through a receptor-mediated system may reveal a potential mechanism to selectively target chemotherapeutics to malignant cells. These findings have great clinical implication for the extent of uptake and bioavailability of the drug within the circulation.
No conflict of interest.

871 POSTER

Syntactic analysis for single agent phase I trials in Japan, from National Cancer Center Hospital (NCCH) experience

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Background: In Japan, to develop investigational new drug, most phase I trials, especially 'first in human' trials are starting from about 50% of MTDs of dosage to the MTD levels based on the initial phase I studies and results in the West, from where the trials are usually started. However, little has been well recognized about actual status in phase I trials in Japan. This study is aimed to evaluate the toxicity profiles including MTD levels as compared with those in the West, anti-tumor response, and survival of patients enrolled in phase I trials in Japan.
Patients and Methods: Between July 1995 and December 2012, we retrospectively analyzed the data of patients enrolled in single agent phase I trials at NCCH. The doses with anti-tumor response observed, DLT profiles, and MTDs were compared with those in the West. Cox proportional hazards model was examined to assess potential prognostic factors for survival.
Results: A total of 777 patients were enrolled in 44 phase I trials including 5 first in human trials. The median age was 57 (range, 18−76) years and 57.9% were male. ECOG performance status (PS) of 0 and 1 were 38.6 and 61.1%, respectively. The common cancer types were lung cancer (31.9%), colorectal cancer (21.0%), sarcoma (13.8%), esophagus cancer (4.6%). DLTs were observed in 12.1% of the patients. The dose levels in which DLTs observed were as follows: 5.3% were in +1 dose level as compared with those in the West, 31.9% were in the same dose level, 28.7% in −1 dose level, 14.9% in −2 dose level, and 3.2% in −3 dose level. Tumor shrinkage was observed in 20.8% of the patients and the response rate was 6.3 (95% CI: 4.6−8.0)%. Almost all (93.9%) responding patients were in and around the MTD levels (34.7, 32.7 and 26.5% were in the MTD, −1, and −2 dose levels, respectively). Median OS was 11.5 (95% CI: 10.5–12.4) months. Male, PS of 1, body weight loss (⩾5% within 3 months), liver metastasis, elevation of AST and LDH (⩾ upper limit of normal), and hypoalbuminemia were independent poor prognostic factors for survival.
Conclusions: This is the first report of syntactic analysis for single agent phase I trials in Japan. Dose levels with DLTs and observed responders were almost similar to those in the West, and these were around the MTD levels (from −2 to +1 dose levels from MTD). Prognostic factors were similar to those in previous reports in the West. Phase I studies in Japan are practically carried out on the same time lines and study qualities with those in the West.
No conflict of interest.

872 POSTER

Cumulative safety experience of telotristat etiprate in clinical trials supports advancement to phase 3

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Background: Telotristat etiprate (TE) (or LX1606) is a novel, oral inhibitor of serotonin synthesis being developed for treatment of carcinoid syndrome (CS). Telotristat etiprate reduced CS symptoms such as diarrhea in Phase 2 studies. In preparation for Phase 3, we conducted a systematic review of safety data up to 19 January 2013 from 3 completed studies of healthy subjects and 2 ongoing clinical studies of patients (pts) with CS.
Material and Methods: To detect potential signals, cumulative safety databases were pooled and examined using analyses of: 1) 77 special MedDRA queries covering 22 disease areas, 2) adverse event (AE) accumulations by study day, 3) System-Organ class (SOC) and preferred term, and 4) laboratory testing. Serious adverse events (SAEs) and other cases of interest were reviewed for potential relationship to study drug.
Results: Of the 121 subjects in this analysis, 88 were healthy subjects who received single- or multiple-dose levels of up to 1500 mg/day for up to 14 days; 33 were pts with CS exposed to at least one dose of TE, with dose levels up to 1500 mg/day for up to 12 weeks of initial treatment, with an option to continue into an open-label phase for a total of 124 weeks. Of the 33 pts with CS, 16 were on TE for ⩾6 months, 11 were on TE for ⩾12 months, and 6 patients were on TE for ⩾24 months. Across the studies, there was no common theme in AEs. All SAEs reported by subjects receiving TE were assessed as unrelated to study drug with the exception of 1 case of severe nausea and vomiting, which resolved in 10 days. Most AEs were assessed as of mild to moderate intensity, and most resolved spontaneously while continuing study drug. In Phase 1 studies of healthy subjects, mild increases in hepatic transaminase levels (mostly <2 x ULN) were noted, with 1 subject discontinuing from therapy at the 500 mg bid dose level. In Phase 2 studies, no signal for transaminase abnormalities has been observed to date. In both active drug and placebo, the most common SOC in which AEs were reported was Gastrointestinal (GI) Disorders. Nausea and vomiting accounted for a large proportion of events in this SOC, and occurred relatively early in treatment, usually without recurrence.
Conclusions: This safety review supports advancement of telotristat etiprate to Phase 3 for treatment of CS. Treatment-related SAEs and discontinuations due to AEs have been rare. The majority of events identified in studies thus far are GI symptoms, consistent with the underlying disease.
Conflict of interest: *Ownership: Stock ownership (Lexicon Pharmaceuticals, Inc.) − DF, GLY, JJ, SJ, PL. Other substantive relationships: employment (Lexicon Pharmaceuticals, Inc.) − DF, GLY, JJ, SJ, PL contract employment − DM*

873 POSTER

Clinical outcomes of patients treated within early phase cancer trials: An audit of the NIHR/Wellcome UCLH clinical research facility

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Background: A number of centres have devised prognostic scores to predict the outcome of patients treated within Phase I trials using baseline characteristics. The Royal Marsden Hospital (RMH) score has demonstrated significantly increased risk with the presence of 2 or 3 of the following factors; low albumin (<35 g/L), elevated lactate dehydrogenase (>upper limit normal) or more than 2 sites of metastases. We assessed the clinical outcomes of patients treated within our early phase trial unit and analysed the relevance of the RMH score within this patient population.
Methods: We retrospectively analysed baseline characteristics and clinical outcomes including best response, progression free (PFS) and overall survival (OS) in 165 sequential patients treated between April 2010 and January 2013. Survival distributions were estimated and differences in survival according to RMH score were analysed using the log-rank test.
Results: Of 165 patients treated in 24 trials, 107 were treated within Phase 1 trials and 58 within Phase II. Median age was 60 years (range 21−83). Best overall response was; partial response in 14%, stable disease in 51% and disease progression in 21%. Ninety-day mortality rate for patients treated in a Phase I trial was 11.9% and 30-day mortality was 3.8%. The median OS for all patients (Phase I and II) was 12.8 months and median PFS was 4.8 months. OS was significantly longer in patients treated within phase II trials than those treated in a phase I trial (median 14 vs 12.5 months, p = 0.043). The RMH score could be applied in 81 patients of which 71% of patients had a 'good' prognostic score of 0−1, and 29% a 'poor' score of 2−3 (no patients scored 3). OS in the 0−1 group was not significantly better compared to the 2−3 group (0−1 group HR = 1.0, 2−3 group HR = 1.02, p = 0.95).
Discussion: In our series of patients, the RMH score was not prognostic however no patients had a high risk score of 3. This may reflect the increasingly stringent eligibility criteria required for current trials. Overall survival and 90-day mortality of our Phase I patient population compares favourably with data reported by other centres. This study demonstrates the possible clinical benefit gained by patients recruited into early phase trials and is in keeping with recently published data.
No conflict of interest.

874 POSTER

Improving patient selection and outcomes in phase I trials: validating the Royal Marsden Hospital prognostic score

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Background: Phase I clinical trials remain an essential step in the development of novel anti-cancer agents. Patient selection is pivotal to maximising patient benefit and avoiding premature study withdrawal of unfit patients and the need for additional recruitment. Performance status (PS) and a life expectancy ⩾3 months are often used to define patients' fitness and trial eligibility. However these methods are subjective and it is reported that up to 20% of patients die within 90 days of starting a phase I trial. The Royal Marsden Hospital (RMH) prognostic score, based on three variables: Lactate dehydrogenase (LDH) > upper limit of normal, albumin <35 g/l and >2 sites of metastases has been shown to predict patient survival. We sought to validate this score in our phase I patient population.

Materials and Methods: Retrospective review of patient referrals for phase I trials to the Sir Bobby Robson Cancer Trials Research Centre, Northern Centre for Cancer Care, Newcastle, UK between January 2009 and December 2011. Baseline characteristics: age, sex, tumour type, WHO PS, number of metastatic sites and baseline blood parameters including haemoglobin, albumin and LDH collected. Clinical outcome assessed by: ⩽90 day mortality rates, best response by RECIST and overall survival defined by date of death or last follow-up. Reasons why individual patients failed to enter phase I trials were recorded.
Results: Data for all 287 patient referrals reviewed. In our centre volume of referrals exceeded trial availability and many patients deteriorated waiting for a trial. 80 (28%) of these patients with a range of advanced solid malignancies entered a total of 21 phase 1 trials (48% combination studies of a novel agent + cytotoxic and 52% single agent). The commonest reason for not taking part was declining PS (59%) and 39% of patients failed screening (52% due to impaired liver function). Median age of trial participants was 63 years (range 23−79) with 23% aged ⩾70 years. Baseline PS was 0 (23%), 1 (70%), 2 (3%). Best response was: partial response 5%, complete response 1% with 50% of patients achieving stable disease. The median survival of all 80 patients was 221 days and the ⩽90 day mortality rate was 9%. Patients with a good RMH score (0−1) at baseline had a longer median survival than patients with poor prognostic scores (2−3); 225 days vs. 207 days; P <0.05. In multivariate analysis the RMH score was an independent variable that predicted survival.
Conclusions: The poor RMH prognostic score predicted a shorter survival in our patients, validating further its use in phase I patient selection.
No conflict of interest.

875 POSTER

Phase I clinical trial investigating maximum tolerated dose, safety and pharmacokinetics of volasertib in Japanese patients with advanced solid tumours

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Background: Polo-like kinase 1 (Plk1) is a key regulator of mitosis and is a promising therapeutic target in cancer. Volasertib (BI 6727; an investigational agent) is a selective and potent Plk inhibitor that induces mitotic arrest and apoptosis. The maximum tolerated dose (MTD) for volasertib was established and volasertib had a manageable safety profile and favourable pharmacokinetics (PK) in Caucasian patients (Phase I studies). Here, for the first time the MTD, safety, PK and clinical benefit of volasertib were investigated in Japanese patients (NCT01348347; sponsored by Boehringer Ingelheim), and the results were compared with those of Caucasian patients.
Material and Methods: In this ongoing, open-label, dose-escalation Phase I study, Japanese patients with refractory advanced solid tumours were treated with escalating doses of volasertib (200, 300 and 350 mg). The primary endpoint of this study was the MTD of volasertib. Secondary endpoints included safety, PK and clinical benefit.
Results: Fifteen patients with advanced solid tumours were treated. Dose-limiting toxicities (DLTs; Common Terminology Criteria for Adverse Events [CTCAE] grade 4 neutropenia for ⩾7 days and CTCAE grade 4 thrombocytopenia) were experienced by 2/6 patients in the 350 mg cohort. The MTD of volasertib in Japanese patients was 300 mg; this is consistent with the recommended Phase II dose (300 mg) and comparable to the MTD (400 mg) in the Caucasian Phase I study. In this study, the most common (⩾3 patients) drug-related non-haematological adverse events included fatigue, decreased appetite and nausea. Exposures of volasertib and its metabolite increased with increasing doses and were comparable with those of Caucasian patients (Phase I). Partial response (n = 1; gastric cancer) and stable disease (n = 11, including 3 patients for >12 weeks prior to disease progression) were observed.
Conclusions: In Japanese patients, volasertib had a manageable safety profile up to the MTD determined as 300 mg. Reversible myelosuppression (neutropenia and thrombocytopenia) constituted DLTs as expected from the mode of action. The results on safety and PK of volasertib in Japanese cancer patients are comparable with those previously obtained in Caucasian patients and support enrolment of Japanese patients in global clinical trials without dose modification.
Conflict of interest: *Other substantive relationships: Taube,T is employed by Boehringer Ingelheim Pharma GmbH & Co KG. Takeuchi, Y is employed by Nippon Boehringer Ingelheim Co Ltd*

876 POSTER

Exploratory study of health-related quality of life in a phase I trial studying Idarubicin-loaded beads for chimioembolization of hepatocellular carcinoma

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Background: Phase I trials aim to identify the recommended phase II dose: the maximum-tolerated dose (MTD) that will be investigated in further trials. In this context, the added value of health-related quality of life (QoL) of patients to complement the usual toxicity assessment should be questioned. The objective was to investigate QoL in a phase I trial.
Methods: A phase I dose-escalation trial of transarterial chemoembolization (TACE) with idarubicin-loaded beads was performed in cirrhotic patients with hepatocellular carcinoma. Idarubicin dose was escalated according to a modified continuous reassessment method. MTD was defined as dose level closest to that causing dose limiting toxicity (DLT) in 20% of patients.
QoL was evaluated using the EORTC QLQ-C30 at baseline and at days 15, 30 and 60 after TACE. Changes in QoL scores were described using mean difference in scores with baseline as reference and scores at each follow-up, for all patients and according to the idarubicin dose level. The time to QoL score deterioration (TTD) was investigated as a modality of longitudinal analysis. TTD was defined as the time from randomization to a first QoL score deterioration with a 5-point MCID as compared to the baseline score or death. Univariate Cox analyses were performed to identify factors influencing TTD.
Results: Between March 2010 and March 2012, 21 patients were included: 9, 6, and 6 patients were treated at idarubicin dose levels of 5-, 10-, and 15-mg, respectively. Calculated MTD of idarubicin was 10 mg. The median TTD was 0.76 months [95% CI 0.62-NA] for Global Health Status, 0.69 months [0.59-NA] for fatigue and 2.50 months [0.76-NA] for pain. At 10-mg idarubicin dose level, patients presented a longer TTD than at 5-mg dose level for Global Health Status (HR 0.87 [95% CI 0.14–5.36]), physical functioning (HR 0.67 [0.11–4.13]), fatigue (HR 0.77 [0.13–4.71]) and pain (HR 0.52 [0.09–3.16]). Women presented a shorter time to pain deterioration than men (HR 14.7 [1.31–164.7]).
Conclusions: These results show the importance to study QoL in phase I trials. These results are consistent to the idarubicin dose level of 10 mg retained. Nevertheless, if we had integrated TTD in DLT, we could retain idarubicin dose level of 15 mg as the MTD. Moreover, it raises the issue of a specific questionnaire for phase I trial which would be more focused on toxicities.
No conflict of interest.

877 POSTER

Adverse and expected drug reactions to therapy with mistletoe extracts (Viscum album L.) in cancer patients

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Background: Mistletoe (*Viscum album L.)* is one of the most frequently prescribed complementary treatments for cancer in Europe. As an immunomodulating substance it can induce local and systemic immune responses. According to product information, dose-finding is related to local reactions (3−5 cm) and temperature increase (up to 38ºC). Formally, these parameters are defined as adverse drug reactions (ADRs). In terms of safety, therefore, it is necessary to distinguish between adequate immune reactions (expected reactions like local erythema, induration or pain and increased body temperature) and other ADRs. The present study investigates ADRs that occurred in cancer patients treated with mistletoe in an integrative oncological setting.
Material and Methods: The Network Oncology is a conjoint clinical registry of German hospitals and out-patient practitioners that systematically records cancer diagnoses, therapies, ADRs and disease progress. This database was analysed for mistletoe related ADRs, which were classified as MedDRA terms (15.0) and rated on severity. Logistic regression analyses were performed.
Results: A total of 1657 cancer patients (1194 females [72%]; 463 males [28%]) were treated with mistletoe extracts by subcutaneous application. Of these, 378 patients (23%) reported a total of 692 formal ADRs. The majority of formal ADRs (64%) were rated as grade I (mild) in severity, while 10 cases (1%) were rated as grade II (moderate) and 9 cases (1%) as

grade III (severe). No cases were judged as grade IV (life threatening). More than 99% of all formal ADRs were expected (increased temperature [49%], erythema [29%], induration [4%] and pain [3%]). Only 11 patients had other ADRs (chills, headache, nausea and vomiting), collectively making up less than 1% of formal ADRs. Based on logistic regression analysis, females were more likely to experience a formal ADR (OR = 1.5; CI = 1.07, 2.12; p = 0.02), while older age (OR = 0.98 per year; CI = 0.97, 0.99; p < 0.001) and UICC stage IV (OR = 0.53; CI = 0.31, 0.92; p < 0.02) were associated with a lower risk.
Conclusions: Less than a quarter of cancer patients treated with mistletoe reported a formal ADR. These were almost exclusively expected reactions, such as increased body temperature and injection site erythema indicating stimulation of the immune system. With increasing age and tumour stage immunoreactivity decreased. Based on these results, treatment with mistletoe extracts is safe.
Conflict of interest: *Advisory board: Weleda AG*

878 POSTER

Chymase inhibitor, TY-51469, attenuates monocrotaline-induced sinusoidal obstruction syndrome in hamsters

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Background: The recent chemotherapy regimens of adding oxaliplatin improve the survival of patients with metastatic colorectal cancer. However, treatment with oxaliplatin induces hepatic sinusoidal dilation and haemorrhage, and sinusoidal obstruction syndrome (SOS) is observed in the most of hepatectomy specimens from these patients as well. To date, however, any useful strategy for prevention of SOS has not been established. Previous reports have demonstrated a significance of matrix metalloproteinase (MMP)-9, which is formed from a precursor proMMP-9 by chymase stored in mast cells, in the progression of SOS. In this study, we investigated the preventive effect of a chymase inhibitor, TY-51469, on monocrotaline (MCT)-induced SOS in hamsters.
Material and Methods: Hamsters were orally administrated with a single dose of MCT (120 mg/kg) to induce SOS. Treatment with TY-51469 (1 mg/kg per day) or placebo was started 3 days before the MCT administration. Blood samples and liver tissue were examined two days after the MCT administration. Furthermore, to determine the survival rate, either TY-51469 or placebo was administered from 3 days before up to 14 days after MCT administration.
Result: Two days after the MCT administration, significant increases of aspartate aminotransferase, alanine aminotransferase and total bilirubin and a significant reduction of albumin were observed in plasma, but their changes were significantly attenuated by treatment with TY-51469. The numerous hepatic necrosis areas were observed in the placebo-treated group, but the ratio of necrotic area to total area in liver was significantly reduced by treatment with TY-51469. Chymase activity and the levels of MMP-9 and tumour necrosis factor (TNF)-α in the liver were significantly augmented in the placebo-treated group. However, these were significantly attenuated in the TY-51469-treated group. Furthermore, both gene expressions of chymase and MMP-9 were significantly augmented in the placebo-treated group, which were significantly attenuated in the TY-51469-treated group. Until 14 days after MCT administration, survival rates in the placebo- and TY-51469-treated groups were 25% and 70%, respectively, and there was a significant difference between the two groups.
Conclusion: Chymase inhibition by TY-51469 may prevent the accelerating of severity in MCT-induced SOS in hamsters.
No conflict of interest.

879 POSTER

MPDL3280A (anti-PDL1): Clinical activity, safety and biomarkers of an engineered PD-L1 antibody in patients with locally advanced or metastatic tumors

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Background: PD-L1 and PD-L2 have been reported to regulate Th1 and Th2 immune responses. Tumor-expressed PD-L1, when bound to PD-1 or B7.1 on activated T cells, can mediate cancer immune evasion. Inhibiting the binding of PD-L1 to its receptors represents an attractive strategy to restore tumor-specific T-cell immunity. However, PD-L2 expressed in the tumor microenvironment may also bind PD-1-expressing T cells, dampening their function. MPDL3280A (anti-PDL1), a human monoclonal antibody containing an engineered Fc-domain designed to promote a Th1-driven response to optimize efficacy and safety, is described here along with Phase I results.
Materials and Methods: A study was conducted with MPDL3280A administered IV q3w in pts with locally advanced or metastatic solid tumors, including 3+3 dose-escalation and expansion cohorts. ORR was assessed by RECIST v1.1 and includes u/cCR and u/cPR. PD-L1 was measured by IHC (pos vs neg), and PD-L2 was measured by qPCR (high vs low) in archival tumor specimens.
Results: As of Feb 1, 2013, 171 pts were evaluable for safety. Administered doses include $\leqslant$1 (n = 9), 3 (n = 3), 10 (n = 35), 15 (n = 57) and 20 mg/kg (n = 67). Pts in the dose-escalation cohorts did not experience DLTs. No MTD was identified. Pts had received MPDL3280A for a median duration of 147 days (range 1–450). 41% of pts reported G3/4 AEs, regardless of attribution. No acute pneumonitis was observed. 122 pts enrolled prior to Jul 1, 2012 were evaluable for efficacy. RECIST responses were observed in multiple tumor types including NSCLC (9/37), RCC (5/39), melanoma (9/35), CRC (1/4) and gastric cancer (1/1). An ORR of 21% (25/122) was observed in nonselected solid tumors with a duration of response range of 1+ to 253+ days. Other pts had delayed responses after apparent radiographic progression (not included in the ORR). The 24-week PFS was 42%. 94 pts had tumors evaluable for PD-L1 status, and 81 pts had tumors evaluable for PD-L2. Median PD-L2 expression was $\approx$2x higher in PD-L1-pos tumors versus PD-L1-neg tumors. The ORR was 39% (13/33) for pts with PD-L1-pos tumors versus 13% (8/61) for pts with PD-L1-neg tumors. Pts with PD-L2^{High} tumors showed an ORR of 27% (11/41), versus 13% (5/40) for pts with PD-L2^{Low} tumors. Updated data will be presented.
Conclusions: MPDL3280A was well tolerated, with no pneumonitis-related deaths. Durable responses were observed in a variety of tumors. PD-L1 and PD-L2 tumor status appears to correlate with responses to MPDL3280A.
Conflict of interest: *Advisory board: Amgen, Boehringer, Bristol-Myers Squibb, Genentech, Imclone, Lilly, Merck KGaA, Millennium, Novartis, Onyx, Pfizer, Roche, Sanofi, Celgene, Genentech. Corporate-sponsored research: Genentech, Roche, BMS, Novartis. Other substantive relationships: Amgen, Merck KGaA, Novartis, Roche, Sanofi, PharmaMar*

880 POSTER

Survival and long-term safety in patients (pts) with advanced solid tumors receiving nivolumab (anti-PD-1; BMS-936558; ONO-4538)

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Background: Blockade of programmed death-1 (PD-1), a co-inhibitory receptor expressed by activated T cells, can overcome immune resistance and mediate tumor regression (Topalian et al, NEJM 2012). We present survival and long-term safety results from a clinical study of nivolumab, a PD-1 receptor blocking monoclonal antibody, in pts with advanced solid tumors.
Methods: Pts received nivolumab (0.1−10 mg/kg IV Q2W) in an outpatient setting during dose escalation and/or cohort expansion. Tumors were assessed by RECIST 1.0 after each 4-dose cycle. Pts received ⩽12 cycles or until discontinuation criteria were met.
Results: 306 pts with non-small cell lung cancer (NSCLC; n = 129; squamous and non-squamous), melanoma (MEL; n = 107), renal cell (RCC; n = 34), colorectal (n = 19) or prostate cancer (n = 17) were treated. Objective responses (OR) were observed in NSCLC, MEL and RCC (Table). Additional pts with NSCLC, MEL and RCC manifested stable disease (SD) for ⩾24 weeks (Table). In these heavily pretreated pts (47% with 3−5 prior systemic therapies), median OS in NSCLC, MEL, and RCC was 9.6, 16.8 and >22 months, respectively. Drug-related adverse events (AEs; any grade) occurred in 75% (230/306) of pts, the most common being fatigue (28%), rash (15%), diarrhea (13%), and pruritus (11%). Grade 3−4 drug-related AEs occurred in 17% (52/306) of pts. Drug-related pneumonitis (any grade) occurred in 4% (12/306) of pts, with grade 3−4 drug-related pneumonitis occurring in 1% (4/306) of pts and associated with 3 deaths in the trial. Exploratory data correlating PD-L1 expression to outcomes using an automated assay with the 28−8 anti-PD-L1 antibody will be presented.
Conclusions: Nivolumab produced durable tumor regression, and was associated with OS and landmark 1−2 year survival values which are unexpected in such heavily pre-treated pts with advanced NSCLC, MEL and RCC. We observed an acceptable safety profile with long-term drug administration in the outpatient setting. These findings support the ongoing clinical development of nivolumab in phase 3 trials with survival endpoints.

Tumor type	Dose, mg/kg	OR Rate, n/N (%)	SD ⩾24 wk, n/N (%)	Median OS, mo (95% CI)	OS Rate, % (95% CI); pts at risk, n 1 y	2 y
NSCLC	1−10	22/129 (17)	13/129 (10)	9.6 (7.8−12.4)	42 (33−51); 43	14 (4−24); 5
MEL	0.1−10	33/107 (31)	7/107 (7)	16.8 (12.5−31.6)	62 (53−72); 55	43 (32−53); 26
RCC	1 or 10	10/34 (29)	9/34 (27)	>22[a] (13.6−NE)	70 (55−86); 23	50 (31−70); 8

[a]Median OS was not reached at 22 mo, the longest time to death so far.
NE, not estimable.

Conflict of interest: *Ownership: JM Wigginton: employee stock ownership, BMS. Advisory board: JR Brahmer: BMS, uncompensated. DF McDermott: BMS. S Gettinger: Nivolumab (April 2013), BMS. JM Taube: BMS. M Sznol, BMS. Corporate-sponsored research: FS Hodi: BMS, institute received clinical trial support. SL Topalian: BMS. DC Smith: BMS, OncoMed, Celgene, MedImmune, Millennium, AstraZeneca, Atterocor, Debiopharm. JM Taube: BMS. Other substantive relationships: FS Hodi: non-paid consultant to BMS. SL Topalian: uncompensated consulting for BMS consulting for Jounce Therapeutics spouse consulting for Amplimmune, Inc spouse royalties through institution from BMS and Amplimmune. JM Wigginton: employee, BMS.*

881 POSTER

A phase I dose-escalation and pk study of continuous oral rucaparib in patients with advanced solid tumors

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Background: Rucaparib, a potent, oral small molecule inhibitor of poly (ADP-ribose) polymerase (PARP) 1 and −2, is being developed for treatment of homologous recombination repair deficient (HRD) ovarian cancer. This study evaluated rucaparib as monotherapy. Primary objectives were to define the maximum tolerated dose (MTD), recommended Phase 2 dose (RP2D), and PK of continuous oral rucaparib.
Materials and Methods: A standard 3+3 dose escalation design was used. Intra-patient dose escalation was allowed. Patients (pts) aged ⩾18 with advanced solid tumor that progressed on standard treatments were recruited. Measurable disease was not required. Rucaparib was taken orally qd or bid continuously until disease progression. Plasma PK assessments included full profile, trough levels, and food effect.
Results: 33 pts (median age 49 yrs [range 21−71]; 30 female; 17 ECOG PS=0; 18 breast cancer (BC), 10 ovarian/peritoneal cancer (OC), 5 other tumor) were enrolled in 7 dose cohorts (40, 80, 160, 300 and 500 mg qd, and 240, 360 mg bid). One pt at 360 mg bid experienced DLT of CTCAE grade 3 nausea. No pts discontinued treatment due to toxicity. Treatment-related adverse events (primarily grade 1−2) reported in ⩾10% of pts include fatigue (n = 8), nausea (n = 5), anorexia (n = 4), vomiting (n = 4), and diarrhea (n = 3). Grade 3/4 toxicities have been minimal and no myelosuppression has been observed. To date, two pts (1 BC, 1 OC; both $BRCA1^{mut}$; 300 mg qd) achieved a PR (duration 14 and 21+ wks, respectively). An additional 10 pts (5 OC, 4 BC, 1 CRC; 7 $BRCA^{mut}$, 2 $BRCA^{unk}$, 1 $BRCA^{wt}$) achieved a best response of stable disease (SD) >12 wks thus far. Three pts (all $BRCA^{mut}$ OC) are ongoing in wks 26, 27, and 40. Five recently enrolled pts are also ongoing. Overall disease control rate (CR+PR+SD>12 wks) to date in all evaluable OC pts across all dose levels is 86% (6/7). Dose proportional PK was observed up to 500 mg qd with mean $t_{1/2}$ of 15 h (range 4.3−29 h). Following qd dosing, steady state was achieved by Day 8. As expected, bid dosing increased trough levels above 2 μM target with low interpatient variability.
Conclusion: Continuous oral rucaparib is well tolerated, with encouraging clinical activity, including objective responses and durable SD, observed during dose-escalation. Once confirmed, the RP2D will be evaluated in platinum-sensitive OC pts with a gBRCA mutation.
Conflict of interest: *Ownership: Heidi Giordano, Jennifer Borrow and Sarah Jaw-Tsai are employees/stock holders of Clovis Oncology, Inc. Advisory board: Rebecca Kristeleit is an advisory board member for Clovis Oncology, Inc. Corporate-sponsored research: The institutions for Drs. Flynn, Shapiro, LoRusso, Kristeleit, Patel, Infante and Burris receive trial funding from Clovis Oncology, Inc.*

882 POSTER

A phase I dose-escalation study of buparlisib (BKM120), an oral pan-PI3K inhibitor, in Chinese patients with advanced solid tumors

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Background: Activation of the PI3K/Akt/mTOR signaling pathway promotes tumor growth. Buparlisib is an oral pan-class I (α, β, γ, δ) PI3K inhibitor that has demonstrated clinical antitumor activity in a range of cancer types. In a first-in-man Ph I study (NCT01068483) conducted in Western patients (pts) with advanced solid tumors (aST), the maximum tolerated dose (MTD) of single-agent buparlisib was declared as 100 mg/d. Here, we present interim results of a Ph Ib trial of single-agent buparlisib in Chinese pts with aST (NCT01626209).
Material and Methods: The primary objective was to determine the MTD or recommended Phase II dose (RP2D) of single-agent buparlisib in Chinese pts, based on clinical safety profile, and supported by PK results. Pts (age ⩾18 y, ECOG PS⩽2) with advanced breast cancer or

other cancers with squamous cell (SC) histology, who progressed on standard therapy, or for whom no standard anticancer therapy exists, received once-daily oral buparlisib. Other key eligibility criteria included availability of archival/fresh tumor biopsy to determine PI3K pathway activation status and measurable/non-measurable disease (RECIST v1.1). A Bayesian logistic regression model guided dose escalation.
Results: As of March 11, 2013, 14 pts (median age 45.5 y [range 24−75]; 43% male; primary cancer site: breast (5), SC lung (6), head and neck (3); 43% ⩾4 prior antineoplastic therapy lines) had received buparlisib at 80 mg/d (n = 6) or 100 mg/d (n = 8). Median exposure duration was 47 d [range 9–105]. DLT only occurred in 1 pt at 80 mg (Grade [G] 3 depression). The MTD was declared as 100 mg/d. Other drug-related G3/4 AEs (CTCAE v4.03) occurred in 2 pts at 80 mg/d (anemia and depression) and 3 pts at 100 mg/d (increased alanine and aspartate aminotransferases [1 pt], decreased platelet count [1 pt], and hyperglycemia [1 pt]). Primary reasons for treatment discontinuation were progressive disease (n = 8), AEs (n = 2 [G3 depression and G3 pneumonia]), patient/guardian decision (n = 2), and death (n = 1 [terminal lung cancer]). Preliminary PK analysis revealed no major difference in PK parameters between Chinese and Western pts.
Conclusions: In these Chinese pts with aST, buparlisib had a favorable safety profile and a similar PK profile to that seen in Western pts. The MTD for single-agent buparlisib in Chinese pts was declared as 100 mg/d. Short duration on treatment may reflect heavily pretreated disease. Antitumor activity is under evaluation in expansion cohorts and will be presented at the meeting.
Conflict of interest: *Ownership: Katharine Hazell owns shares in Novartis. Corporate-sponsored research: Li Zhang, Bhinge Xu, and Yi-Long Wu are investigators on Novartis-sponsored clinical trials. Other substantive relationships: Katharine Hazell, Anil Gaur, Junfang Xu, and Lucia Trandafir are employed by Novartis.*

883 POSTER

A multiple ascending dose phase I clinical, pharmacokinetic, and pharmacodynamic study of CG200745, a histone deacetylase (HDAC) inhibitor, in patients with advanced solid tumors

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Background: The aim of this study was to assess the safety, maximum tolerated dose (MTD), pharmacokinetics, pharmacodynamics, and efficacy of multiple dose of intravenous CG200745, a novel histone deacetylase (HDAC) inhibitor, in patients with advanced solid malignancies.
Materials and Methods: Two to six patients received intravenous CG200745 weekly for 3 weeks, then 1 week off according to the '2+4' dose-escalating method. Pharmacokinetic sampling and pharmacodynamic sampling of acetylated histone H4 (Acetyl-H4) in peripheral blood mononuclear cells (PBMCs) were performed on day 1 and 15 of the 1st cycle. Pre- and post-biopsy for acetyl-H4 in tumor tissue was performed in accessible patients.
Results: Eighteen patients were treated at one of nine doses (24.0–250 mg/m^2) and received 1.5 (1−11) cycles of CG200745 (median, range). No dose-limiting toxic effects or QTc prolongations were noted. Dose proportionality was observed for both Cmax and AUC. The elimination half-life and mean residual time was 5.67±2.69(mean±SD) and 3.97±1.63 hrs. An increase in PBMC acetyl-H4 correlated with dose and Cmax up to 51 mg/m^2 and plateaued in higher dose levels. At 24 hrs post administration, acetyl-H4 values higher than two times of baseline values in tumor tissue were observed in 50% (4/8) of measured patients. Stable disease was seen in half of the patients (9/18).
Conclusions: CG200745 can be safely administered at the effective dose levels that inhibit HDAC in PBMCs and tumor tissue. Although MTD was not reached, further escalation was not performed as the acetyl-H4 plateaued at dose levels higher than to 51 mg/m^2. Further phase II trials are recommended at 250 mg/m^2 due to the tolerability.
No conflict of interest.

884 POSTER

Hyperglycemia in patients treated with the pan-PI3K inhibitor buparlisib (BKM120): characterization, management, and assessment for pharmacodynamics

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Background: PI3K serves a central role in glucose homeostasis. Here, we characterize hyperglycemia (HG) observed in two clinical trials of the pan-class I PI3K inhibitor buparlisib (BKM120), assess its relevance as a pharmacodynamic marker, and evaluate the relationship of HG and insulin release (assessed by C-peptide [C-pep]) with clinical response.
Methods: Pts were treated with single-agent buparlisib in two completed studies in pts with advanced solid tumors: S1 − a Ph I dose-escalation (DE) study (CBKM120X2101; 12.5–150 mg/d [N = 83]); and S2 − a Ph I DE study in Japanese pts (CBKM120X1101; 25–100 mg/d [N = 15]). Here, we report observations for pts treated with 80 mg/d (n = 11) and 100 mg/d (n = 55) in S1, and 100 mg/d (n = 9) in S2, unless otherwise stated. C-pep was measured throughout the studies. HG was assessed according to CTCAE v3. Clinical response was assessed by best % change from baseline in sum of longest diameters (SLDs) and best overall response as per RECIST v1.0 and v1.1 in S1 and S2, respectively.
Results: In S1, mean max % change in C-pep at baseline and at C_{max} on C1D1 was −10, 13, 58, 41, 70, and 72% at 12.5, 25, 50, 80, 100, and 150 mg/d, respectively. There was a slight inverse correlation between max post-baseline C-pep value in C1 and best % change in SLDs (Pearson's r = −0.17) in pts treated at 80 or 100 mg in S1. All-grade (G) HG was noted in 25 of 75 (33%) pts at 80/100 mg in S1/S2; although most cases were mild (G1/2) and transient, G3/4 HG was noted in 6 (8%) pts. HG was managed with glucose-lowering medications, such as metformin and insulin when needed, and with buparlisib interruption/dose reduction. Only 1 pt permanently discontinued buparlisib due to HG (treated at 100 mg in S1). Among pts reporting no HG (n = 50), 2% had PR, 44% had SD, and 46% had PD; among those with HG G1−4 (n = 25), 36% had SD and 48% had PD.
Conclusions: HG is observed in buparlisib clinical trials and is well managed with glucose-lowering agents. Buparlisib exhibited a dose-dependent effect on C-pep levels and is a potential pharmacodynamic marker. There was a slight inverse correlation between C-pep and tumor shrinkage in this preliminary analysis, indicating a potential relationship between PI3K pathway inhibition and tumor response. No clear relationship between HG grade and clinical response was observed. Further analyses investigating the relationship between HG/change in C-pep and tumor shrinkage in additional single-agent buparlisib studies will be presented at the meeting.
Conflict of interest: *Ownership: D Mills owns shares in Novartis. Advisory board: J Rodon serves as a consultant for Novartis, Lilly, Servier, and Lipopharma. Corporate-sponsored research: A Azaro, J Rodon, JF Vansteenkiste, Y Ando, T Doi, and RW Naumann are investigators on Novartis-sponsored clinical trials. Other substantive relationships: D Mills, C Sarr, E di Tomaso, and C Massacesi are employed by Novartis. Y Ando is a speaker for Novartis, receiving honoraria.*

885 POSTER

Phase 1b study of albumin-binding doxorubicin (aldoxorubicin) plus free doxorubicin

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Background: Preclinical studies of aldoxorubicin, a doxorubicin conjugate that binds covalently to circulating albumin, plus free doxorubicin, have demonstrated complete and prolonged remissions of pancreatic and ovarian cancer xenografts when administered at 50% of their MTD, and with less toxicity than each drug administered at their MTD. The safety

and activity of a fixed dose of free doxorubicin and escalating doses of aldoxorubicin were evaluated in patients with advanced solid tumors who had no other accepted therapeutic options.
Methods: Open label dose-escalation study of aldoxorubicin administered at either 175, 240 or 320 mg/m^2 (130, 180 or 240 mg/m^2 doxorubicin equivalents) iv + 35 mg/m^2 doxorubicin iv, both on Day 1 of 21 day cycles, up to 8 cycles. MTD is the dose level immediately below where 2/6 patients experience a dose limiting toxicity (DLT), or the maximum dose of 320 mg/m^2 of aldoxorubicin.
Results: 10 subjects have been treated as of March 31, 2013. 7 subjects received 230 mg/m^2 aldoxorubicin and 3 patients received 320 mg/m^2 aldoxorubicin. No DLT was observed. The MTD thus was 320 mg/m^2 aldoxorubicin + 35 mg/m^2 doxorubicin administered as above. Patients were able to receive 4.5 cycles (median). 4 subjects were terminated either due to progressive disease or death. No subjects stopped treatment due to an adverse event. Grade 3/4 neutropenia occurred in 8/10 patients, grade 3/4 thrombocytopenia in 6 patients and grade 3/4 anemia in 4 patients. Febrile neiutropenia was observed in 3 patients. Grade 3/4 liver enzyme elevations or fatigue occurred in 1 and 2 patients, respectively. An objective partial tumor response was documented in one patient with advanced soft tissue sarcoma that had not responded to previous doxorubicin as well as a patient with advanced breast cancer. 7 patients had stable disease.
Conclusion: The combination of aldoxorubicin at 320 mg/m^2 and doxorubicin at 35 mg/m^2 can be safely administered to patients with solid tumors and shows anti-tumor activity. Since neutropenia is very common, prophylactic use of G-CSF is rexcommended. The dose of aldoxorubicin is 90% of the MTD of aldoxorubicin. Thus, doxorubicin does not appear to add to the toxicity of this combination.
Conflict of interest: *Ownership: CytRx Corporation. Corporate-sponsored research: CytRx Corporation. Other substantive relationships: Employment, CytRx Corporation*

886 POSTER

Pharmacokinetic study of aldoxorubicin, a novel albumin-binding drug, in solid tumor patients

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Background: Aldoxorubicin consists of doxorubicin conjugated to a pH sensitive linker that binds covalently to the cycteine 34 position in circulating serum albumin. Previous studies demonstrated that aldoxorubicin can be administered at doses up to 350 mg/m^2 (260 mg/m^2 doxorubicin equivalents) every 21 days for up to 8 cycles. We have investigated aldoxorubicin pharmacokinetics, including albumin-bound and free doxorubicin, and doxorubicinol after administration of 2 dose levels of aldoxorubicin in patients with advanced solid tumors.
Methods: Patients with solid tumors and no standard therapy were eligible. Other entry criteria: ECOG PS 0−2; LVEF>45% of predicted normal; ANC. 2000/mm^3; platelets >100,000/mm^3; Hct >25% (male), 28% (female). Patients were administered either 230 mg/m^2 aldoxorubicin (165 mg/m^2 doxorubicin equivalents) or 350 mg/m^2 aldoxorubicin (260 mg/m^2 doxorubicin equivalents) iv over 30 minutes on day 1 of each cycle. Blood samples were taken prior to administration and at multiple time points up to 72 hr post administration during cycles 1 and 3. Serum concentrations of albumin-bound doxorubicin, unbound doxorubicin and doxorubicinol were analyzed.
Results: As of March 31, 2013, 10 subjects have been entered in the study. 7 subjects have received 230 mg/m^2 aldoxorubicin and 3 patients 350 mg/m^2 aldoxorubicin. No serious adverse events have been reported. Grade 3 and 4 adverse events include neutropenia, thrombocytopenia and anemia. A partial response has been documented in 1 patient with small cell lung cancer that had received 3 prior chemotherpy regimens, and ongoing stable disease in another patient with previously-treated small cell lung cancer, both at the 230 mg/m^2 dose. Results for the 230 mg/m^2 cohort are complete and show for the albumin-bound doxorubicin during cycle 1: C_{max}=64 μg/mL; t_{max}= 0.25 hr; $t_{1/2}$= 19.7 hr; $AUC_{t-\infty}$=1500 h*μg/mL; CL_{pred}= 0.153 L/h/m^2; V_{sspred}= 3.91 L/m^2. Results are similar for cycle 3. Free doxorubicin accounted for less than 0.8% of total doxorubicin at each time point, and doxorubicinol for less than 0.0007% of total drug. Results from the 350 mg/m^2 cohort are pending.
Conclusion: Aldoxorubin binds rapidly and almost completly to albumin, has a narrow V_d and is cleared slowly from circulation, which distinguishes it from doxorubicin. Very little free doxorubicin is released into the circulation, potentially mitigating some of the drug's toxicity.
Conflict of interest: *Ownership: CytRx Corporation. Corporate-sponsored research: CytRx Corporation. Other substantive relationships: Employment, CytRx Corporation*

887 POSTER

Description and impact of topotecan dosing in ovarian cancer and SCLC

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Background: Topotecan (topo) is a treatment (tx) for advanced ovarian and small cell lung cancer (SCLC). Weekly (WK) dosing vs. conventional (daily x 5, Q21D) (CO) has shown similar outcomes in both diseases with less severe neutropenia. We describe patterns of use in the community, measure tx duration, and capture WBC growth factor (GF) utilization during topo.
Methods: Eligible pts: in US Oncology's (USO) iKnowMed^{TM}(iKM) EHR; SCLC or ovarian cancer diagnosis; tx with single agent topo. Pts were classified as WK or CO dosing cohorts. Percent of pts crossed over from CO to WK was captured. Age, sex, KPS, line of therapy (LOT), tx duration, and GF use were collected. Chi squared tests assessed the association of clinical factors with CO vs. WK dosing. Wilcoxon rank sum tests assessed continuous variables.
Results: From 1/1/2007 to 10/31/12, 2,534 pts were included (1071 ovarian; 1463 SCLC). CO: WK dosing for ovarian and SCLC were 168: 903 and 624: 839, respectively. Characteristics for SCLC pt were similar for both cohorts. In the ovarian population, a higher percent of pts age >65 yo received WK ($p = 0.005$). Less than 1% of pts crossed over from CO to WK. Pts receiving CO topo received more administrations in ovarian and SCLC (mean: 15 vs. 6, $p < 0.001$ SCLC and 18 vs. 10, $p < 0.001$ ovarian), but overall treatment duration was not different for CO dosing. Pegfilgrastim (PEG) was used less frequently with WK tx in ovarian and SCLC (OR: 0.1, $p < 0.01$) and average number of PEG admin was greater in CO tx (SCLC: 2 vs. 1, $p < 0.01$; ovarian: 3 vs. 2, $p = 0.014$).
Conclusions: Published data support topo WK as an alternative to CO dosing with less toxicity. This report shows more use of WK topo in a community oncology setting in ovarian and SCLC; more PEG use in CO topo dosing and similar tx duration for CO and WK dosing.
No conflict of interest.

	Cohort	Mean	Median	Standard deviation	P-value
SCLC N: CO=624; WK=839					
# Topo admin	CO	15.5	10.0	12.0	<0.001
	WK	6.1	5.0	4.6	
# peg admin	CO	3.1	2.0	2.3	<0.001
	WK	2.1	1.0	1.6	
# filgrastim admin	CO	4.9	3.0	7.4	NS
	WK	5.0	3.0	6.3	
Topo tx (mths)	CO	67.5	46.0	79.3	NS
	WK	52.9	42.0	63.7	
Ovarian N: CO=168; WK=903					
# Topo admin	CO	18.1	15.0	12.4	<0.001
	WK	9.6	7.0	8.5	
# peg admin	CO	3.7	3.0	2.5	0.014
	WK	3.4	2.0	3.4	
# filgrastim admin	CO	6.5	3.0	9.0	0.50
	WK	7.2	4.0	7.9	
Topo tx (mths)	CO	84.4	67.0	73.1	0.93
	WK	89.8	70.0	95.3	

888 POSTER

Phase I, open-label, dose-escalating clinical and pharmacokinetic study of the novel antimicrotubulin agent PM060184 administered over 10 Minutes on day 1 and 8 every three weeks to patients with advanced malignant solid tumors

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Background: PM060184 is a new chemical entity that inhibits tubulin polymerisation, causing microtubular fragmentation and mitotic arrest. *In vitro*, it has activity against solid tumours, especially breast, colon, renal and ovarian tumour cell lines. *In vivo,* evaluation of PM060184 demonstrated significant antitumour activity in patient-derived xenograft models (AVATAR) of gastric, NSCLC and pancreatic ductal adenocarcinoma.
Materials and Methods: Patients (pts) with advanced solid tumours were enrolled in a phase I, open-label, accelerated dose-escalating clinical and pharmacokinetic (PK) study of intravenous (i.v.) PM060184 given over 10 min on Day 1 and 8 every 3 weeks.
Results: 30 pts were distributed in 9 dose levels (DLs). Median age was 60 y (range, 36−78 y), 19 pts (63%) were males. ECOG PS was 1 in 67% of pts (range, 0−2). Most common tumours were colorectal (33%), GIST, NSCLC and breast cancer (13% each). Most pts were heavily pretreated, with a median of 4 (range, 1−13) lines. Pts received a median of 2 (range, 1−23) PM060184 cycles. Starting DL was 1.3 mg/m^2. DLTs occurred at 10.4 mg/m^2 [1 pt G3 peripheral neuropathy (PN)], 11.6 mg/m^2 (1 pt G3 PN), 14.5 mg/m^2 (2 pts G3 PN; and G3 vomiting and G4 neutropenia), and 12.0 mg/m^2 (3 pts G3 abdominal pain; symptomatic G3 hyponatremia; and G3 myalgia and G3 arthralgia). The MTD was 12.0 mg/m^2 and the RD was 9.3 mg/m^2. Most toxicities and abnormalities were mild. G3 AEs were: peripheral neuropathy (n = 3 pts), vomiting, fatigue, abdominal pain, intestinal obstruction, arthromyalgia, hyperkalaemia and hyponatraemia (n = 1 each). Haematological abnormalities were G3 thrombocytopenia (n = 2), G3 neutropenia (n = 2) and G4 neutropenia (n = 1). Preliminary PK data show a short half-life (4.4 h), wide distribution (251 L) and moderate inter-patient variability. Evidence of activity was observed in 2 breast carcinoma pts with tumour shrinkage around 20% and one partial response as per Choi criteria in one pt with GIST (resistant to 2 prior lines of standard therapy) who is still on treatment after 23 cycles. Overall, stabilisation for >3 mo has been observed in 4 pts.
Conclusions: The RD of PM060184 for further development was 9.3 mg/m^2 and has shown an acceptable safety profile; early non-cumulative PN was the main DLT. The antitumour activity observed in heavily pretreated pts warrants further study.
Conflict of interest: *Corporate-sponsored research: Funding to STAT for conduct of clinical trial*

889 POSTER

First-in-man phase I, open-label, dose-escalating clinical and pharmacokinetic study of the novel antimicrotubulin agent PM060184 administered over 10 minutes on days 1, 8, and 15 every four weeks to patients with advanced malignant solid tumours

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Background: The new chemical entity PM060184 inhibits tubulin polymerization, causing microtubular fragmentation and mitotic arrest. It has activity *in vitro* against several solid tumours (especially breast, colon, renal and ovarian tumour cell lines). *In vivo,* evaluation of PM060184 demonstrated significant antitumour activity in patient-derived xenograft models of gastric, NSCLC and pancreatic ductal adenocarcinoma.
Materials and Methods: Patients (pts) with advanced solid tumours were enrolled in a phase I, open-label, accelerated dose-escalating clinical and pharmacokinetic (PK) study of PM060184 given i.v. over 10 min on Days 1, 8 and 15 every 4 weeks.
Results: 22 pts were distributed in 8 dose levels (DLs) during escalation. Median age was 58 y (range, 22−72 y), 15 pts (68%) were males. ECOG PS was 1 in 36% of pts (range, 0−1). Most common tumours were colorectal (50%) and pancreas (14%). Most patients were heavily pretreated, with a median of 4 (range, 1−9) lines. Pts received a median of 2 (range, 1−7) PM060184 cycles. The starting DL (DL1) was 1.3 mg/m^2. The highest DL (DL7) 14.5 mg/m^2 was the MTD, as 2 pts (both pretreated with oxaliplatin) had DLT (G3 peripheral sensory neuropathy). One DLT (G3 peripheral sensory neuropathy) occurred at (DL8) 12.0 mg/m^2 in the expansion cohort, which is still ongoing. Common toxicities were fatigue, alopecia, peripheral sensory neuropathy, nausea, vomiting, musculoskeletal pain and diarrhoea. Most were mild (G1−2); G3 toxicities were peripheral sensory neuropathy (3 pts), fatigue and abdominal pain (1 pt each). Myelosuppression was mild, 5 pts had G2 neutropenia and 3 pts had G3 anaemia. G3 biochemical abnormalities comprised transient AST increase (2 pts) and AP increase (2 pts). Preliminary PK data show a short half-life (5 h), a wide distribution (286 L) and moderate inter-patient variability. Remarkable tumour shrinkage (~20%) occurred in 2 pts: 1 with head and neck carcinoma and 1 with breast carcinoma. Stabilization >3 mo also occurred in 3 pts with colorectal carcinoma.
Conclusions: PM060184 has acceptable safety and tolerability profile; non cumulative peripheral neuropathy is the only DLT observed. Evidence of activity has been found. Recruitment into the expansion cohort is ongoing; updated data will be presented at the meeting.
Conflict of interest: *Advisory board: PharmaMar*

890 POSTER

A phase I study in patients with advanced solid tumors for the human monoclonal antibody vantictumab (OMP-18R5; anti-Frizzled) targeting the WNT pathway

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Background: The WNT pathway is a key oncologic pathway in numerous tumor types and implicated in cancer stem cell (CSC) function. Vantictumab is a first-in-class anti-CSC antibody that interacts with the extracellular domain of 5 Frizzled receptors (Fzd 1, 2, 5, 7, 8) and blocks canonical Wnt signaling. In patient-derived xenograft models, vantictumab inhibits growth of many tumor types, reduces CSC frequency, promotes differentiation of tumor cells, and synergizes with many chemotherapy agents (*PNAS 109, 11717*).
Methods: Using a 3+3 design, vantictumab was given intravenously, first every 1 week (q1w) or q2w, and, ultimately, q3w. Objectives were to determine maximum tolerated dose, safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy.
Results: 23 patients have been treated in 7 dose-escalation cohorts (0.5 & 1 mg/kg q1w; 0.5 mg/kg q2w; 1, 2.5, 5 and 10 mg/kg q3w). Most common related Grade 1 and 2 adverse events (AEs) included fatigue, vomiting, abdominal pain, constipation, diarrhea and nausea. Only related Grade $\geqslant$3 AEs were dose-limiting toxicities of Grade 3 diarrhea and vomiting in one patient at 1 mg/kg q1w. Vantictumab clearance was dose-dependent, consistent with target-mediated drug disposition, with the half-life ranging from 1.5 (0.5 mg/kg) to 3.3 days (5 mg/kg). Exposure at current dose levels correlates with efficacy in nonclinical tumor models. PD biomarkers indicate inhibition of WNT pathway in patient tumors and surrogate tissue. One patient at 0.5 mg/kg q1w had a bone fracture on Day 110 and a ~4-fold increase by Day 28 of β-C-terminal telopeptide (β-CTX), a marker of increased bone turnover. A revised safety plan, including Vitamin D_3 and $CaCO_3$ prophylaxis, and q3w dosing enabled further dose escalation. Upon β-CTX doubling, 2 patients received zoledronic acid, and β-CTX returned to baseline. Three patients with neuroendocrine tumors (NETs) with investigator-confirmed progressive disease on prior therapy had stable disease (SD) for ~4, 9+ and 12+ months; 2-, 0.8- and 8.4-fold length, respectively, of prior therapy. One patient with pancreatic NET (12+ months) had tumor shrinkage of −21%.
Conclusions: Vantictumab is well tolerated at current dose levels. An increase in bone turnover can be managed with increased monitoring and intervention with zoledronic acid. Prolonged SD in 3 NET patients, with a minor response in a pancreatic NET patient, may represent single-agent activity. The cohort for 10 mg/kg q3w continues to enroll.
Conflict of interest: *Corporate-sponsored research: KP Papadopoulos, AW Tolcher: Oncomed support for conduct of clinical trials to START. LS Rosen: research funding to institution from OncoMed. R Chugh: research funding from Novartis, Mabvax and Infinity. D Smith: Bristol-Myers Squibb, OncoMed, Celgene, MedImmune, Millennium, AstraZeneca, ImClone Debiopharm.*

891 POSTER

Properties of pyrrol derivate as potential anticancer compound

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Introduction: Gastrointestinal organs are the first to be affected by drugs including anticancer ones and provide major alterations because gut epithelium sensitivity through its high proliferative activity and liver vulnerability through xenobiotics detoxification. Targeted inhibitors of proliferative activity such as protein kinase inhibitors are known as high-efficiency and low-toxic anticancer agents, but only few ones have received US Food and Drug Administration approval as colorectal cancer treatments. Therefore, evaluation of 'small molecule' protein kinase inhibitor pyrrol derivate (D1, 5-amyno-4-(1,3-benzothyazol-2-yl)-1-(3-methoxyphenyl)-1,2-dihydro-3H-pyrrol-3-one) as anticancer agent, based on assessment of its anticancer efficacy and gut toxicity in comparison with common therapeutic 5-fluorouracil (5FU) ones was aimed.
Methods: Macroscopic analysis of colon internal surface, histological (light microscopy and morphometry of stomach, liver, small and large intestine sections), biochemical (serum liver enzymes activities, urinary 7,8-dihydro-8-oxoguanine (8-oxoG) concentration as a marker of DNA oxidative damage).
Results: D1 ingested for 10, 50 and 190 days (2.3 mg/kg daily) to normal rats didn't alter gut mucosa unlike 5FU, inhibited colon mucosa cell proliferation by 27% only after 190 days action (as opposed to 40−50% inhibition by 5FU after all investigated terms), caused no inflammation, had practically no effect on submucosa vascular bed, caused no hepatotoxicity. 1,2-Dimethylhydrazine(DMH)-induced rat colon cancer model was used to evaluate D1 antitumor activity. Total tumor lesions area decrease by 41−46% caused by D1 when acts concomitantly or following DMH (by 43% caused by 5FU) was revealed. Concomitant action of D1 and 5FU following DMH increased this rate to 54%.
Protective effect of D1 against DMH alterations in 'normal' gut mucosa and liver, manifested by recovery of gut mucosa and liver morpho-functional state and vascular bed, decrease of inflammation in stomach and intestine mucosa, normalization of serum aspartate aminotranspherase and alkaline phosphatase, diminution of elevated (by 5 times) urinary 8-oxoG, was found. On the contrary 5FU caused aggravation of DMH alterations in gut organs, urinary 8-oxoG further enhancing. Partially neutralization of 5FU toxic effects, caused by D1 under concomitant action, was also detected.
Conclusions: Low toxicity of pyrrol derivate and its efficacy against experimental colorectal cancer was concluded, so further D1 preclinical investigations are suggested.
No conflict of interest.

892 POSTER

A phase I trial assessing the safety and pharmacokinetics of afatinib and weekly vinorelbine in patients with advanced solid tumours

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Background: Afatinib (A) is an irreversible ErbB Family Blocker. Final safety and pharmacokinetic (PK) data from a phase I trial of A + vinorelbine (V) intravenous (iv) or oral (po) are presented. PK data focus on V po, as data for V iv were previously shown.
Methods: Eligible patients (pts) were ⩾18 years old with refractory advanced, non-resectable and/or metastatic tumours known to overexpress EGFR and/or HER2, had an ECOG performance status (PS) 0−1, and adequate organ and bone marrow function. In a 3+3 dose-escalation design, pts received escalating doses of daily A po (20/40/50 mg) continuously + V iv (25 mg/m^2; Part A) or V po (60 mg/m^2 for 3 weeks, escalated to 80 mg/m^2 thereafter; Part B) on Days 1, 8, 15 and 22 of a 4-week course. Primary endpoint was maximum tolerated dose (MTD) of A + V iv or po (the dose at which ⩽1/6 pts had a dose-limiting toxicity [DLT] during Course 1). A and V PK parameters were analyzed by intra-individual comparison to assess possible drug–drug interactions.
Results: 55 pts were treated (24 male/31 female) with A + V iv (n = 28) or A + V po (n = 27); median age 54 years, ECOG PS 0/1 36%/64%. MTD for both combinations was A 40 mg daily based on 1/6 DLTs in the MTD cohort (Table). Febrile neutropenia (8/55 pts) and diarrhoea (7/55 pts) were the most frequently reported DLTs during Course 1. Three pts had a confirmed partial response (PR) at A 40 mg + V po (RECISTv1.0); median duration of response was 114 days. Stable disease was seen in 16 pts in the A + V iv arm (4 of which had an unconfirmed PR at A 40 mg/50 mg [1/3]) and in 11 pts in the A + V po arm. In PK expansion cohorts for both combinations at the MTD, geometric mean $C_{max,ss}$ and $AUC_{\tau,ss}$ of A with/without V iv/po were similar, as were C_{max} and AUC_{0-24} of V iv/po with/without A. Intra-individual comparisons did not show any systematic trend with higher/lower exposure of A in the presence of V iv/po or *vice versa*.

	DLTs in Course 1					
	A + V iv − Part A			A + V po − Part B		
	20 mg A	40 mg A	50 mg A	20 mg A	40 mg A	50 mg A
MTD cohort	0/3	1/6	4/6	0/4	1/6	3/5
PK expansion cohort	NE	7/13	NE	NE	2/12	NE

NE = not evaluated.

Conclusions: The recommended Phase II/III dose of A was determined to be 40 mg daily in combination with iv or po V weekly. Final PK analyses suggest no drug–drug interactions between A and V iv or po. Both combinations had a manageable safety profile and showed signs of clinical activity in pretreated pts with solid tumours.
Conflict of interest: *Other substantive relationships: Martina Uttenreuther-Fischer and David Schnell are employed by Boehringer Ingelheim GmbH & Co. KG.H*I*ne de Mont-Serrat and Inga Tschoepe are employed by Boehringer Ingelheim France S.A.S.Antoine Hollebecque, Rastislav Bahleda, Yann Berg*, Christophe Massard, Jean-Charles Soria and Jean-Pierre Delord have nothing to disclose.*

893 POSTER

Design and development of active and selective FGFR kinase inhibitor CPL-043 as potential anticancer targeted therapy

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Background: Fibroblast growth factor receptors (FGFRs) family of receptors with tyrosine kinase activity comprises a group of extensively studied targets for small molecule inhibitors development. Alterations in gene copy number of different FGFRs and their point mutations have been correlated with many types of cancer, making FGFR kinases an interesting target for novel anticancer therapy. There are several FGFR inhibitors in clinical development but there is still a niche for the drug with properly balanced selectivity profile.
Material and Methods: Using sophisticated drug design methods we have designed CPL-043 − a small molecule FGFR kinase inhibitor with high potency in vitro. To establish the activity and the selectivity of the compound we have used kinase activity assay based on recombinant kinases and cell proliferation assay, using the cell lines dependent on FGFR signaling − SNU-16 and UM UC-14. To confirm biological activity of the inhibitor we performed immunoblot assay detecting the level of FGFR pathway related proteins.
Results: Our results indicate that CPL-043 inhibits FGFR1, 2 and 3 activity in vitro in low nanomolar concentrations. Concurrently the IC50 for the most common FGFR off-targets − KDR and PDGFR is over ten times higher. CPL-043 inhibits proliferation of FGFR-dependent cell lines including SNU-16 and UM-UC-14. Treatment of cells with CPL-043 for 1 h evokes dramatic decrease in the level of pFGFR, pFRS and pErk proteins in a dose dependent manner. Moreover the inhibitor has no effect on the lines with low FGFR activity like HCT-116 or H1703, suggesting that the compound is not cytotoxic.
Conclusion: We have designed a very potent and selective FGFR inhibitor, which displays biological activity in selected cellular models without evoking cytotoxic effects on the FGFR-independent cell lines. The compound has proper ADME predicted profile as is currently under investigation in the in vivo study.
No conflict of interest.

894 POSTER

First-in-human phase I trial investigating the oral selective c-Met inhibitor MSC2156119J (EMD 1214063) in patients (pts) with advanced solid tumors

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Background: MSC2156119J is a highly selective, reversible, ATP-competitive inhibitor of c-Met, a frequently deregulated oncoprotein. In preclinical models, MSC2156119J inhibited tumor growth and induced regression of hepatocyte growth factor-dependent and -independent tumors.
Methods: This phase I dose-escalation trial (3+3 design) included pts with advanced solid tumors not amenable to standard therapy (NCT01014936; ongoing; sponsored by Merck KGaA). Primary objective was to assess the MTD of MSC2156119J; secondary endpoints included safety, antitumor activity, pharmacokinetics (PK), and pharmacodynamics (Pd). Pts were treated once/d with oral MSC2156119J: d1−14 followed by 7d rest (regimen [R]1), continuously 3 times/wk (R2), or continuously d1−21 (R3), all 21-d cycles. In Aug 2011, an optimized formulation (OF) was introduced.
Results: Until Dec 04, 2012, 100 pts were treated (R1=42; R2=41; R3=17). Doses were escalated from 30–230 mg/d in R1 and 30–115 mg/d in R2 with the initial formulation, and from 30–400 mg/d in R1, 60–175 mg/d in R2, and 300–500 mg/d in R3 with the OF. Bioavailability was higher with the OF; AUC and C_{max} increased with dose. DLTs were reported in 4 pts: G4 lipase and G3 amylase increase (R1; 115 mg/d), G3 lipase increase (R2; 60 and 100 mg/d OF), and G3 nausea and vomiting (R2; 130 mg/d OF). One pt experienced drug-related G3 peripheral edema (R3; 300 mg/d OF). G2 drug-related AEs (R1−3) included fatigue (n = 8), lipase increase (n = 3), nausea (n = 2), decreased appetite (n = 2), vomiting (n = 2), and neutropenia (n = 2). Most pts (80%) had no drug-related AE >G1. Paired tumor biopsies (pre-/on-therapy) revealed phospho–c-Met inhibition in 13/15 evaluable pts. Two pts (NPC and NSCLC) experienced unconfirmed partial responses. Fifteen pts had SD >4 mo, including 1 pt with SD >32 mo. This pt (sarcomatoid bladder cancer) had multiple MET copies due to Chr 7 polysomy. In line with preclinical PK/Pd models, 500 mg was considered biologically active and sufficient for target inhibition. In the 500-mg cohort, no DLTs were observed in 12 evaluable pts. 500 mg once/d was confirmed as the recommended phase 2 dose (RP2D). Since the cutoff date in Dec, doses were further escalated to 700 and 1000 mg to explore effects of MSC2156119J above the RP2D. At 1000 mg, one DLT was observed (G3 AST/ALT elevation). This cohort is currently expanded to 6 pts.
Conclusions: MSC2156119J was well tolerated and showed antitumor activity. 500 mg was defined as the RP2D.
Conflict of interest: *Advisory board: GS Falchook has an advisory relationship with EMD Serono to disclose. K Kohler has a consultancy/advisory relationship with Merck KGaA to disclose. Corporate-sponsored research: GS Falchook, HM Amin, and R Kurzrock have received a research grant from EMD Serono. Other substantive relationships: MB Klevesath and A Johne are Merck KGaA employees.GS Falchook has received honoraria from EMD Serono.*

895 POSTER

Epidermal growth factor receptor (EGFR)-mediated adverse events (AEs) in patients (pts) with EGFR mutation positive (EGFR M+) non-small cell lung cancer treated with afatinib

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Background: Afatinib (A) is an oral, irreversible ErbB Family Blocker showing superior efficacy to first-line pemetrexed/cisplatin (PC) in EGFR M+ pts. In the LUX-Lung 3 trial, median progression-free survival was 11.1 months for A and 6.9 months for PC (hazard ratio=0.58; p = 0.0004). A similar Phase III trial, LUX-Lung 6, comparing A with gemcitabine/cisplatin in Asian pts was recently reported (ASCO 2013). Here, we present the data on common EGFR-mediated AEs from both Phase III trials.
Methods: 345 (LUX-Lung 3) and 364 (LUX-Lung 6) EGFR M+ pts were randomized (2:1) to receive A or chemotherapy. A was administered until progression or intolerable AEs. The A starting dose of 40 mg could be escalated to 50 mg daily or reduced to 30 mg or 20 mg daily based on study criteria. On-treatment AEs were summarized by preferred and grouped terms. No AE diaries were supplied; pts recalled start and stop dates for each AE during clinic visit. AEs were graded using NCI-CTCAE version 3.0.
Results: In LUX-Lung 3, 229 pts received A and median exposure was 336 days (range 7–827 days). All pts reported at least one AE and the commonly observed EGFR-mediated AEs in LUX-Lung 3 are included in the table.

	Diarrhoea	Rash*	Stomatitis*	Paronychia
All grades (%)	96.1	90.0	73.4	56.8
Grade 3 (G3) (%)	14.8	16.2	8.7†	11.4
First G3 before/after 6 weeks (%)	11.8/3.1	3.9/12.2	6.6/2.2	0.4/10.9
Median duration of G3 (days)	5.0	10.0	8.0†	14.0
G3 recurred after dose reduction (%)	2.6	1.3	0.4	1.3
Serious AE (%)	6.6	0.4	1.3	0.0
Led to dose reduction (%)	19.7	19.2	10.0	13.1
Led to treatment discontinuation (%)	1.3	0.0	0.0	0.9

*Group term; † Includes one pt with G4 AE.

Two-thirds of pts who reported diarrhoea experienced two episodes (25%) or less (46%). The majority of pts with G3 diarrhoea, rash, stomatitis or paronychia had a single occurrence. Other drug-related EGFR-mediated AEs included dry skin (29.3%), cheilitis (12.2%), conjunctivitis (8.3%) and dry eyes (4.8%). Related interstitial lung disease-like events occurred in three pts (one G1, one G3 and one G5). Additional information on the AE profile of A and data from LUX-Lung 6 will be presented.
Conclusions: The most common AEs observed with A were characteristic of EGFR-inhibiting agents. G3 AEs were short-lived, and responded to dose interruptions/reductions with little recurrence at a lower dose of A. Treatment discontinuation due to EGFR-related AEs was low, which indicates that A has a manageable safety profile and is suitable for the long-term treatment of EGFR M+ lung cancer pts.
Conflict of interest: *Other substantive relationships: James Yang has held compensated consultant or advisory roles for Roche, Astrazeneca, Genetech, Pfizer, Novartis, Takeda, Clovis, Innopharma. He has held uncompensated consultant or advisory roles for Eli Lilly, Boehringer Ingelheim. He has held honoraria for Bayer, Astrazeneca, Roche, Merck, Pharmengine. Lecia Sequist has held uncompensated consultant or advisory roles for Boehringer Ingelheim, Merrimack, Clovis, AstraZeneca, GlaxoSmithKline. Kenneth John O'Byrne has held consultant or advisory roles for Boehringer Ingelheim, and has received honoraria from Boehringer Ingelheim, and has received other renumeration from Boehringer Ingelheim. Martin Schuler has received research funding from Boehringer Ingelheim and has received travel support from Eli Lilly. Tony Mok has held consultant or advisory roles for Astrazeneca, Boehringer Ingelheim, Roche, Eli Lilly, Beigene, Pfizer, Merck Serono, Bristol-Myers Squibb, Jannsen, Taiho. He has held honoraria from Astrazeneca, Boehringer Ingelheim, Roche, Eli Lilly, Pfizer, Merck Serono, Taiho. Dan Massey and Victoria Zazulina are employed by Boehringer Ingelheim Limited, Bracknell, UK. Dennis O'Brien is employed by Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, USA. Yi-Long Wu has received honoraria from Roche, Eli Lilly, AstraZeneca, Pfizer, Sanofi, and research funding from Roche, Eli Lilly, AstraZeneca, Pfizer, Sanofi. Sarayut L Geater has nothing to disclose.*

896 POSTER

Pharmacokinetic analysis of Asian patients in a phase 2 study of dovitinib (TKI258) in metastatic renal cell carcinoma

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Background: Dovitinib potently inhibits FGFR (IC_{50} = 8−40 nM) as well as VEGFR and PDGFR (IC_{50} <40 nM), drivers of tumor growth, angiogenesis, and anti-angiogenic escape in renal cell carcinoma (RCC) and other solid tumors. In a phase 2 study of dovitinib in patients with RCC, tolerability was within the known safety profile of dovitinib (Angevin E, et al. ASCO 2011, abstract 4551). Here, we provide the pharmacokinetic (PK) results from this study in Asian and non-Asian patients.
Materials and Methods: Patients with advanced or metastatic RCC with predominant clear cell histology who failed both VEGF and mTOR therapy were eligible, as were small subsets of patients who were refractory to standard treatment or treated with agents that were not VEGFR or mTOR inhibitors. Patients of Asian ethnicity who failed standard treatment or for whom no standard treatment existed were also included. Patients were treated with dovitinib 500 mg/day on a 5-days-on/2-days-off schedule. PK parameters were determined using a noncompartmental method for area under the curve (AUC), maximum concentration (C_{max}) and time to maximum concentration (T_{max}).
Results: PK results for Asian (n = 12) and non-Asian (n = 53) patients are summarized in the Table. Asian patients had a higher coefficient of variation (as high as 68%) due to a smaller number of patients than that of non-Asian patients. Both day 1 AUC and C_{max} for Asian patients were similar to those for non-Asian patients. For both Asian and non-Asian patients, the day 15 AUC and C_{max} were 16%-33% lower than those of day 1.
Conclusions: PK parameters were similar between Asian and non-Asian patients. Day 15 PK was lower than that of Day 1 in both Asian and non-Asian patients due to auto-induction of CYP1A2 as shown in other in vitro and in vivo studies.

PK Parameter	Asian patients n = 12 (day 1) n = 11 (day 15)	Non-Asian patients n = 53 (day 1) n = 45 (day 15)
Geometric mean AUC_{0-last}, h·ng/mL (coefficient of variation [CV%])		
Day 1	5381 (68)	5221 (29)
Day 15	4428 (50)	3501 (34)
Geometric mean C_{max}, ng/mL (CV%)		
Day 1	333 (62)	300 (31)
Day 15	281 (41)	239 (36)
Median T_{max}, h		
Day 1	7.1	6.1
Day 15	6.0	6.0

Conflict of interest: *Ownership: M. Shi (Novartis). Advisory board: C.C. Lin (Novartis) Y.H. Chang (Pfizer, Novartis, GlaxoSmithKline, Bayer, Millennium-Takeda, Janssen, IPSEN) V. Grunwald (Novartis, Pfizer, GlaxoSmithKline, Roche) B. Escudier (Novartis, Pfizer, Bayer, GlaxoSmithKline, Aveo). Corporate-sponsored research: V. Grunwald (Pfizer). Other substantive relationships: C.C. Lin, honoraria (Novartis) V. Grunwald, honoraria (Novartis, Pfizer, GlaxoSmithKline, Roche) J. Chang, employment (Novartis) E. Tan, employment (Novartis) N. Pirotta, employment (Novartis) M. Shi, employment (Novartis)*

897 POSTER

A phase I/II study of cancer peptide vaccine S-288310 in patients with advanced urothelial carcinoma

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Background: S-288310 is a cancer peptide vaccine composed of two kinds of HLA-A*24:02-restricted peptides, S-288301 and S-288302, that were developed from two oncoproteins, DEP domain containing 1 (DEPDC1) and M-phase phosphoprotein 1 (MPHOSPH1), highly expressed in urothelial carcinoma (UC).
Purpose: The objective of this study was to examine the safety, tolerability and immune response (induction of cytotoxic T lymphocytes, CTLs) specific to S-288301 and S-288302 in patients with advanced UC.
Patients and Methods: HLA-A*24:02-positive patients with histologically confirmed UC after documented progression or intolerance to prior platinum-based chemotherapy(ies) were eligible. 1 or 2 mg of each peptide emulsified with Montanide ISA51VG was administered s.c. once a week in the axillary or inguinal region.
Results: Three patients each were treated with S-288310 at 1 or 2 mg/each peptide in the phase I study. S-288310 was well-tolerated and no DLTs were observed. In the phase II study, 32 patients were treated with either 1 or 2 mg/shot in a random manner. The protein expression of DEPDC1 and MPHOSPH1 was confirmed by immunohistochemical analysis in 36 (97.3%) and 35 (94.6%) of the 37 tissues examined, respectively. The CTL responses to S-288301 and S-288302 were detected in 22 (66.7%) and 24 (72.7%) of the 33 patients so far examined, respectively, and 87.9% of the patients responded to at least one peptide. No significant difference in CTL induction or safety was observed between the 1 and 2 mg groups. In the phase II study, 2 of the 32 cases (6.3%) revealed irPR, and 16 of the 32 (50.0%) were judged to be irSD assessed by the immune-related response criteria. Seven of the 16 patients with irSD showed tumor necrosis or regression although they did not meet the criteria of partial response. The median progression-free survival and overall survival (OS) was 1.9 months (90% confidential interval [CI] of 1.2−2.2 months) and 9.4 months (90% CI of 4.2–12.2 months). The OS of cases, in which CTL induction to both peptides was observed, tended to be improved, compared with those that showed the response to one peptide. The most frequently observed AE was the injection site reaction.
Conclusion: S-288310 was well-tolerated and induced antigen-specific CTLs in 87.9% of the patients and revealed clinical responses. Our results suggested S-288310 is a promising drug for the treatment of UC.
Registration: JapicCTI-090980
No conflict of interest.

Poster Session (Sat, 28 Sep)
Regulatory/Trial Methodology/Pharmacy

900 POSTER

Defining dose limiting toxicity (DLT) for phase I testing molecularly targeted agents: results of an international survey

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Background: Using traditional definitions of dose limiting toxicity (DLT) in phase I trials of molecularly targeted agents (MTA) is challenged by their specific toxicity profiles and often continuous administration. For instance we recently reported that 50% of patients receiving MTAs have their worst toxicity after cycle 1 (Postel-Vinay, JCO 2011). An international survey to

collect expertise on defining DLT for MTA phase 1 trials was initiated by the EORTC-led research group.
Material and Methods: A 15-question electronic survey was sent to corresponding authors of phase I reports identified in EJC, JCO, Annals of Oncology, Lancet as well as to phase I experts identified by the co-authors. Questions included: DLT assessment period duration, incorporation of specific grade 1 (G1) or G2 adverse events (AEs), and their minimum duration to qualify as DLT, exclusion of specific G3 AEs, inclusion of dose modification/delay, and relative worsening of AEs. The potential impact of schedule, both oral and IV dosing was considered.
Results: Among the 400 investigators contacted, 119 replied; 67 questionnaires were 100% complete. In the last 5 years, 30% participated in more than 10 trials, 35% were principal investigators of 5 or more. 11% (8/67) opted for a DLT assessment period of 1 cycle, 33% for 2 cycles and 54% requested all cycles to be assessed, with the proviso not to delay patient accrual. Suggestion was made to define maximum tolerated dose on cycle 1 data only, to reanalyze all accumulated data before the expansion cohort and to recommend the phase II dose based on the toxicity data from multiple cycles. 90% evaluated pre-existing symptoms to qualify a DLT. 92% suggested including dose modification and temporary interruption in the DLT definition when dose intensity drops down to 50−60% (13% of the responders) and to 70−80% (50%).
Moderate toxicity was deemed relevant by 70% (IV treatment) and 80% (oral). Selected G1/2 varied: visual disorders and confusion (30%); QTc prolongation, dyspnoea, some GI disorders (diarrhoea, pancreatitis) (20%). For G2 events, >1 week duration was relevant by 40 to 58% depending on AEs. Responses for IV and oral routes were consistent in 70%.
Conclusions: The majority of experts favoured a longer assessment period as well as the incorporation of specific G2 AE. However, no clear agreement on a re-definition of DLT was reached. A large international data warehouse is being evaluated to develop guidelines.
No conflict of interest.

901 POSTER

A population-based analysis of outcomes in cancer patients who do not satisfy clinical trial eligibility criteria (CTEC)

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Background: Trials have stringent inclusion and exclusion criteria in order to maintain internal validity. However, study findings are subsequently applied to patients in routine practice who frequently do not meet CTEC. Our aim was to characterise the outcomes and magnitude of treatment benefit, if any, in these patients.
Material and Methods: Patients diagnosed with stage 3 colon cancer from 2006 and 2008, referred to any 1 of 5 regional cancer centers in British Columbia, and assessed for adjuvant chemotherapy (AC) within 12 weeks of surgery were analysed. Patients were considered trial-eligible (TE) if aged 18 to 79 years, ECOG 0/1, CEA <10, did not receive prior chemotherapy or radiation, and had adequate blood counts and normal cardiac, liver and kidney function. All other patients were deemed trial-ineligible (TI).
Results: A total of 820 patients were identified: median age was 69 years (range 60−76), 423 (52%) were men, 365 (45%) were ECOG 0/1 and 592 (72%) received AC. Among patients treated with AC, 370 (63%) were TE and 222 (37%) were TI. Compared to TI patients, those who were TE were younger (63 vs 70 years, $p < 0.01$) and more likely to receive combination rather than single agent AC (56 vs 33%, $p < 0.01$). Outcomes were significantly different among patients who were TE, TI, and those who did not receive AC (Table). In multivariate analyses that adjusted for confounders such as age, ECOG and T and N stages, both TI patients and those not treated with AC had worse prognoses than TE patients (HR for colon cancer deaths 1.32, 95% CI 0.86–2.02 and 2.77, 95% CI 1.92–3.99, respectively, p trend <0.01; HR for all deaths 1.24, 95% CI 0.85–1.80 and 2.95, 95% CI 2.17–4.00, respectively, p trend <0.01).

Group	5 year CSS rate	p-value	5 year OS rate	p-value
TE and received AC	82%		74%	
TI and received AC	75%	<0.001	65%	<0.001
No AC	57%		35%	

CSS=cancer-specific survival; OS=overall survival.

Conclusions: In this population-based cohort, patients who did not fit CTEC were frequently treated with AC. Outcomes in this TI group were inferior to those in the TE group, but they were better than the subset that did not receive AC. Trials specifically designed for patients traditionally deemed TI are needed.
No conflict of interest.

902 POSTER

Adherence to CONSORT adverse event reporting guidelines in medical oncology clinical trials, a systematic review

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Background: The Consolidated Standards of Reporting Trials (CONSORT) guidance was extended in 2004 to provide a set of 10 specific and comprehensive guidelines regarding adverse event (AE) reporting in randomized controlled trials (RCTs). There is little data though regarding adherence to these guidelines by published oncology RCTs.
Material and Methods: All phase III RCTs published between 2007 and 2011 were reviewed using a 16-point adverse event reporting quality score (AERQS) based on the 2004 CONSORT extension. Multivariable linear regression was used to identify features associated with improved reporting quality. All statistical tests were two-sided.
Results: A total of 325 RCTs were reviewed. The mean AERQS was 10.1 on a 0-to-16 scale. The most common items that were poorly reported were the way adverse event data were collected (adequately reported only in 10% of studies), the description of AEs' characteristics leading to withdrawals (15%) and the attribution of AEs to trial interventions (38%). Even when reported, the methods of AE data collection and analysis were highly heterogeneous. The multivariable regression model revealed that industry funding, intercontinental trials and trials in the metastatic setting were predictors of higher AERQS. The quality of AEs reporting did not improve over time and was not better among manuscripts published in high-impact-factor journal.
Conclusion: In conclusion, our findings show that methodological aspects of AEs collection and analysis were poorly reported. Given the potential impact of poorly reported trials, oncology journals should emphasize the importance of conformity to the 2004 CONSORT guidelines regarding adverse event reporting.
No conflict of interest.

903 POSTER

Area-based measures for assessing survival benefit in Kaplan–Meier's curves

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Background: Medians comparison in survival curves is erratic and doesn't sometimes provide good assessment of survival benefit.
Objectives: The aim is to test a new area-based method for assessing survival in a set of Kaplan–Meier's curves. The primary outcome is to analyze the correlation between survival increments by the area method and excess risk calculated by hazard ratio (HR). A second outcome is to compare area-based vs. median-based results.
Methods: A 30 curves sample for R 0.7, α 0.05 and β 0.8 was calculated, and a Pubmed search for articles with survival analysis in colon, lung and breast cancer was conducted. Articles with an overall survival figure showing patients at risk, both curves reaching the median and $p < 0.05$ for HR, were included.
Three lines were defined for each figure: V: vertical cut line intersects abscissa at the longest time (t) with at least 10 patients at risk in each group or 30 in total. H: horizontal cut line crosses the intersection of V with the upper survival curve. T: Horizontal top line intersects ordinates in its maximum value (100%). Area under curve (AUC) was defined among the ordinates axis, the curve and H. Reference area (RA) was defined as the rectangle among ordinates axis, V, H and T. It represents the survival time in case no patient died (t). Survival was calculated as AUC/RA*t. SISA, R-code and Photoshop CS6 were used.
Pearson's correlations were calculated between excess risk in A vs. B group (HR-1)% and survival increment in B vs. A (B survival time/A survival time −1)%, assuming longer survival for B group. Survival increments were calculated by medians and area methods. Steiger's z-test was used to compare which method (area or medians) correlated better with HR-calculated excess risk. A Bland-Altman's concordance analysis was performed.
Results: The search identified 485 articles, 41 of them had survival curves that met inclusion criteria. By excluding tails with few patients at risk, area-based measures included survival data from 71% patients.
Concordance analysis showed a standard deviation of 85%, and a mean difference in survival (area minus median) of −1.9 months.

Method	Correlation survival increment – excess risk (HR-based)	
	R	p
Medians	0.854	<0.01
Area	0.922	<0.01
p(Medians vs Area)	0.036	

Conclusions: Area- and medians-based results show discrepancies between them. Area method benefits more from curve information, correlates better with HR-based excess risk and provides a measure of survival time.
No conflict of interest.

904 POSTER

Quality of reporting of phase II trials in oncology in highly ranked oncology journals

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Background: Phase II trials represent an essential step in the development of anti-cancer drugs. The aim of this study was to assess the quality of their reporting in highly-ranked oncology journals, to investigate predictive factors of quality and to develop better reporting guidelines for authors.
Material and Methods: We reviewed the tables of contents of 8 peer-reviewed oncology journals published between January 2011 and December 2011 and with a 2011 impact factor >4: Ann Oncol, Br J Cancer, Clin Cancer Res, Eur J Cancer, J Clin Oncol, J Natl Cancer Inst, Lancet Oncol and Oncologist. Two reviewers assessed the quality of each report by using a 44-point overall quality score (OQS; range, 0 to 44 points) inspired from the revised Consolidated Standards of Reporting Trials statement. Primary endpoint definition, justification of sample size and definition of the evaluable population for each endpoint, were assessed separately because of their crucial methodological importance using a 3-point key methodological score (KMS; range, 0 to 3). Exploratory analyses were used to identify predictive factors associated with the different scores.
Results: 156 articles were included. Agreement between the reviewers for each item was good (kappa coefficient range: 0.62−1). The median OQS was 28 (range: 9−35). OQS sub-score analysis showed that reporting of statistical methods was particularly low with a mean of 2.5 (6 items). The median KMS was 2 (range 0−3). Primary endpoint definition, justification of sample size and definition of the evaluable population were reported only in 107 (68.6%), 121 (77.6%), and 52 (33.3%) cases, respectively. On multivariate analysis, reporting of clinicaltrials.gov registration was associated with improved OQS, OR = 3.2 (95CI, 1.5 to 7.1). No predictive factor for KMS were identified.
Conclusions: Phases II trials reporting is still poor even in journals with strict editorial policies. This may lead to biased interpretation of phase II trial results. We have developed a checklist for use by authors, reviewers, and editors to improve reporting of these studies. As well as using a checklist during the preparation of their manuscript, we recommend that authors provide reviewers and readers with the last version of the study's protocol.
No conflict of interest.

905 POSTER

Quality of reporting of chemotherapy compliance in randomized controlled trials of breast cancer treatment

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Background: The adoption of any therapy in clinical practice requires a detailed knowledge of treatment administration and expected compliance as reported in the literature. The Consolidated Standards of Reporting Trials (CONSORT) statement requires detailed reporting of interventions in publications of randomized controlled trials (RCTs). We hypothesized that there was variable reporting of chemotherapy compliance in published randomized controlled trials in breast cancer and surveyed the literature to assess the quality of reporting chemotherapy compliance and to determine the study characteristics associated with a reporting quality.
Materials and Methods: MEDLINE, EMBASE, and CENTRAL were searched systematically for published original articles (Jan 2005 through Dec 2011; English language) of Phase III RCTs evaluating chemotherapy in breast cancer. Selected articles were scored 1 point for reporting each of 4 measures − number of chemotherapy cycles, dose modification, early treatment discontinuation and relative dose intensity (RDI). Logistic regression was performed to identify study characteristics associated with higher reporting quality score of $\geqslant 2$.
Results: Key study characteristics of the eligible 115 RCTs were: published in high impact journals, 79 (69%); published 2008 onward, 66 (57%); advanced-stage disease, 43 (37%); industry sponsorship, 37 (32%). RDI, number of cycles received, dose modification, and early treatment discontinuation rates were mentioned in 70 (61%), 53 (46%), 65 (57%) and 81 (70%) of the articles, respectively. Only 25 (22%) articles mentioned all 4 compliance measures. Quality score was $\geqslant 2$ for 82 (71%) articles. Study characteristics associated with a significantly higher quality of reporting chemotherapy compliance were articles published 2008 onward ($P = 0.035$) and advanced-stage disease ($P < 0.001$).
Conclusions: Our study demonstrates that there is variable reporting of chemotherapy compliance in published RCTS, although a modest improvement is seen in recent years. Incorporating standards for reporting chemotherapy compliance in scientific guidelines or the journal peer review process may decrease the variability and improve the quality of reporting.
No conflict of interest.

906 POSTER

Poor quality of adverse event reporting in oncology phase III trials: A systematic review

D. Maillet[1], B. You[1], J. Peron[1]. [1]*Hôpital Lyon Sud, Pierre Bénite, France*

Background: In the present study, we assessed the quality of toxicity reporting (description and impacts of AEs) in oncology phase III trials.
Material and Methods: This is a systematic review of all medical oncology phase III studies published in 10 major oncology journals (NEJM, JCO,

Table 1 (abstract 906). Reporting of the consequences of AEs on trial or patient outcomes (n = 325)

Adverse event reporting	RCTs	
	n	%
AEs leading to patient death: lethal adverse events		
Existence of lethal adverse events		
Not reported: unknown	88	27
Reported	237	73
• No lethal AE (n = 0)	60	18
• One or more lethal AEs (n⩾1)	177	54
• Including those with reporting of type of specific adverse events leading to death	130	73% of RCT with n⩾1 lethal AEs reported
Adverse events leading to drug discontinuation		
Existence of AEs leading to trial discontinuation		
Not reported: unknown	85	26
Reported	240	74
• No AE leading to drug discontinuation (n = 0)	4	1
• One or more AEs leading to discontinuation (n⩾1)	236	73
• Including those with type of adverse events reported	49	21% of RCT with n⩾1 AEs leading to drug discontinuation reported
Adverse events leading to dose modification		
Existence of AEs leading to dose modification		
Not reported	197	61
Reported	128	39
Type of AEs reported	32	10

Lancet, Lancet Oncol, JNCI, Ann Onc, EJC, BJC, BCRT, Cancer) between 2007 and 2011 using PubMed. For each publication, we analyzed the trial characteristics; the presentation of AEs (including the description clarity) and the reporting of AE consequences on trial or on patient outcomes (i.e. AEs leading to patient death or to trial discontinuation/dose modification).
Results: Total of 325 published randomized control trials (RCT) were analyzed. Results are presented in Table 1. The potential existence of lethal AEs was reported in only 73% of them. Among 177 RCT publications where one or more lethal AEs were mentioned, the specific type of AE leading to patient death was mentioned in 73%. The existence of AEs leading to trial discontinuation was mentioned in 74% RCT publications. Among them, the types of AEs responsible of discontinuation were reported in only 21%. Only 39% of publications reported the existence of AEs leading to dose modifications. Regarding descriptions of AEs, aggregations of AEs were used in 29% of studies. For example, the most commonly reported aggregated outcomes were reported as 'dermatologic AEs' (45%); 'cardiologic AEs' (33%), and 'neurologic AEs' (26%) without any additional definitions. Although these aggregations were considered, only 25% were clearly described. Sources of confusion in definition of AEs were found in 10% reports.
Conclusions: Our findings suggest the quality of AEs reporting in oncology RCTs published in 10 major oncology journals is insufficient. In particular, the proper reporting of potential lethal AEs, as well as the types of AEs leading to death, to trial discontinuation or dose alteration is found in 50% of the trials only. Moreover, although unclear in essence, aggregated AE outcomes are too frequently used in publications.
No conflict of interest.

907 POSTER

Pneumatic conveying systems and physical stability of monoclonal antibodies: example of cetuximab

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Background: Proteins such as monoclonal antibodies (mAb) are sensitive products which could undergo complex degradation pathways during the various manipulation steps also during transport. Aggregation can be induced by mechanical stresses which can occur during manipulations and transport and could induce loss of efficacy and/or toxic effects such as immunogenicity. Currently pneumatic conveying systems are in place in some hospitals but are not currently used for transport of proteins. Previous studies with Rituximab showed that the use of these systems were possible on the condition of removing air of bags. The objective of this study was to confirm these results with another antibody, Cetuximab.
Material and Method: Various protein characterization methods: size exclusion chromatography (SEC), dynamic light scattering (DLS) describing submicronic populations and corresponding mean diameters, turbidity (350 nm) and infra-red spectroscopy (FTIR) were used to determine changes in physical properties of Cetuximab aggregation mechanically induced. Several conditions were tested: presence of residual air in bags, travel time, number of travel cycles (1 to 3). One concentration was tested (2 mg/ml). All experiments were performed in the same day.
Results and Discussion: Considering the results obtained with Rituximab, we have limited our experiments to 3 travel cycles. Up to 3 travel cycles and without head space or bubbles into the bags, no modification was noticed in comparison with the control (no run). Indeed, we observed only one peak by SEC with a retention time of 18, 42$\pm$0.01 min, a monodisperse population (polydispersity index $\leqslant$ to 0.1) with a mean diameter of 12.56$\pm$0.121 nm by DLS, a slightly increased of optical densities (OD) at 350 nm (0.00123 up to 0.00216) and no modification of the FT-IR spectra (similarity coefficients were close to one). In the opposite, in presence of air, significant modifications were found after 1 cycle since OD reached to 0.00264 and 2 populations were found by DLS with a polydispersity index of about 0.22. Moreover, modifications of FTIR spectra were also observed (similarity coefficient <1) suggested alteration of the secondary structure.
Conclusion: As shown for Rituximab, aggregation of monoclonal antibodies during the pneumatic conveying is strongly dependant on the presence of air/liquid interfaces.
No conflict of interest.

Poster Session (Sat, 28 Sep)
Diagnostics/Biomarkers

950 POSTER

Randomised phase II trial comparing therapy based on tumour molecular profiling versus conventional therapy in patients with refractory cancer: results of the feasibility part of the SHIVA trial

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Background: Two recent studies suggest that a histology-independent approach consisting in selecting molecularly targeted agents based on the molecular profile of patients' tumours, whatever the tumour location and histology are, improves patients' outcome [Von Hoff et al., 2010; Tsimberidou et al., 2012]. However, the lack of randomisation versus standard of care in these studies did not allow drawing robust conclusions.
Material and Methods: The SHIVA trial is a multicentric randomized proof-of-concept phase II trial comparing molecularly targeted therapy based on tumor molecular profiling versus conventional therapy in patients with any type of refractory cancer. The primary endpoint is progression-free survival (PFS). The molecular profile performed on a mandatory biopsy includes the assessment of 1) hot spots mutations using the AmpliSeq cancer panel on Ion Torrent/PGM (Life Technologies), 2) gene copy number alterations using Cytoscan HD/Affymetrix, and 3) expression of oestrogen, progesterone and androgen receptors by immunohistochemistry on formalin-fixed sample. The algorithm used by a Molecular Biology Board (MBB) to guide treatment in the experimental arm is presented in the Table. The efficacy analysis will be performed on 200 randomized patients. A cross-over is proposed at disease progression. Feasibility included the first 100 patients.
Results: Between 10/2012 and 04/2013, 143 patients have been included in the study. Results of the feasibility part are available for the 53 first patients at the time of the abstract submission. Full feasibility results will be presented at the meeting. Biopsy was performed in 50 out of 53 patients (94%). Complications occurred in 1 patient (2%). Median time between the biopsy and the MBB was 26 days [range: 14−42]. Mutations, gene copy number alterations and IHC profile were obtained in 32 (64%), 34 (68%) and 45 (90%) patients, respectively. A molecular abnormality leading to randomisation was present in 21 patients (42%).
Conclusions: The establishment of a comprehensive tumour molecular profile is safe, feasible and compatible with clinical practice. A molecular abnormality matching with the approved drugs available in the trial was present in 42% of patients.
No conflict of interest.

Molecular abnormalities	Type of molecular abnormality	Molecularly targeted agents
KIT, ABL, RET	Activating mutation or amplification	Imatinib
PI3KCA, AKT1	Activating mutation or amplification	Everolimus
AKT2,3, mTOR, RAPTOR, RICTOR	Amplification	Everolimus
PTEN	Inactivating mutation and LOH	Everolimus
STK11	Inactivating mutation and LOH	Everolimus
BRAF	Activating mutation or amplification	Vemurafenib
PDGFRA/B, FLT-3	Activating mutation or amplification	Sorafenib
EGFR	Activating mutation or amplification	Erlotinib
HER-2	Activating mutation or amplification	Lapatinib + Trastuzumab
SRC	Activating mutation or amplification	Dasatinib
EPHA2, LCK, YES	Amplification	Dasatinib
ER, PR	Protein expression >10%	Tamoxifen (or letrozole if contra-indication)
AR	Protein expression >10%	Abiraterone

ER = Estrogen receptor; PR = Progesterone receptor; AR = Androgen receptor; LOH = Loss of heterozygosity

951 POSTER

Evaluation of HER2 expression status using multiple chromosome 17 reference probes

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Background: Targeted therapies to HER2(+) breast cancer have improved outcomes in this aggressive phenotype. A recent unconfirmed study suggested that HER2 gene status may be misidentified in a small group of patients due to co-amplification of HER2 and CEP 17, leading to low HER2/CEP17 ratio with high HER2 gene copy number. We used alternate probes to chromosome 17 to reinterpret HER2 status in a group of patients in a single center to attempt to confirm these findings.
Methods: We identified 60 breast cancer biopsies done at the University of Pittsburgh Medical Center in 2012 with equivocal HER2 protein expression (2+ on IHC) that underwent FISH, had an increased HER2 copy number ($\geqslant$4), but were categorized as either equivocal or negative due to an elevated CEP17 (>2.6) copy number. We used Abbott Laboratory probes to SMS (17p11.2) and RARA (17q21.2) to reclassify cases based on HER2:SMS and HER2:RARA ratios. Equivocal was defined if either ratio was 1.8−2.2; and positive if either ratio was >2.2.
Results: For 60 cases, the average HER2 copies/cell ranged from 4 to 7.83. Eight cases had >6 HER2 copies/cell. Of these 8 cases, 7 (88%) became unequivocally positive on re-interpretation using HER2:SMS or HER2:RARA ratio. Fifty-two cases had 4−6 HER2 copies/cell. Of these 52 cases, 18 (34%) became unequivocally positive on re-interpretation using HER2:SMS or HER2:RARA ratio. The status remained negative on 30 cases (58%), 2 (4%) changed from negative to equivocal and 2 (4%) changed from equivocal to negative. Overall, the HER2 status changed in 29 of 60 cases (48%) using an alternate probe; however, the alternate probe that resulted in change of status was SMS in 23 cases (79%), both SMS and RARA in 5 cases (17%) and RARA alone in 1 case (4%).
Conclusions: Tumors with a HER2 gene copy number >6/cell may be assumed to be HER2(+) as they generally have ratios >2.2 using alternate reference probes. The reference probe implicated in changing amplification status in majority of cases is SMS, which is located on 17p while RARA is located on 17q (similar to HER2). Elevated CEP17 and RARA mean copy numbers may skew the ability for these probes to accurately assess HER2 gene status, especially when average HER2 copies/cell range between 4−8 copies.
No conflict of interest.

952 POSTER

Feasibility and safety of image-guided biopsy procedures for personalized cancer treatment

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Background: For implementing tumor DNA guided personalized cancer treatment in daily clinical practice it is important to determine the feasibility and safety of real-time image-guided fresh frozen tumor biopsies.
Material and Methods: An umbrella protocol (CPCT-02; NL35781.041.11) has been developed by the Dutch Center for Personalized Cancer Treatment (www.CPCT.nl), a collaboration between three Dutch cancer centers, to prospectively acquire fresh frozen tumor tissue as well as radiological response data from patients with advanced solid tumors. Image-guided biopsy procedures were performed before initiation of systemic anti-cancer treatment. The protocol allowed 2−4 specimens per time point with a maximum of four time points. DNA isolation of macrodissected tumor rich areas was performed if tumor cellularity exceeded 20%. Another pre-set criterium for performing Next Generation Sequencing (NGS) was a DNA yield of >50 ng for limited (but deep) sequencing of common somatic mutations in approximately 50 genes. A tumor cellularity of at least 50% and DNA yield >500 ng was required for performing extended sequencing of nearly 2000 cancer related genes using sequence enrichment technology. All clinical and genetic data was stored in the CPCT database allowing us to identify biomarkers for response. CPCT-02 (sponsored by the UMC Utrecht) is still recruiting.
Results: Currently, we report on 189 consecutive biopsy procedures performed in 182 patients, the majority being ultrasound-guided liver biopsies (40%). There were over 30% superficial tissue biopsies and in 9% CT-guided lung biopsy was performed. Biopsies were generally well tolerated. No pneumothorax $\geqslant$ grade 2 occurred and no bleeding or other major complications were observed. In 1.1% local pain at the biopsy site (grade 3) occurred. In almost 50% of samples tumor cellularity exceeded 70% and in general more than sufficient quantities of DNA were isolated (85% over 1000 ng). Given the pre-set criteria limited sequencing could be performed on 86% and extended sequencing on 65% of samples.

Feasibility of image-guided tumor biopsies for personalized oncology

	Feasibility (%)
Tumor percentage	
<20%	12
20−50%	20
>50%	68
DNA yield	
<500 ng	7
500–1000 ng	8
>1000 ng	85
Sequencing	
No	14
Limited	86
Extended	64

Conclusions: In daily clinical practice, image-guided tumor biopsies are feasible yielding sufficient material to perform NGS in 86% of patients and can be safely (99%) performed and implemented for personalized cancer treatment.
Conflict of interest: *Ownership: PIFA Therapeutics B.V., Naarden, the Netherlands. Advisory board: InteRNA Technologies, Nijmegen, the Netherlands*

953 POSTER

Genomic testing in cancer (GTC): Patient knowledge, attitudes and expectations

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Background: Genomic testing in cancer (GTC) characterizes oncogenic genes within a patient's cancer. This form of DNA testing is currently being studied for its ability to guide cancer therapy. The objective of this study was to describe patients' knowledge, attitudes and expectations towards GTC.
Materials and Methods: The 42-item self administered GTC questionnaire was developed by a multidisciplinary group (n = 9) and pilot patient pretesting (n = 8). The questionnaire was distributed to advanced stage cancer patients referred to The Drug Development Program at Princess Margaret Cancer Centre, Toronto, Canada, for a phase I clinical trial or for GTC testing as part of an ongoing research study.
Results: Results are reported from 93 surveyed patients with a response rate of 75% (n = 70). Patient characteristics: female 52 (74%); median age 57 years (range 22−77), prior chemotherapy 65 (93%), prior targeted therapy 35 (50%), current or prior clinical trial enrollment 49 (70%), high school diploma 16 (23%), university degree 30 (43%). A total of 73% of patients were interested in learning more about GTC and 60% reported that GTC would significantly improve their cancer care. The mean score of a 12-item questionnaire to assess knowledge of cancer genomics = 8/12 (67%) (SE: 0.25; 95% CI: 7.57–8.55). Patients' knowledge scores significantly correlated with their education level ($p < 0.0001$) and desire for further genetic counseling ($p = 0.004$). A needle or surgical biopsy for GTC if required would be acceptable to 66% and 37% of patients respectively. The primary reason for testing reported by 69% of patients was to help guide their ongoing treatment. The risk of a serious biopsy complication and potential for a treatment delay were listed as the most important reasons to avoid GTC. More than 78% of patients requested disclosure of incidental test results that might impact their own health or increase their family's risk of developing cancer. A reported 87% of patients agreed with biobanking their GTC results and tissue samples for future scientific research. Only

42% of patients reported having sufficient knowledge to make an informed decision to pursue GTC while 36% of patients indicated a need for formal genetic counseling prior to GTC.
Conclusions: Advanced cancer patients are motivated to participate in GTC. Educational tools and counseling programs need to be developed to support understanding and decision-making among patients interested in pursuing GTC.
No conflict of interest.

954 POSTER

Integrated microRNA and mRNA signature associated with the transition from the locally confined to the metastasized renal cell carcinoma

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Background: MicroRNAs (miRNAs) are endogenous small non-coding RNAs that regulate gene expression by interfering translation or stability of target transcripts. One miRNA can interact with several hundred mRNAs, while one mRNA can be regulated by several miRNAs. This interplay between miRNA and their mRNA has been proposed as an important process in cancer development and progression. We have investigated molecular networks impacted by predicted mRNA targets of differentially expressed miRNAs in patients with clear cell renal cell carcinoma (ccRCC) diagnosed with or without metastasis.
Material and Methods: miRNA and mRNA microarray expression profiles derived from primary clear cell renal cell carcinomas from patients with (in total 16 samples) or without diagnosed metastasis (in total 22 samples) were used to identify anti-correlated miRNA-mRNA interaction in ccRCC. For this purpose, Ingenuity pathway analysis microRNA Target Filter, which enables prioritization of experimentally validated and predicted mRNA targets was used. By applying an expression pairing tool, the analysis was focused on targets exhibiting altered expression in our analysis, finding miRNAs and their target genes with opposite or same expression. The resulting identified interactions were revalidated by RT-qPCR in another cohort of RCC patients. The predicted miRNA-mRNA interactions were also tested by functional analyses using miRNA knock-down and over expression experiments in renal cancer cell lines.
Results: Among the significantly differentially expressed miRNAs, we have identified 3 miRNAs (miR-146a, miR-128a and miR-17-5p) that were upregulated in primary tumors from patients without metastasis and down regulated in primary tumors from patients with metastasis. We have further identified the mRNA targets which expression were inversely correlated to these 3 miRNAs, and have been previously experimentally demonstrated in cancer setting in humans. Specifically we showed that BRAC1, MCM10, CDKN3, UHRF1, IL8 were downregulated and targeted by miR-146a-5p. The relation between these identifies target genes and miRNA-146a was validated in cell culture experiments.
Conclusions: We identified novel target genes of dysregulated miRNA which are involved in the transition from primary RCC without metastases into tumors generating distant metastasis.
No conflict of interest.

955 POSTER

Clinical application of molecular profiling in treatment selection for rare and advanced refractory solid tumours: An Australian experience

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Background: Patients with advanced refractory solid tumours including rare cancer types present significant treatment challenges. In many cases, patients have either exhausted standard of care options or, for the more rare cancer types, there are limited treatment options known to be effective. The correlation of biomarkers to associated clinical treatments in a number of cancer types, has allowed for a more targeted and personalised approach to cancer management. The aim of this study was to explore molecular profiling (MP) as a tool for guiding treatment selection in these difficult-to-treat patients within a clinical practice setting.
Materials and Methods: Tissue samples from rare cancer patients (n = 10) and heavily pre-treated ($\geqslant$2 lines of prior therapy) advanced cancer patients (n = 30) with an ECOG performance score $\leqslant$2 underwent MP based on immunohistochemistry, microarray, q/RT-PCR, Sanger and Next-Generation Sequencing (NGS) analyses (Caris Molecular Intelligence®; Caris Life Sciences, Irving, USA).
The rare cancer cohort included: ethmoid sinus, adrenal cortex adenocarcinoma, anaplastic thyroid, fibro sarcoma, astroblastoma, cervical carcinosarcoma, pseudopapillary mucinous neoplasm, endometrial stromal sarcoma, and medullary thyroid. The heavily-pretreated cohort included: cervical, gall bladder, skin (Merckel), colorectal, lung, pancreas, gastric, breast, ovarian, melanoma, oesophagus, cholangiocarcinoma and mesothelioma. MP-guided therapy was considered to have clinical benefit if the patient showed complete response, partial response or stable disease.
Results: In the rare cohort, two patients showed progression and two had non-evaluable disease. Six of the eight (75%) evaluable patients with rare tumours were shown to have clinical benefit following MP-guided treatment. In the heavily pre-treated cohort, 17 of the 30 evaluable patients (56.7%) have demonstrated clinical benefit, while 13 (43.3%) progressed following MP-guided therapy. Of the 23 patients with clinical benefit, eight have sustained clinical responses ranging from 140 days (breast cancer $ER^{-}HER2^{+}$patient) to 365 days (lung pleomorphic patient).
Conclusion: MP-guided treatment selection resulted in clinical benefit in over half of the patients in this study. While requiring further clinical validation, these data lend support to the use of MP in identifying therapeutic interventions for advanced refractory and rare solid tumours who have limited treatment options and poor prognosis.
No conflict of interest.

956 POSTER

DNA damage response deficiency signature predicts response to platinum-based therapy in ovarian cancer

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Background: Ovarian cancer is the leading cause of death from gynaecological malignancies among women. The standard first line therapy is a combination of carboplatin and paclitaxel. Although this treatment regimen confers a response rate in the region of 70%-80%, the majority of women subsequently relapse. Acquired resistance to further chemotherapy is generally responsible for treatment failure, resulting in an overall 5-year survival rate of only 10−30% for late-stage ovarian cancer. At present, empiric-based treatment strategies are used and result in a significant number of patients with chemotherapy-resistant disease, receiving multiple cycles of toxic therapy before the lack of efficacy is identified.
Materials and Methods: We have developed and validated a DNA damage response deficiency (DDRD) signature from microarray data, which predicts response to DNA damaging agents in breast cancer. This assay is based on a molecular subgroup defined by loss of the DNA damage response FA/BRCA pathway, which results in extreme sensitivity to DNA damaging chemotherapeutic agents. We have investigated the utility of the DDRD signature in its ability to predict response to platinum based therapy in 1078 ovarian cancer samples profiled on the Affymetrix microarray platform. Samples were tested with the signature and using the 70th percentile cut-off value, 30% of samples were classified as DDRD-positive and 70% as DDRD-negative.
Results: For overall survival, the DDRD signature yielded HR = 0.56 (95% confidence interval [CI] = 0.46 to 0.68) with a 5-year overall survival rate of 0.42 and 0.24 for patients in the gene signature DDRD-positive and DDRD-negative groups respectively. For relapse free survival, the DDRD signature yielded HR = 0.57 (95% CI = 0.48 to 0.69). The 5-year relapse free survival rate was 0.17 and 0.10 for patients in the DDRD-positive and DDRD-negative groups respectively.
Conclusions: This analysis demonstrates that the DDRD assay, identifying the DDRD molecular subgroup, enriches for patients with an improved overall and relapse free survival following DNA damaging carboplatin-based chemotherapy. We propose that the DDRD assay could be used as a patient stratification tool for existing chemotherapy or as a clinical trial enrichment tool for DNA-damaging or repair targeted drugs in development for use in ovarian cancer.
Conflict of interest: *Other substantive relationships: Almac Diagnostics*

957 POSTER

Soluble CXCL16 in urine as biomarker for bladder cancer diagnostics

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Background: The non-invasive thus patient-friendly detection of bladder cancer by determination of protein biomarkers in urine remains a challenge in cancer diagnostics. Here we present the identification of soluble CXCL16

in urine as a sensitive and specific biomarker for diagnosis of bladder cancer.
Material and Methods: Urine samples from patients with primary bladder cancer and healthy control volunteers were collected. Differential protein expression analysis in urine was carried out using antibody arrays. The results were reproduced in an additional and independent set of urine samples of 31 tumour patients and 31 healthy controls using immunoassays. In addition, urine samples from 21 patients with acute inflammation of the bladder were analysed in order to further verify the diagnostic specificity of CXCL16. Finally, we evaluated expression and distribution of CXCL16 and its receptor, CXCR6, in formalin-fixed patient tissue by immunohistochemistry.
Results: Urinary CXCL16 was found to be significantly higher in patients with primary bladder cancer (median 332.7pg/mg creatinine) in comparison to healthy controls (median 150.1pg/mg creatinine; $p = 0.0026$). In addition, soluble CXCL16 in bladder cancer patients was significantly increased compared those with bladder inflammation only (median 132.7 pg/mg creatinine; $p = 0.0002$). Results did not differ between men and women, smokers and non-smokers, or patients with and without leukocytes in urine. In contrast to the results in urine, most prominent expression of transmembraneous CXCL16 was detected in tissue samples from patients with urocystitis, whereas cancer cells from tumour patients showed only weak or no immunoreactivity.
Conclusions: We were able to identify and successfully confirm soluble CXCL16 as a promising target protein for the diagnosis of bladder cancer. Thereby, CXCL16 is capable of distinguishing tumour patients from patients with urocystitis rather than tumour patients and healthy controls only. Thus, analysis of CXCL16 offers a significant step forward in non-invasive bladder cancer diagnosis.
No conflict of interest.

958 POSTER

Osteomodulin expression profile in human breast cancer

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Background: Osteomodulin (OMD) a cell-binding keratin sulphate proteoglycan, also referred to as osteoadherin, was originally isolated from bovine bone. OMD belongs to the family of leucine rich repeat proteins found in the mineralised matrix of bone and is primarily expressed by mature osteoblasts, whilst also been shown to bind other osteoblasts via the $\alpha_5\beta_3$ integrin. Breast cancer preferentially metastasises to the bone primarily forming osteolytic lesions characterised by loss of bone density. OMD has been proposed to be involved in the regulation of cell proliferation and migration, and therefore this may of particular interest in breast cancer progression to bone metastasis.
Materials and Methods: The expression profile of OMD transcript was examined in a cohort of human normal breast (n = 22) and breast cancer specimens (n = 122) using quantitative polymerase chain reaction (qPCR). This was subsequently used in conjunction with clinical and pathological data, as well as clinical outcome after 10 years follow up, to explore the importance of this molecule in breast cancer progression.
Results: In patients with a good prognosis and survival OMD transcript levels were shown to be high. OMD transcript levels were significantly lower in patients with a Nottingham Prognostic Index of $\geqslant 5.4$ ($p = 0.032$) compared to those who have an index of $\leqslant 3.4$. When comparing clinical outcomes, patients who were disease free at the time of 10 year follow up had significantly higher levels of OMD compared to patients with metastasis ($p = 0.0009$), local recurrence ($p = 0.0079$) and those who had died of the disease ($p = 0.0025$). This trend continued when comparing patients who had developed bone metastasis ($p = 0.009$).
Discussion: In our cohort high OMD expression is associated with a better prognosis and clinical outcome. Reduced levels were associated with metastasis, local recurrence and of particular interest in this study bone metastasis. OMD might therefore provide a potentially novel new biomarker for breast cancer progression and clinical outcome.
No conflict of interest.

959 POSTER

A microarray-based gene expression analysis identified diagnostic biomarkers for unknown primary cancer

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Background: Patients with cancer of unknown primary (CUP) present with metastatic disease for which the primary site cannot be found, despite extensive standard investigation. Clinically, CUPs exhibit common characteristics, such as rapid progression and early dissemination, with a silent primary tumor that may either have a slow growth pattern or may become involuted and undetectable. Existence of such common properties prompts us to hypothesize that there may be potential biological markers that elucidate CUP as a whole.
Methods: We are presently involved in a multicenter clinical study to predict the primary site of CUP based on the analysis of gene expression patterns. Tumor mRNA samples from 60 patients with CUP were measured for the expression of ~22,000 genes using the Affymetrix U133A Plus 2.0 GeneChip® and analyzed by applying normalization and classification algorithms to the gene expression data. The similarity of each tumor specimen's gene expression pattern is then compared to the gene-expression profiles specific to non-CUP groups (containing tumors from 24 known primary sites) that were constructed using publicly available raw microarray datasets. The t-tests were performed to compare the CUP with non-CUP groups and the top 59 CUP specific genes with the highest fold change were selected (p-value <0.001).
Results: This study enabled the identification of genes that exhibited a unique expression pattern in CUP. As a high metastasis potential and vulnerability to apoptosis would explain the properties of CUP well, we first searched for genes related to metastasis and apoptosis and found 14 genes among 44 that were up-regulated by more than 2.5-fold in the CUP samples. Some of these genes were associated with the epithelial-to-mesenchymal transition (EMT), a function that has been increasingly recognized as a key step in cancer metastasis. We also identified 6 genes for ribosomal proteins among 44 up-regulated genes, two of which (*RPS7* and *RPL11*) were known to be involved in the Mdm2 − p53 pathway. Of 15 genes that were down-regulated by more than 2.5 fold in the cup samples, we focused on *CD24*, *KRAS* and *DICER1*.
Conclusions: The protein products of the up-regulated and down-regulated genes identified in this study suggest a biological attribute of CUP and, therefore, may become clinically useful biomarkers for CUP.
No conflict of interest.

960 POSTER

Serological detection of specific protein fingerprints of collagen and laminin degradation can differentiate cancer patients from healthy controls

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Background: In normal tissue extracellular matrix (ECM) remodeling and composition is tightly controlled to ensure homeostasis. In the tumor microenvironment, however, stromal cells deposit increased amounts of ECM components and the proteolytic activity is altered with matrix metalloproteinase (MMPs) as key actors in ECM protein degradation. As the ECM is an important and dynamic part of the tumor microenvironment due to the mutual interaction between cells and the ECM, many cancer hallmarks are promoted by an abnormal ECM composition. Thus, the alterations in the ECM remodeling and composition associated with cancer has a significant impact on the development and progression of the disease. The aim of this study was to investigate whether specific MMP generated ECM protein fragments (neoepitopes) of the ECM components collagen type I, III, IV and laminin may differentiate cancer patients from healthy controls when measured in serum.
Material and Methods: Using well-characterized and validated competitive ELISAs the levels of MMP degraded collagen type I (C1M), III (C3M), IV (C4M, C4M12) and laminin (LAM) were assessed in serum from patients with gastric cancer (n = 11), non-small cell lung cancer (NSCLC) (n = 10), pancreatic cancer (n = 10) and healthy controls (n = 9).
Results: In all three groups of cancer patients analyzed, serum biomarkers reflecting MMP-9 degraded collagen type IV (C4M, $p < 0.001$) and laminin (LAM, $p < 0.05$) were elevated compared to healthy controls. Biomarkers of

MMP-12 degraded collagen type IV (C4M12) were elevated only NSCLC ($p < 0.05$) and gastric cancer ($p < 0.01$) and MMP degraded collagen type III (C3M, $p = 0.05$) only in NSCLC ($p < 0.05$). No significant differences were observed with the biomarkers reflecting MMP degraded collagen type I (C1M).
Conclusion: Serum biomarkers reflecting specific MMP generated ECM-protein neoepitope fragments of collagen and laminin are able to differentiate cancer patients from healthy controls. Although validation in larger clinical settings is needed, this small study emphasizes that highly specific biomarkers for assessing alterations in the ECM remodeling and composition may prove valuable for diagnosing cancer.
No conflict of interest.

	Gastric cancer (n = 11)		NSCLC (n = 10)		Pancreatic cancer (n = 10)		Normal (n = 9)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Age	*56*	*49–63*	*57*	*51–63*	*64*	*59–66*	*70*	*65–76*
C1M	95	53–137	118	54–182	85	47–123	57	40–73
C3M	30	23–36	33	24–42	30	22–39	23	17–29
C4M	83	66–100	98	82–115	91	69–113	46	36–57
C4M12	191	139–244	212	143–282	176	117–236	124	88–159
LAM	12	8–17	11	7–14	9	6–11	5	4–7

961 POSTER

Expression profile of amphyphysin I in normal and breast cancer specimens

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Introduction: Breast cancer is currently the second leading cause of cancer-related death among women. Amphyphysin, a neuronal protein encoded by the *AMPH I* gene, is not only the auto-antigen of Stiff-Man Syndrome (patients are positive for auto-antibodies against this protein) but is also associated with breast cancer. Currently there is little data on the role of AMPH I in the biology and involvement in breast cancer progression therefore our study looked at the expression profile of *AMPH I* gene in a cohort of breast cancer patients.
Methods: The expression profile of Amphyphysin I was examined in a cohort of human normal (n = 20) and breast cancer specimens (n = 91) with 10 year follow-up. Gene transcript expression in the samples was analysed using Real Time RT-PCR and compared to patient data. Additionally, immunohistochemistry technique was used to visualise amphyphysin protein in normal and cancerous tissue sections.
Results: Immunohistochemistry results show expression of the amphyphysin protein to be higher in normal tissues when compared to tumour tissues. Normal breast epithelial cells stain mostly within the cytoplasm with some degree of staining in the nuclei regions. These results seem to correlate with gradually lowered expression levels of *AMPH I* observed throughout breast cancer grading: the highest expression for low grade 1 (mean = 633) and the lowest for the high grade 3 (0.2) breast cancer specimens.
Especially significant are the *AMPH I* expression differences between samples from patients classified as disease free (expression level mean=299) and patients with cancer metastasis (mean=8.8) and local recurrence of breast cancer (mean=1.25) with *p values* 0.037 and 0.032, respectively. The slight increase in expression of *AMPH I* in the samples from patients who died of breast cancer was revealed (mean=28) but it was still significantly lower (*p value* = 0.055) than in cancer-free samples.
Elevated *AMPH I* gene expression seems to correlate with Nottingham prognosis index staging. Its expression levels means were increased from 93.2 in samples from patients with good prognosis to 278 in moderate stage with the highest expression level mean of 526 being observed for patients with the poorer prognosis.
Conclusion: Together the data suggests that amphyphysin I expression may be a useful molecule to identify poorer prognostic breast cancers in patients.
No conflict of interest.

962 POSTER

PRAME gene and protein expression in bone marrow of patients with acute myeloid and lymphoid leukemia

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PRAME is a cancer-testis antigen highly expressed in a number of solid and leukemia tumors. PRAME protein has brought attention due to its ability to activate T-cell cytotoxic PRAME-specific antitumor response. It is used as a diagnostic marker of MDR in leukemia. While RT PCR is used for PRAME expression evaluation, PRAME-based immunophenotyping has not yet been involved into leukemia diagnosis due to the lack of appropriate anti-PRAME antibodies. We have developed recently two hybridoma cell lines producing anti-PRAME moAbs highly specific to detect PRAME protein both in Western blotting and inimmunophenotyping tests.
Aims: To evaluate PRAME expression and cellular localization of this protein in bone marrow (BM)cells of leukemia pts by means of anti-PRAME moAbs and to compare these results with the data of RT PCR analysis. To stain PRAME protein in BM cells we have used two moAbs produced by hybridoma cell lines 5D3F2 and 6H8F12. In order to generate fluorescent signal we have performed additional treatment by secondary fluorescent Ab (Invitrogen) giving green signal. Images were analyzed by Karl Zeiss Axiovert 40CL and AxioVision software to detect the exact cellular PRAME localization.
Results: BM of AML (N = 8) and ALL (N = 2) leukemia pts has been investigated. According to the level of PRAME gene expression all pts subdivided into two groups with relatively high PRAME expression (0.587−6.3% PRAME/Abl) and with low level of PRAME expression (0–5.87×10^{-3}%). Using PRAME staining on the fixed cells we have obtained the following results. In the group of high PRAME expression (AML M7,M5) we have observed PRAME protein both inside the cells (in the nuclei − 33.3%, in the cytoplasm − 23.3%) and on the cell surface (43.3%). In the group of low PRAME expression (AML M7, M3, ALL) there have been no PRAME signal in nuclei, in the cytoplasm it has been observed in 26.6% cases, in most cases it has been on the cell surface (46.2%), some cases (27.2%) have been PRAME-protein negative. When we have performed PRAME staining on the alive none-fixed cells, fluorescent signals have been found in 13.5−14% on the cell surface of both group. Our study suggests that in leukemia pts PRAME protein is very frequently localized on the cell surface. In the cases with low PRAME expression it is nether found in thenucleus. When PRAME expression in leukemia BM cells is increased, it is localized not only on the cell surface and within the cytoplasm but also in the nucleus.
No conflict of interest.

963 POSTER

Oncomodulin is a novel early marker of urinary bladder carcinogenesis in F344 rats

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Background: Short-term carcinogenicity assay using molecular biomarkers that can predict the results of long-term rodent cancer bioassays is greatly desired. The purpose of the present studies is to identify early markers of bladder carcinogenesis in F344 rats.
Material and Methods: Microarray analyses were conducted on 12 *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (BBN)-induced rat bladder cancers, 11 dimethylarsinic acid (DMA)-induced rat bladder cancers and 4 normal bladder urothelium using Affymetrix GeneChip Rat Genome 230 Array. mRNA expression analysis was perform using Taqman real-time PCR.
Results: Microarray analyses of BBN and DMA-induced bladder cancers revealed that 85 genes were commonly overexpressed in all cancers compared to control bladder urothelium. To select the candidate markers capable of predicting carcinogenicity of chemicals at the early stage of bladder carcinogenesis, mRNA expression levels of 20 of above genes which were selected based on the overexpression levels and the results of ingenuity pathway analysis, were examined in bladder urothelium of rats treated with BBN for 2, 4 and 8 weeks, respectively. Twelve of the above 20 genes were found to be consistently overexpressed from the week 2, and therefore were selected as candidate early marker genes and their mRNA expression levels were examined in bladder urothelium treated with 7 genotoxic and nongenotoxic bladder carcinogens ((DMA, 2-acetylaminofluorene, sodium o-phenylphenol, phenethylisothiocyanate, benzyl isothiocyanate, uracil and BBN)), bladder carcinogens and 3

nonbladder carcinogens (liver carcinogen: diethylnitrosamine; kidney carcinogen: N-ethyl-N-hydroxyethylnitrosamine; colon carcinogen: 1.2-dimethyhydrazine) and 3 nonbladder carcinogens(liver carcinogen: diethyl-nitrosamine; kidney carcinogen: N-ethyl-N-hydroxyethylnitrosamine; colon carcinogen: 1.2-dimethyhydrazine) respectively, for 4 weeks. Oncomodulin was consistently significantly overexpressed in all urothelium treated with various bladder carcinogens regardless of the degree of histopathologic changes, but not in the urothelium treated with any of nonbladder carcinogens. The functional analysis of oncomodulin is in progress.
Conclusion: Oncomodulin is a novel early marker of bladder carcinogenesis in rats. The 4-week oncomodulin-based bioassay is useful to predict bladder carcinogenicity of chemicals in rats.
No conflict of interest.

965 POSTER

Is HPV-16 integration a predictor biomarker of cervical lesions?

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Background: Persistent infection with oncogenic types of *human papillomavirus* (HPV) has been established as the main etiological factor for the development of cervical lesions and invasive carcinoma. The integration of HPV genome into hosts' genome is considered the hallmark of HPV-associated carcinogenesis, however, the significance of HPV physical status detection remains unclear. The aim of this study was to characterize the physical status of HPV-16 in samples with different histological classifications.
Material and Methods: We have selected 53 cervical specimens from women with different histological classification that have been identified with HPV-16 infection (45 single infection and 8 co-infections). The physical status of HPV16 was analyzed using a multiplex Real-time PCR that allows simultaneous amplification of the E2 and E6 regions. HPV-16 status classification was based on the principle that, when integration occurs, the E2 gene is partially or totally disrupted while the E6 gene remains intact.
Results: In this study, the prevalence of HPV16 integration was of 26.4% (14/53, 13 mixed forms and 1 integrated only). Results showed no significant differences when comparing HPV-16 integration within single vs co-infections ($p = 0.647$). The prevalence of HPV-16 integration among different cervical lesions was 28.6% (2/7) in samples without cytological lesion (normal), 13.3% (2/15) in atypical squamous cells of unknown significance (ASC-US), 33.3% (4/12) in low-grade squamous intraepithelial lesions (LSIL), 33.3% (5/15) in HSIL high-grade squamous intraepithelial lesions and 25.0% (1/4) in invasive cervical cancers (ICC). Additionally, we no found statistical significant differences among the histological specimens ($p = 0.735$).
Conclusion: Our study revealed that HPV16 integration is not exclusive event of high-grade lesions/ICC. Moreover, it was not possible to detect integrated forms in all cases of HSIL/ICC. This study shows that HPV16 integration occurs early during HPV-associated carcinogenesis and therefore there is an emergent requirement to reconsider the role of viral genome integration in HPV-associated carcinogenesis.
No conflict of interest.

966 POSTER

An innovative approach for in-vivo isolation of circulating tumor cells (CTCs)

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Background: Currently, circulating tumor cells (CTCs) are isolated *in vitro* from a small volume of blood samples. Furthermore, CTC results for different kinds of cancer as a prognostic and stratification biomarker are scarce. The aim was to assess a medical device (CellCollector) for *in vivo* isolation of CTCs directly from the blood of non-small cell lung cancer (NSCLC), breast cancer (BC), prostate cancer (PC) and colorectal cancer (CRC) patients prior surgery/ therapy start and partially in the course of therapy. Additionally, CTC enumerations were compared to the Cell Search® method.
Material and Methods: The device was inserted in a cubital vein through a standard cannula for thirty minutes. The interaction of target CTCs with the CellCollector was mediated by an antibody directed against the epithelial cell adhesion molecule (EpCAM). To confirm the CTCs binding to the wire, the immunohistochemical staining against EpCAM and/or Cytokeratin as well as CD45 for negative cell selection was performed. There were more than 380 applications of the wire in NSCLC, BC, PC and CRC patients and over 45 applications in control subjects. Enumeration data was available for 159 cancer patients and 37 control subjects. For 98 cancer patients and 22 control subjects, samples were also tested in the CellSearch® system.
Results: The device was well tolerated in more than 380 applications without side effects. We obtained in vivo isolation of CTCs in 126 of 159 cancer patients (79.2%) with a median (range) of 3 (0–515) CTCs and a mean of 17 CTCs. The sensitivity was similar for early and late stage in cancer patients. In the control groups, only in 6 of 37 subjects CTCs were detected (84% specificity). The sensitivity and specificity for CTC detection by the CellSearch® method was 16.7% and 79.5%, respectively. With exception of three samples, in all 78 paired samples the number of CTCs detected with the CellCollector was higher or equal to CellSearch®, regardless of the disease stage.
Conclusions: Whilst well tolerated without side effects, the CTC detection rate of the CellCollector in NSCLC, BC, PC and CRC patients was 79.2%. In contrast, 16.7% detection was obtained using the CellSearch® analysis. A specificity of the medical device of 84% could be reached. This innovative method may have important clinical implications, as the implementation of the device into clinical practice may improve early detection, prognosis and therapy monitoring of NSCLC, BC, PC and CRC patients. The method may also allow the molecular analysis of the CTCs, with the possibility of establishing more personalized treatment regiments.
No conflict of interest.

967 POSTER

Early technology foresight for the development of biomarkers for prostate cancer screening: Prospective Health Technology Assessment (ProHTA)

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Background: Currently, screening for prostate cancer is mostly performed using the digital rectal examination (DRE) and the measurement of the prostate-specific-antigen (PSA). Although PSA-testing is very sensitive, it lacks in specificity. Therefore an additional biomarker with high specificity could lead to a significant reduction of the biopsies performed unnecessarily.
Foresight methods such as modeling and simulation can help to assess the impact of future health technologies. 'Prospective Health Technology Assessment' (ProHTA) aims to develop a platform targeting health care manufacturers and decision makers that facilitates the assessment of innovative health technologies prior to their launch.
Methods: The objective of this work is to reduce the number of biopsies by introducing a novel and fictive biomarker additional to PSA-measurement. The potential impact of this biomarker is investigated in a simulation. Using clinical pathways, a model for the diagnostic process of prostate cancer is designed. This model serves as the basis for 'hybrid simulation' that consists of system dynamics models for macro-simulation and discrete event models for micro-simulation.
Results: The simulation shows that the use of a fictive biomarker in addition to DRE and PSA measurement will reduce the biopsies performed. The extent of the reduction depends on the sensitivity and specificity of PSA and DRE testing, as well as on the parameters determined for the biomarker. For example, if the estimated sensitivity of the biomarker is 100% and the specificity is 80%, then 25% of all biopsies can be avoided.
Conclusions: The ProHTA simulation approach is innovative and shows with the example of the fictive prostate cancer biomarker the potential to predict if an innovation and research in this field will be successful. Thus, ProHTA represents a useful decision-making tool for foresight and adds value to existing methodologies for pre-assessing health technology at a very early stage of technology research and development. It offers a valuable approach with an emphasis on strategic planning and therefore helps to improve the efficiency of health care delivery in different care settings.
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No conflict of interest.

968 POSTER

Opportunities and pitfalls in developing imaging biomarkers (IB) in oncology clinical trials

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Background: The assessment of tumor progression is fundamental to cancer clinical trials. Progression-free survival or disease-free survival tend to substitute overall survival as trial endpoint whenever feasible and meaningful. Those endpoints are based on imaging evaluation of tumor size. However, new technologies have been developed that provide additional information according tumor location or treatment administered, e.g. metabolic assessment provided by FDG-PET. Those advanced techniques have been widely used in routine clinic for staging or evolution of the disease. Up to date, they also play an increasingly important role in response assessment. Nevertheless, the assessment by functional imaging is different from that by anatomic imaging, where tumor size is a reproducible measure. Functional imaging has the additional requirement that an observed change of the parameter in response to treatments must be greater than the intrinsic and extrinsic variability of the parameter in the absence of treatment.
Methods: In order to use IB in clinical practice, robust criteria taking into account all the sources of variability of the measurement must be developed. Four steps are needed in such development: 1) evaluation of the different source of variability (multicentric test-retest) 2) development of imaging guidelines (standardization, quality assurance, central review) 3) evaluation of the treatment effect on the imaging measurement (correlation with pathological assessment) 4) validation studies (correlation with long term endpoints).
Results: We will detail the process and trial designs needed to fully develop robust IB and will illustrate how to do this in an imaging protocol that fits with the constraints of the primary clinical trial to which it is attached. When an IB is developed through a clinical trial as an (optional) translational research project, the imaging protocol has to be adapted to not negatively impact on the main protocol as the assessment of the tumor with the new techniques will not be blinded to the investigator. The sample size of the imaging protocol will also be constrained by that of the main clinical trial.
Conclusion: Appropriately used, IB could offer interesting treatment options and help fasten and target treatment development in clinical trials. Therefore we propose guidelines to help researchers to develop add-on IB protocols to therapeutic trials.
No conflict of interest.

969 POSTER

NGS panel V1.1 for the routine deep sequencing-based diagnostic of somatic hotspot theranostic mutations on FFPE tumours: A prospective study of 500 cancer samples

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In cancer, targeted therapies development induces an increasing number of mutations with theranostic values. Improving of patient care now relies on tumour genetic profiling that will guide treatment strategy. This implies the ability of parallel genotyping of a growing number of mutations. By providing an increase in sequencing throughput, NGS technology is suitable for routine implementation of such diagnostic in the near future. To address this challenge, we tested whether NGS sequencing detects somatic alterations in formalin-fixed, paraffin-embedded tumour samples. We aimed at determining the sensitivity and specificity of NGS compared to pyrosequencing (PS) and allele-specific PCR (ARMS) methods on 500 patients. A panel of 48 amplicons covering a 5kb region was designed to detect hotspot mutations in 17 key cancer genes. Low amount of input FFPE DNA was used to generate libraries on 48.48 Fluidigm access arrays for targeted sequence library. Libraries were sequenced using 150bp paired-end reads on an Illumina MiSeq. Trimmed reads were aligned to the hg19 genome using BWA in single end mode. Local indel realignment was performed with GATK. Calling algorithms were used to detect mutations even at a low frequency (SNVmix, lofreq, samtools, GATK and freebayes). NGS data was obtained on 500 patients (240 NSCLC, 230 colorectal cancers and 30 melanomas) and compared with reference technics (PS and ARMS) used in the routine molecular diagnostic. Deep sequencing of our custom gene panel results in a minimum of 3000X coverage for all amplicons with a mapping quality greater than 30. NGS detects 219 mutations in the 500 patients, including single nucleotide substitutions, small deletions (*EGFR* exon 19) and insertions (*ERBB2* exon 20). Among theses, 193 were also found with the two reference methods. NGS lead to 10 false negative mutations due to poor DNA quality. Sixteen false positive mutations were detected very likely due to the increased sensibility of NGS. Considering pyrosequencing and ARMS as references, deep sequencing provides a 95% sensitivity and a 98% specificity. We demonstrate that our deep sequencing approach can be reliably implemented as a diagnostic test for routine detection of somatic mutations. Our strategy allows the simultaneous analysis of more than 100 somatic hotspot mutations in 17 key cancer genes for 96 samples in a single assay and thus improves the molecular diagnosis of tumours in a cost and time efficient manner.
No conflict of interest.

970 POSTER

A comprehensive low-cost germline genetic test for over 260 conditions, including 50 affecting cancer diagnosis and treatment

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Background: Historically it has only been feasible to sequence 1 or 2 genes to test for hereditary cancer in a patient. Hence, cancer-related genetic conditions such as Bloom syndrome and Fanconi anemia can go undiagnosed. Also, conditions not directly related to a patient's cancer often go untested, although they can affect treatment and outcome, such as bleeding syndromes (i.e. surgery) and cardiomyopathies (i.e. chemotherapy).
Materials and Methods: A single assay was developed to test for 264 germline genetic conditions, including 50 hereditary cancer conditions. This assay covers nearly all published clinically-relevant variants (both coding and non-coding) in the associated genes and also detects novel likely-pathogenic variants, such as previously unseen loss-of-function mutations in tumor suppressors, in the full gene sequence. Extensive scientific review was conducted to curate these clinical conditions, storing the validated genes, variants and risk models in a database that informs our targeted next-generation sequencing platform. Custom variant interpretation software describes known and novel substitutions, insertions and deletions, and copy number variants, including those in traditionally hard to assay sites such pseudogenes and homopolymer stretches. Clinical reports are automatically generated and variants reported according to ACMG guidelines, with an additional category for variants observed in patients but which have uncertain pathogenicity. This test requires less than 2 weeks from arrival of blood sample to clinical report delivery.
Results: Analytical validation was performed on a panel of reference samples with >11,000 known variant sites and ~2.1 million non-variant sites. For coding sequence substitutions, we demonstrated 99.7% sensitivity and 99.998% specificity. For insertions/deletions in coding sequence, we demonstrated 98.3% sensitivity and 99.994% specificity. In direct comparisons against established diagnostic laboratories using traditional Sanger sequencing, we saw 100% concordance with those results, both in terms of analytical concordance and clinical interpretation.
Conclusions: We report progress in aggregating many genetic tests into one comprehensive assay at low cost, including a comprehensive inherited cancer test. This curation approach enables scalable, automatable, and reproducible diagnostic reporting, using accurate and scalable DNA sequencing methods.
Conflict of interest: *Ownership: employees of InVitae and stock ownership in InVitae*

971 POSTER

The diagnostic value of one step nucleic acid amplification (OSNA) for sentinel lymph nodes in colon cancer

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Background: Colorectal carcinoma (CRC) is the second most commonly diagnosed malignancy in the Netherlands. Determining the lymph node (LN) status is a good prognostic factor in CRC and is critical in the staging of these tumors. Earlier studies have shown that 20−30% of the Dukes stage I−II patients will still develop metastases within 5 years. Literature has also shown that with the use of the ex vivo sentinel lymph node

mapping procedure (SLNM) and the immunohistochemical Keratin Pan staining at 4 levels an upstaging of 20% can be achieved in these patients. The examination of SLN in breast cancer with One Step Nucleic acid Amplification (OSNA) has been proved to be valuable. The aim of this study was to determine the value of the sentinel node mapping procedure and the diagnostic value of OSNA in colorectal cancer.
Materials and Methods: In this study 313 SLNs of 122 patients from the Jeroen Bosch Hospital in 's-Hertogenbosch and the Leiden University Medical Center were investigated by the routine examination (H&E), fine examination (H&E and Keratin Pan immunohistochemical straining) and OSNA. The SLNs were harvested by the ex vivo sentinel lymph node mapping procedure, using Patent blue or Indocyanine green. Half of the SLN was used for the routine and fine examination and the other half for the OSNA assay. OSNA uses the reverse-transcription loop-mediated isothermal amplification (RT-LAMP) for mRNA amplification.
Results: The diagnostic value of OSNA, determined on all 122 patients was 81% and 100% for the fine examination and combined method (OSNA and fine examination together). An upstaging rate of 21% was obtained with the use of OSNA and 37% with the use of fine examination. An upstaging rate of 48% was obtained by combining these two methods together.
Conclusion: SLNM proved to be of value in CRC. OSNA and Fine examination both showed a good diagnostic value. The combination of OSNA and Fine examination was associated with an increased diagnostic value and also showed more upstaging of patients. Future research needs to be done to show whether routine examinations should be replaced by the investigation of sentinel lymph nodes using the OSNA assay and the fine examination together and the amount of SLNs to be investigated.
No conflict of interest.

972 POSTER

High resolution in vivo imaging for cancer detection and evaluation of tumor heterogeneity

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Background: Early tumor diagnostics and imaging of solid tumors are critical areas of cancer research. Imaging of tumor heterogeneity gives insights into proliferation, metastases and response to therapies. The majority of imaging methods does not demonstrate competitive resolution, penetration depth or cannot utilize fluorescent imaging agents widely used in preclinical research. In this work, we analyze *in vivo* spatial distribution of nanoparticle-based vascular and targeted contrast agents using novel imaging methods: hybrid fluorescent molecular tomography-X-Ray computer tomography (FMT-XCT) and high-resolution multispectral optoacoustic microscanner (microMSOT) in different animal models: transgenic model for Non-Small Cell Lung Cancer (NSCLC) and tumor xenograft/allograft one.
Material and Methods: The animals of transgenic K-ras model for NSCLC were injected with different targeted and activatable contrast agents and imaged *in vivo* with FMT-XCT imaging system. Foxn athymic nude mice were used for inoculation of subcutaneous (s.c.) 4T1 murine breast cancer allografts or HT29 human colorectal xenografts. The tumors were grown up to the size of 7−8 mm. Then the animals were injected with nanoparticles or vascular contrast agents and imaged with microscanner MSOT. The results of *in vivo* imaging were validated and analyzed with cryo-slicing epifluorescence imaging system and immunofluorescence.
Results: FMT-XCT *in vivo* imaging demonstrated the potential of $\alpha v\beta 3$-integrin targeting for detection of early lesions in K-ras mouse model of NSCLC. $\alpha v\beta 3$-integrin targeted fluorescence could selectively resolve pulmonary lesions in mice from 2 weeks of age vs. wild type. FMT-XCT imaging showed tumors and heterogenic profiles for $\alpha v\beta 3$-integrin spatial distribution in the lung tumors of 4-week-old animals. *In vivo* studies were verified versus immunofluorescence.
Heterogenic profiles of s.c. tumors were studied by microMSOT visualizing development of tumor vasculature with high resolution. Distribution profiles of nanoparticles, oxy- and deoxygenated hemoglobin were detected *in vivo* through entire tumor. *In vivo* optoacoustic signal correlated with *ex vivo* cryo-slicing and immunofluorescence profiles.
Conclusions: Our results demonstrated potential of FMT-XCT imaging of targeted contrast agents for early detection of lung lesions and *in vivo* study of heterogenic tumors.
MicroMSOT could offer high resolution imaging of intrinsic contrast and extrinsically applied probes for *in vivo* investigation of tumor vascular properties with impact on cancer research.
No conflict of interest.

973 POSTER

Development of a next generation sequencing assay for the identification and quantitation of fms-like tyrosine kinase internal tandem duplication sequences, and mutation analysis

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Background: Activating mutation in fms-like tyrosine kinase (FLT3) gene aberrations, internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations, play an important role in pathogenesis of acute myeloid leukemia. FLT3 Internal Tandem Duplications (ITD) are in frame duplications occurring most frequently in the juxtamembrane and less frequently in the tyrosine kinase domains. FLT3 ITDs cause ligand independent dimerization and activation of FLT3 leading to uncontrolled cellular proliferation. About 30% of AML patients are FLT3 ITD+ and demonstrate a worse prognosis and response to chemo therapy. Treatment of FLT3 ITD+ patients with the appropriate tyrosine kinase inhibitor represents a viable option for these patients. Selection of the appropriate tyrosine kinase inhibitor is dependent on patient FLT3 genotype and the presence of any resistance conferring mutations vs. the candidate treatment. To this end, we developed and characterized a next generation sequencing assay for the simultaneous detection, identification, and quantitation of FLT3 ITDs and TKD point mutations.
Methods: DNA fragment libraries prepared from 100 or 1000 ng of test sample gDNA are hybridized to enrichment oligos specific for FLT3 exonic sequences. Captured libraries are amplified and sequenced via Ion Torrent. TMAP aligned data were realigned for larger INDELs and filtered for the identification/quantitation of ITD sequences. Additionally, point mutations were called by VarScan and further characterized by SIFT/PolyPhen2/COSMIC for their damaging effects.
Results: Using model cell lines (MV4−11, MOLM-13), the assay demonstrates a sensitivity (LOD) of 10% for the detection of ITD sequences and 5% for point mutations. Further assay validation in AML patient samples demonstrates detection of ITDs between 30–178 bp at frequencies as low as 10% in addition to identifying resistance conferring point mutations within the tyrosine kinase domain.
Conclusions: The developed FLT3 genomic assessment assay simultaneously determines FLT3 ITD status, monitors ITD clonal populations for the presence of specific ITD's and TKD point mutations, and may be useful in determining patient response to tyrosine kinase inhibitors.
No conflict of interest.

974 POSTER

Automated large-volume extraction of circulating, cell-free DNA to improve the sensitivity of tumor biomarker detection

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Background: Because of its low concentration and high degree of fragmentation, the extraction and detection of tumor-derived circulating cell-free DNA (ccfDNA) is technically challenging. An optimized ccfDNA extraction method was developed and evaluated by comparison to existing manual and automated reference methods.
Material and Methods: ccfDNA was bound from 5.8 ml EDTA plasma of healthy donors (with IRB approval) to novel magnetic particles and recovered in 150 µl. The QIAamp® Circulating Nucleic Acid (CNA) Kit was used as a reference and for the purification of any residual ccfDNA from the plasma supernatant after binding. Alternatively, the 'Virus cell-free 1000 protocol' using the QIAsymphony® DSP Virus/Pathogen Midi Kit was modified for the processing of higher sample volumes. ccfDNA was extracted from 4 ml plasma and eluted in 90 µl. ccfDNA yield was quantified by qPCR (66bp within the 18S rDNA). To determine the DNA fragment size-dependent recovery, targets from 67bp to 475bp within the APP gene were quantified by qPCR.
Results: The mean ccfDNA recovery (18S 66bp target; compared to the QIAamp® CNA Kit) was 7% (N = 12; +/−4.1%) for the supernatant and 95% (N = 12; +/−19.2%) for the eluate. For the APP assay, ratios between the copy numbers of different target sizes were calculated. The mean ratios were: 67/476bp = 11 (N = 12; +/−6.2), 180/476bp = 8.1 (N = 12; +/−3.6) and 67/180bp = 1.4 (N = 12; +/−0.3). The modified Virus cell-free 1000 protocol led to a mean ccfDNA recovery of 140% (N = 24; +/−48.4) compared to the QIAamp® CNA Kit.
Conclusions: The automated protocol versions led to an overall similar ccfDNA recovery compared to the QIAamp® CNA Kit (complete ccfDNA binding to magnetic particles). Using the new extraction chemistry an improved recovery of tumor-derived ccfDNA is possible and allows for a higher sensitivity of tumor DNA detection, which is, besides a high specificity, critically important for the application of tumor ccfDNA biomarkers as a tool in cancer diagnosis and prognosis. The presented

applications are for research use only. Not for use in diagnostic procedures. This work has received funding from the European Union FP7 Programme under grant agreement no. 222916, SPIDIA project (www.spidia.eu).
Conflict of interest: *Other substantive relationships: All authors are employed at QIAGEN GmbH.*

975 POSTER

Is there a place for the UCA1 test in bladder cancer detection?

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Background: Bladder cancer detection and surveillance are traditionally performed by cystoscopy and urine cytology. Recently, *Urothelial Carcinoma Associated 1 (UCA1)* was identified as a very sensitive and specific urinary marker of bladder cancer. This study aimed to compare the clinical value of the *UCA1* test with routine diagnostic methods.
Material and Methods: Between October 2009 and December 2011, 564 *UCA1* tests were performed on urinary samples collected from 467 patients. Histological diagnoses were available in 108 cases. Patients were divided into screening and follow-up groups based on the absence or presence of prior urothelial carcinoma. The test performance was evaluated in each group and compared to cystoscopy, urine cytology and routine follow-up results.
Results: The overall sensitivity, specificity and positive and negative predictive values for the *UCA1* test were 69, 67, 86 and 42%, respectively. We observed no difference in performance for tumors of higher grade or stage, but sensitivity was increased in the screening population (84%) compared to patients under follow-up (58%). The *UCA1* test successfully detected 8/8 cases of *carcinoma in situ* and 2/4 cases of urothelial dysplasia. The positive predictive value of the test was comparable to cystoscopy.
Conclusion: The *UCA1* test can be used as a complementary method to cystoscopy and cytology for the detection of bladder cancer. While we found no evidence supporting the use of the *UCA1* test as a replacement for cystoscopy, it does seem beneficial for detection of *carcinoma in situ* lesions and, in some cases, for urothelial dysplasia.
No conflict of interest.

976 POSTER

Prevalence of KRAS-LCS6 polymorphism (rs61764370) within three different tumour types (breast, colorectal and non small cell lung cancer, NSCLC): A study of Czech population

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Background: KRAS is one of the most frequently mutated oncogenes in human cancer, with almost a quarter of different tumor types showing altered functions of KRAS. The let-7 family of microRNAs were found to regulate KRAS activity by binding to the 3'UTR of human KRAS gene. A germline SNP (rs61764370) is located in a let-7 complementary site (LCS6) in the 3'UTR of KRAS oncogene. The LCS6 SNP consists of a T-to-G base change and it was found to alter the binding capability of the mature let-7 miRNA to the KRAS mRNA. In several studies G-allele of rs61764370 was found to be associated with higher risk of breast cancer, colorectal cancer, melanoma, oral cancer and ovarian cancer. It is potential biomarker of poor response to targeted therapies in colon cancer too. Controversially, other authors did not find significant association with cancer risk. Thus, the relevance of rs61764370 in cancer predisposition is still debated and deserves further investigations.
Material and Methods: DNA of tumours tissues was isolated from fixed, fresh-frozen, cytology specimens and formaline fixed paraffin embedded tissue from 262 mCRC, 158 breast and 117 NSCLC patients. DNA from 387 healthy controls was isolated from peripheral blood. Analysis of SNP rs61764370 (KRAS-LCS6) was performed by PCR and RFLP method.
Results: The KRAS-LCS6 G-allele (T/G genotype) was detected in 9.9% (26/262) of mCRC cases; 15.2% (24/158) of breast cancer cases and 14.5% (17/117) of NSCLC patients. T/G genotype of the SNP (rs61764370) was identified in 15.8% (61/387) of healthy controls. In our study we did not find G-allele carriers in homozygous state (G/G genotype) among the cancer patients and healthy controls.
Conclusions: The frequency of the LCS6 G-allele varies across geographic populations, with European populations exhibiting the variant allele most frequently 5−10%. In our study, in healthy Czech population (controls), frequency the LCS6 G- allele was 15.8%. Prevalence of the KRAS-LCS6 G-allele was not significantly different among stadied tumours (NSCLC, breast cancer) and the healthy controls. The acquisition of new data from different populations could have a paramount importance to establish the real contribution of each polymorphism to the cancer risk. The study of polymorphisms, affecting miRNA-dependent pathways and involved in cancer susceptibility is rapidly growing and is becoming increasingly important on the fast growing field of the personalized medicine.
No conflict of interest.

977 POSTER

microRNA expression in BRCA 1/2 hereditary breast cancer: Exploratory analysis

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Background and Objectives: microRNAs (*mirs*) are small non-coding regulatory RNAs involved in gene expression regulation at posttranscriptional level. *mirs* expression is deregulated in breast cancer, but there is very limited data about their expression in hereditary breast cancer (HBC). The objectives of this study are: 1- to analize if there is any difference in the expression of a *mirs* pannel (*mir*21, *mir*155, *mir*195, *Let*7a and *mir*16) between sporadic breast cancer (SBC) and *BRCA1/2* HBC; and 2- to analize the change of expression of the mirs pannel, prospectively, in *BRCA1/2* HBC.
Methods: RNA was extracted from whole peripheral blood, reverse transcribed and quantified by real-time quantitative polymerase chain reaction analysis for *mir* 21, *mir* 155, *mir* 195, *Let* 7a and *mir* 16 (endogenous control). We have 3 groups of patients (pts): (A) 20 with *BRCA1/2* HBC, (B) 13 with SBC (*BRCA1/2* wildtype) and (C) 15 healthy individuals. Five of 20 *BRCA1/2* HBC started this study prospectively, at breast cancer diagnosis, and *mir* expression was evaluated before surgery, 2 weeks after surgery and after adjuvant treatment. All other pts in group A were breast cancer survivors. All pts in group B were breast cancer survivors.
Results: Group A- 18 female, 2 male; BRCA1: 3 pts, BRCA2: 17 pts; median age: 58 years. Group B- 12 female, 1 male; median age: 45 years. Group C- 11 female, 4 male; median age: 45 years. For *mir*21, *mir*155 and *mir*195 *BRCA1/2* HBC and SBC cancer survivors had significant different levels of *mir* 195 expression. In the exploratory analysis of the first 4 prospective pts a trend for decreasing levels of *mirs* 21, 155 and 195 after surgery was observed (but not significant after log conversion). The only case already measured after adjuvant treatment had more pronounced descent of *mirs* 21 and 155 than after surgery. Analysis for *Let*7a is not yet complete.
Conclusions: This exploratory analysis, suggests two study hypotheses: 1- *mirs* expression may not be similar in HBC and SBC and 2- change in *mirs* expression before and after cancer treatment of HBC may be more significant after completion of adjuvant treatment than after surgery. These are very rare pts but enrollment in the prospective study continues.
No conflict of interest.

978 POSTER

Sensitive detection of EGFR mutations using mutant-enriched PCR and reverse-hybridization teststrips

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Background: Activating mutations in the epidermal growth factor receptor gene (EGFR) allow the therapeutic use of tyrosine kinase inhibitors (TKI), such as erlotinib or gefitinib in non-small cell lung cancer (NSCLC) therapies. In contrast, the presence of the T790M mutation in tumor tissue predicts resistance to TKI.
Materials and Methods: We have developed a reverse-hybridization StripAssay for the detection of three mutations in exon eighteen, twenty-four deletions and complex mutations in exon nineteen, the T790M mutation in exon twenty and two mutations in exon twenty-one of the EGFR gene. The test is based on mutant-enriched PCR in the presence of EGFR wild-type suppressors, followed by hybridization of biotinylated PCR products to teststrips presenting a parallel array of allele-specific oligonucleotide probes. The hybridization and detection steps can be carried out fully automated using commercially available instrumentation.
Results: StripAssay performance was evaluated using genomic DNA obtained from cultured cell lines and formalin-fixed paraffine-embedded

(FFPE) tumor tissue. Plasmid clones harbouring the respective EGFR mutations served as reference templates to control for test specificity. By using normal DNA spiked with serial dilutions of DNA from EGFR-mutant tumor cell lines all mutations were shown to be detectable at a level of 1%.
Conclusions: The simultaneous detection of EGFR mutations with a sensitivity of 1% makes the StripAssay a very useful tool for the assessment of the EGFR mutation status of cancer patients.
No conflict of interest.

979 POSTER

Relationship between insulin resistance and tumor burden in cancer patients

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Background: Insulin resistance (IR) is a risk factor for various cancers in many epidemiologic and preclinical studies. Prevalence of IR remains unknown in cancer patients.
Methods: We measured homeostasis model assessment (HOMA) defined as fasting glycaemia (mmol/l) x fasting insulinemia (mU/l)/22.5 and recorded criteria of metabolic syndrome (waist circumference, hypertension, triglyceridemia, HDL cholesterol level and fasting glycaemia) and C Reactive Protein (CRP) in a cohort of cancer patients. Patients with diabetes mellitus and corticosteroid treatment were excluded.
Results: We included 101 patients, 54 males, with a median age of 59 years (range 20−89), and with a WHO Performance Status $\geqslant$2 in 21.8%. Median HOMA was 2.1 [95% CI 2.148–2.719] and 23% of patients had a metabolic syndrome. HOMA was not related to waist circumference, BMI or CRP. The most frequent primary tumors were sarcoma, genito-urinary and gastro-intestinal (21.8% each). HOMA was found in the highest quartile (HOMA>3.15) in 8 out of 22 (36%) patients with sarcoma. Cancer status was long-term remission (n = 11), adjuvant setting (n = 10) and macroscopic disease (n = 80). HOMA was significantly lower in long-term remission patients versus adjuvant setting and macroscopic disease ($p = 0.0149$ and $p = 0.0011$ respectively). Among the 25 patients with HOMA>3.15, median age was 55 years (range 24−82) and all had macroscopic disease ($p = 0.003$ by Chi2 test). Twenty of these patients (80%) had no metabolic syndrome.
Conclusion: We could identify insulin resistant cancer patients. These results should guide the selection of the patients for inclusion in metformin or IGF-R inhibitors clinical trials.
No conflict of interest.

980 POSTER

Neutrophil gelatinase-associated lipocalin in platin induced renal injury

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Background: Acute renal injury (ARI) is an important issue in chemotherapy receiving patients. Neutrophil gelatinase-associated lipocalin (NGAL) is a novel marker used in early detection of ARI. In this study we aimed to assess the role of urine NGAL levels in patients receiving platin compounds.
Material and Method: Patients who had treated with cisplatin or carboplatin or oxaliplatin containing regimens at Cumhuriyet University Medical Faculty Cancer Center, included in this study. Patient's baseline and postchemotherapy serum urea, creatinine, urine NGAL and urine creatinine level had determined. To avoid false urine NGAL levels due to hydration during chemotherapy infusion urine NGAL/urine creatinin ratio had used to determine ARI. To examine the relationship between pre and post chemotherapy urine NGAL change, Wilcoxon Signed Ranks Test had used. A p-value of <0.05 had considered significant. The analysis had performed by SPSS version 14.0 software (SPSS Inc., Chicago, USA).
Results: A total of 42 patients, receiving platin compounds, included in this study. Fourteen of them (33.3%) received cisplatin containing regimes, 14 patients (33.3%) received carboplatin and 14 patients (33.3%) received oxaliplatin. The median age was 60 (37−76) years. Sixteen of the patients (38.1%) were lung cancer, 15 were (35.7%) colorectal cancer and 11 were (26.2%) other cancers. The median pre and post chemotherapy urine NGAL/urine creatinin ratio in cisplatin group was 15.6 ng/mg and 35.8 ng/mg ($p = 0.016$), in carboplatin group was 32.5 ng/mg and 86.3 ng/mg ($p = 0.019$) and in oxaliplatin group was 40.9 ng/mg and 62.3 ng/mg ($p = 0.3$).
Conclusion: Nephrotoxicity is a serious side effect of chemotherapeutic agents. Although not statistically significant, oxaliplatin may also have nephrotoxic effect. So all platin compounds must be used carefully and urine NGAL measurement seems to be promising in detecting ARI earlier then creatinin.
No conflict of interest.

981 POSTER

HER2-based treatment decisions in breast cancer (BC): Test accuracy and its clinical, economic and social impact

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Background: Treatment choice for patients with BC is guided in part by HER2 status. Although FDA-approved *in vitro* diagnostic (IVD) tests are available, nonapproved IVDs are used in many laboratories (approx 30% in Nordic region). Incorrect HER2 results can impact greatly on patient outcomes and healthcare budgets. We analysed the accuracy of HER2 testing approaches using pooled data from the Nordic Immunohistochemical Quality Control (NordiQC) real-world testing programme and used the results in an economic BC treatment model.
Methods: Data were obtained from the NordiQC HER2 BC test programme run from 2008–2012 (www.nordiqc.org). False-negative (FN; a 3+/2+ amplified tumour but stained as 0 or 1+) and false-positive (FP; a 0/1+/2+ unamplified tumour but stained as 3+) rates were calculated for approved vs nonapproved IVDs and used to calculate economic costs of inaccurate results, loss of survival, productivity benefit and QALYs. Costs were extrapolated to numbers of US patients with BC (early BC [EBC] n = 209 737; metastatic BC [MBC] n = 20 743) using a 1-y time horizon. US costs and population sizes were used because of the homogeneity of the US healthcare system pricing framework.
Results: 1703 tests were performed (1145 [67%] approved IVDs; 558 [33%] nonapproved IVDs). Pooled FN rates were 11% and 25%, respectively; FP rates were 0% and 5%, respectively. Incorrect results were largely due to misclassified 2+ samples. The total direct cost/patient of inaccurate tests in the model was $69 for approved and $263 for nonapproved IVDs. Extrapolation to the US EBC population gave a potential $41 million cost saving for approved vs nonapproved IVDs. Costs and benefits are shown below. Results were similar for MBC although cost savings were reduced due to the lower incidence of MBC.

Outcome	EBC		
	Approved IVD	Nonapproved IVD	Difference
Total direct cost of inaccurate test, $	14,378,394	55,112,205	40,733,810
Missed QALYs	158	361	203
Lost productivity, $	3,285,434	7,510,050	4,224,615
Missed survival benefit, y	187	426	239

Conclusions: This analysis suggests that incorrect HER2 test results have far-reaching clinical, social and economic consequences that should be considered when requesting a test. Oncologists and pathologists need to be aware that differences between available tests impact patient outcome in terms of missed survival benefit and exposure to unnecessary toxicity, as well as costs. Adhering to testing guidelines ensures accurate results and correct treatment for patients with BC.
Conflict of interest: *Ownership: None. Advisory board: None. Board of directors: None. Corporate-sponsored research: None. Other substantive relationships: Ventana employees * Ranger-Moore, Sheppard, Walk; Hoffmann-La Roche employees * Gartemann, Teichgr*ber, Rohr.*

982 POSTER

A new imaging biomarker to predict anti-angiogenic therapy efficacy in phase 1 trials: AUC changes with dynamic contrast enhanced-ultrasonography (DCE-US)

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Background: Antiangiogenics compounds are widely prescribed but lack a predictive biomarker of efficacy. The objective of this analysis was to confirm the decrease of AUC in DCE-US at day 15 and day 30 as a tool able to predict time to progression (TTP) in phase 1 trials enrolling patients exposed to anti-angiogenic compounds.
Material and Methods: All patients (pts) included in phase 1 trials with anti-angiogenic compounds, between 2005 and 2013 in our institution and having underwent standardized DCE-US evaluation at baseline, D15 and D30 were retrospectively reviewed. DCE-US methodology: a bolus injection of contrast medium, 3 minutes of recorded raw linear data with 4 frames per second and the quantification using ESFUMB guidelines. Pts were identified from a prospective database. TTP and OS were calculated from the initiation of the new agents, according to clinical data and using RECIST v1.1 criteria. A decrease of more than 40% of AUC at D15 and one month was assumed to be predictive of TTP.
Results: Two hundred and seven patients were analyzed from September 2005 to March 2013. Seventy pts were excluded: no anti-angiogenic agents (n = 31), screen failure (n = 27), discontinuation of study participation before day 30 (n = 2), no US-evaluation at 1 month (n = 7), no US-target (n = 3). A total of 137 pts from 7 trials were included: 32 pts with vascular disrupting agent (VDA), 93 pts with a TKI, 2 pts with monoclonal antibodies (mAb), 10 pts with both VDA and mAb. The median overall survival was 15.5 months, with 110 deaths at the time of statistical analysis. In the training cohort (n = 26), pts with a decrease of more than 40% of AUC at one month had a median TTP of 5.5 months, versus a median TTP less than 2 months for the other patients. The decrease of AUC at one month was correlated to TTP (p = 0.004). The 111 patients from the validation cohort are under radiological review (349 CT scans) for TTP.
Conclusion: The decrease of more than 40% of AUC with DCE-US at one month is a potential predictive biomarker of response for anti-angiogenic treatments in metastatic patients. The final results will be presented on 137 patients.
No conflict of interest.

983 POSTER

Tumor–stroma ratio as a predictor for response to neoadjuvant chemotherapy (TAC) in breast cancer (BC): A Dutch Breast Cancer Trialists' Group (BOOG) side-study

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Background: Intra-tumoral stroma has profound influences on tumor behavior. The tumor–stroma ratio (TSR) has previously been shown to be of prognostic value in breast cancer and other types of solid tumors. However, the role of this parameter regarding the prediction of pathological complete responses (pCR) after neoadjuvant chemotherapy is unknown.
Methods: 250 patients were included in the NEOZOTAC trial: a national, multicenter, randomized study comparing the efficacy of TAC (docetaxel, adriamycin and cyclophosphamide i.v. day 1) chemotherapy followed by G-CSF on day 2 with or without zoledronic acid 4 mg i.v. 3 weeks in patients (pts) with stage II/III, measurable, HER2-negative BC. The percentage of intra-tumoral stroma was visually estimated on diagnostic sections from primary tumor tissue by two observers. A third independent observer was consulted in case of outcome discordances. The cut-off point between stroma-rich and stroma-poor tumors was set to 50% (as determined in previous investigations). Tumor–stroma ratio was related to centrally revised pCR data. Reproducibility of results will be further investigated by comparing CNB and resection specimens.
Results: 194 specimens were evaluated. Cohen's kappa coefficient for inter-observer agreement showed a substantial agreement in classification (k=0.64, 82% concordance). 37% of the specimens were classified as stroma-rich. Stroma-rich tumors were significantly associated with T-stage (P = 0.08) and ER-status (P = 0.004). In univariate analysis, TSR predicted for pathological complete response (P = 0.03) with greater pCR rates observed in tumors with a a low percentage of intratumoral stroma (22.7% vs. 10.3%). After multivariate analysis, this effect did not persist (OR 1.58, 95% C.I. 0.63–3.93), presumably because of a current low number of patients across groups. Final results will be presented at the ECCO.
Conclusions: These results suggest that the TSR is a reproducible marker for response to treatment with neoadjuvant chemotherapy. Considering the simplicity and low cost of TSR assessment, it should be considered as a candidate for further investigation and eventually for implementation in pathology reports.
No conflict of interest.

984 POSTER

Evaluation of a chemoresponse assay as both a prognostic and predictive marker in the treatment of persistent or recurrent ovarian cancer

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Background: A recent study demonstrated significant improvement in clinical outcome in recurrent epithelial ovarian cancer (EOC) patients treated with therapies identified as sensitive (S) based on an in vitro chemoresponse assay. Together with previous studies, these results support that the assay provides prognostic value. The assay's ability to function as a predictive biomarker of patient outcome is investigated in this analysis.
Material and Methods: Women with persistent or recurrent EOC (n = 262) were treated with one of 15 therapies based on the medical judgment of the treating physician, blinded to assay results. Each patient's tumor was assayed for response to the 15 therapies in vitro. Three approaches were used for estimating the assay's predictive value. First, the assay's relative ability to predict progression-free survival (PFS) for patients treated with a therapy for which they were considered to be S vs. resistant (R) (match) was compared to the average prognostic value of S vs. R to a randomly selected treatment (mismatch) based on repeated resampling of the patient population. Next, patients were classified into groups based on assay results and clinical treatment: S to all tested therapies and treated with a S therapy (SA), S to some therapies and treated with a S therapy (SP), R to all therapies and treated with a R therapy (RA), and R to some therapies and treated with a R therapy (RP). Clinical outcome was compared among groups whose response was primarily dependent on tumor biology (SA, RA; prognostic) and groups whose assay results were heterogeneous and may benefit from specific treatment choice(s) (SP, RP; predictive). Third, the percentage of S therapies was included in multivariate analysis.
Results: The assay result for 'match' was significantly associated with PFS (HR = 0.67, 95% CI=0.50–0.91, p = 0.009). Based on 1000 simulations, the mean HR[mismatch] was 0.81 (95% range = 0.67–0.91), suggesting that HR[match] was predictive of response to a specific treatment. The improvement in median PFS for both SA vs. RA (HR = 0.72, 95% CI=0.44–1.18, p = 0.191) and SP vs. RP (HR = 0.70, 95% CI=0.46–1.05, p = 0.081) was consistent. The association between assay result for administered therapy and PFS remained statistically significant in multivariate analysis (HR = 0.61, 95% CI=0.41–0.89, p = 0.010), independent of the percentage of S therapies, indicating the value of the assay for predicting outcome was not due to tumor biology alone.
Conclusions: These results support that the chemoresponse assay is likely both predictive and prognostic of patient outcome. Further, these results suggest that recurrent EOC patients treated by assay-sensitive therapies may obtain improved clinical outcomes.
Conflict of interest: *Ownership: M Gabrin, S Brower, C Tian hold stock options from Precision Therapeutics, Inc. Other substantive relationships: D Sargent received consulting income from Precision Therapeutics, Inc.*

985 POSTER

Relationships of peripheral blood lymphocyte counts (PBLC) with antitumor activity of NGR-hTNF in combination with chemotherapy (CT)

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Background: NGR-hTNF, a tumor-targeted antivascular agent, produces antitumor effects at low dose by inducing an early vessel stabilization that greatly improves both intratumoral CT uptake and T-cell infiltration.

Synergism with CT has been shown in immunocompetent mice, but not in nude mice lacking functional T cells.
Methods: The associations of baseline PBLC with the antitumor activity of N (with or without CT) and CT alone was assessed by means of an individual patient pooled analysis of 427 patients (pts) from 7 phase II trials in 6 tumor types. NGR-hTNF was given at low dose (0.8 μg/m^2) in combination with CT in 183 pts. As control groups, 140 and 104 pts receiving N and CT alone, respectively, were also analyzed. CT consisted of doxorubicin or a platinum-based regimen. In all trials, response to treatment according to RECIST was evaluated every 6 weeks. Endpoints of interest were response rate (RR, complete plus partial response), disease control rate (DCR, RR plus stable disease), duration of response (DOR) and progression-free survival (PFS). Continuous PBLC data were categorized into high vs low levels using the median cutpoint (1.5/mL; 95% CI, 1.4−1.6). In multivariate logistic and Cox regression models, age, sex, PS and tumor type were included as covariates.
Results: There were no statistically significant differences in treatment effect according to baseline PBLC in both N-alone and CT-alone groups. Conversely, in the N plus CT group, high PBLC were related to better outcomes, as compared with low PBLC. In this N plus CT group, high PBLC (vs low) were associated with higher RR (OR=2.3; 95% CI, 1.0−5.3; p = 0.04) and DCR (OR=2.7; 1.4−4.9; p = 0.002), and with longer DOR (HR = 0.31; 0.12–0.79; p = 0.01) and PFS (HR = 0.59; 0.43–0.81; p = 0.001). For high vs low PBLC, RR was 23% vs 11%, DCR 74% vs 51%, median DOR 8.7 vs 6.3 months, and median PFS 5.0 vs 3.0 months, respectively. On multivariate analyses, high PBLC remained an independent predictor of increased RR (OR=2.4; 1.0−5.5; p = 0.04) and DCR (OR=2.7; 1.4−5.2; p = 0.003), and improved DOR (HR = 0.24; 0.08−0−80; p = 0.02) and PFS (HR = 0.59; 0.43–0.82; p = 0.002).
Conclusions: Consistently with preclinical data, these results highlight the potential value of PBLC in predicting tumor response to NGR-hTNF in combination with CT, which merits further clinical investigation.
No conflict of interest.

986 POSTER

Identification of the activated form of the estrogen receptor (ER) in breast cancer (BC)

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Background: About 50% of ER positive (ERpos) BC are resistant to hormone treatment. In absence of ligand, ERs are evenly distributed in nuclei in normal tissue. Upon ligand binding, ERs dimerizes and form a discrete focal subnuclear distribution pattern (FDP), which are associated with transcriptional activation of ER. This ER FDP is observed in BC. We hypothesized that in BC that the presence/absence of ER in the FDP could predict antiestrogen activity. This study describes an immunohistochemistry (IHC) method, by which a biomarker could be developed to investigate this hypothesis.
Methods: 37 paraffin embedded, formalin fixed archived BC samples were processed using 4 ER-alpha antibodies (Ab) under different IHC conditions to develop and refine this biomarker, the ER nuclear morphology was analyzed with standard microscopy at x1000. Interpretation of the IHC slides was done by an experienced pathologist. Standard ER, progesterone receptor (PR), and Ki67 testing were done. Tumor grade was obtained from the patients' records. Analysis of the different Ab was with the kappa statistics. Comparison of the IHC technique to immunofluorescence (IHF) was done on 8 samples.
Results: Consistent with prior research observations, tumors had two ER nuclear morphologies: 1. Diffuse pattern (D) where the ER was distributed evenly in a fine granular pattern, 2. Aggregate pattern (A) where the ER is distributed in distinct clumps or aggregates.
This defined 3 tumor phenotypes: A cells only (A) 1% (4/37), D cells only (D) 65% (24/37), and a heterogenous mix of A + D cells (AD) 18% (7/37), ER Neg 14% (5/37). IHC and IHF analysis for ER nuclear morphology was concordant. The ER activation status (A/AD or D) was not correlated with staining ER intensity, ERpos %, PRpos%, but was correlated with % Ki67 staining (p = 0.09) and tumor grade (0.035).
Conclusions: ERpos early BC biopsies can be grouped in two categories based on ER nuclear morphology: A group with diffuse and homogenous nuclear staining, and a different group with heterogeneous area of cells having a nuclear pattern consistent with a functional or activated ER. These observations warrant clinical pathological studies to determine if this biomarker is potentially predictive of clinical outcomes.
Conflict of interest: *Ownership: Invivis Pharmaceuticals, Arno Therapeutics*

987 POSTER

Pharmacogenetic assessment of toxicity in patients treated with taxane-based chemotherapy for solid tumors

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Background: Taxanes are active agents widely used to treat many solid tumors. However, the utility of taxane-based therapy could be limited by gastrointestinal toxicities, hematological toxicities, hypersensitivity and cumulative neurotoxicity. Taxanes are metabolized by CYP3A4 and CYP3A5 isoenzymes, and they are a substrate for the ATP binding cassette multidrug-transporters ABCB1. Metabolic pathways of these antitumor agents need a thorough evaluation to understand why some patients experience severe adverse effects. Aim of our study was to evaluate the association between taxane-related toxicities and their metabolism-related genetic polymorphisms in patients affected by solid cancers undergoing taxane-based chemotherapy regimens.
Material and Methods: We examined 182 adult patients, ECOG Performance Status ⩽1, affected by solid tumors who underwent treatment with taxane-based regimens in adjuvant or metastatic setting, planned for at least 3 courses of therapy. Through a peripheral venous blood sampling we genotyped them for selected polymorphisms and ABC-transporters that may influence cellular sensitivity to taxanes: CYP3A4*1B (A> G), CYP3A5*3 (G> A) and ABCB1 (1236 C> T; 3435 C> T). SNPs (Single Nucleotide Polymorphism) were characterized by pyrosequencing. Statistical analysis was conducted by MINITAB 16.2.3 software. A value of p < 0.05 was considered statistically significant.
Results: Toxicities and polymorphisms were evaluated in 182 patients (12 males and 170 females). Median age of patients was 59 (range 30−82). Patients who received taxanes were 95 in adjuvant setting and 87 in the metastatic one. We observed a significant association between normal homozygous genotype for ABCB1 polymorphism (3435 C> T) and lower toxicity during therapy with taxane-based regimens (p = 0.012). An association between mutant homozygous and normal homozygous genotypes with dose limiting toxicities was demonstrated, even though not statistically significant (p = 0.058). A larger cohort of patients must be investigated. The multivariate analysis results were independent from the different taxane-based regimens adopted, age and stage of disease.
Conclusions: ABCB1 3435 C>T polymorphism seems a toxicity predictive biomarker for taxanes. On the other hand, a larger cohort of patients must be investigated to define the role of CYP3A4, CYP3A5 and ABCB1 (1236 C>T) polymorphisms.
No conflict of interest.

988 POSTER

EGFR homodimers in tumor samples quantified by a new antibody based TR-FRET assay are associated with colorectal cancer progression

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Background: Following the development of targeted therapies against EGFR and HER2, two members of the human epidermal receptor (HER) family of receptor tyrosine kinases, much interest has been focused on their expression in tumors. EGFR is frequently expressed on colorectal cancer tumors and EGFR targeted therapies are currently used in the metastatic setting. Data on EGFR homodimerization, an index of receptor activation, are lacking.
The aim of the study was the description and clinical relevance of EGFR protein and dimer expression levels in colorectal tumors.
Material and Methods: Analysis of EGFR was assessed in a series of 60 frozen tumor samples from patients with colorectal cancer by using recently developed antibody-based time-resolved Förster resonance energy transfer (TR-FRET) assays. Quantification of EGFR protein expression levels was determined together with EGFR:EGFR homodimers. EGFR and EGFR-EGFR fluorescence signals were normalized for cell content in the tumor samples and correlated to clinicopathological parameters and outcome of patients.
Results: The median absolute EGFR protein expression levels was 7 400 (range 2 700−1 474 400) and EGFR:EGFR homodimers were detected in 19 (31.7%) tumors. Correlations with clinicopathological patients' characteristics demonstrate that EGFR:EGFR homodimer presence was

significantly associated with advanced pTNM stage (P = 0.003). The potential role of EGFR:EGFR dimers as predictive markers could be assessed in twenty chemotherapy-refractory metastatic patients that were treated with cetuximab. In this subgroup of patients no significant correlation was observed between EGFR activation observed through EGFR:EGFR homodimer presence and response to EGFR-targeted therapy.
Conclusion: Quantitative measurement of expression and dimerization of EGFR by the novel TR-FRET assays provides new information on colorectal cancer patients. Indeed, the signaling pathways triggered by EGFR:EGFR homodimers seems to play an important role in colon cancer dissemination. Validation is ongoing in an independent cohort of 134 patients with colorectal cancer and will be presented.
No conflict of interest.

990 POSTER

Fragmented peptides of prostate-specific antigen (PSA) as novel urinary biomarker candidates for diagnosis of prostate cancer

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Background: Prostate cancer (PCa) will affect one in five men and is now the second leading cause of cancer deaths among men in the Western countries. Biomarkers, such as prostate specific antigen (PSA) level in serum, play pivotal roles in the management of the cancer patients. However, currently used biomarkers for PCa are sub-optimal. Therefore, great emphasis has been placed on the need to discover novel biomarkers for PCa diagnosis.
Methods: We focused on urine samples voided after prostate massage (digital rectal examination [DRE]) and conducted peptidomic and proteomic analyses of the urine samples using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS^n). The urinary biomaterials were concentrated and desalted by a weak cation-exchange resin prior to MALDI-TOF/MS analyses.
Results: A high-resolution and high-sensitivity MALDI digital ion trap (DIT) TOF/MS^n was utilized in order to analyze the urinary peptides and protein-fragments in this study. Mass profiles of urine samples from healthy, BPH, and PCa subjects were compared. Several differences among these mass profiles were detected, especially between PCa and BPH. The most pronounced peak was detected around m/z 2,300. Other characteristic peaks in PCa were also detected around m/z 1,200, 1,300 and 4,700. Two peaks around m/z 1,200 and 1,300 became larger than those in the BPH mass profiles, whereas the peak around m/z 4,700 of the BPH became larger than that of PCa. The most pathognomonic peptide around m/z 2,300 in the DRE urine samples of PCa patients was confirmed as a C-terminal PSA fragment. It was verified that the C-terminal peptide was produced from PSA in prostate glands and was secreted into the urine by DRE. The two peptides around m/z 1,200 and 1,300 were also confirmed as the fragments of PSA near the center.
Conclusions: Our findings indicate: 1) the peptide fragments, especially the C-terminal fragment, of PSA in the DRE urine may become a novel pathognomonic biomarker candidate for PCa diagnoses; and 2) the fragmentation may be a pathognomonic bio-reaction in microenvironment of the PCa cells. Further examinations are underway to prove this possibility regarding the PSA fragmentation in the urine samples after prostate massage.
No conflict of interest.

991 POSTER

The predictors for micro-invasion of hepatocellular carcinoma ⩽2 cm

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Background and Aims: Hepatocellular carcinoma (HCC) of 2 cm diameter or less (⩽2 cm) is considered to have a low potential for malignancy based on the so-called stepwise progression hypothesis. But in fact, there have been cases with HCC⩽2 cm accompanied by micro-invasion (MI) and poor prognosis based on an alternative hypothesis of de novo development. The aim of present study was to identify independent predictors for MI of small HCC⩽2 cm.
Methods: A retrospective review was undertaken of 149 patients with primary solitary HCC⩽2 cm who underwent initial hepatic resection. The independent predictors of the MI such as portal venous, hepatic vein, or bile duct infiltration and/or intra-hepatic metastasis were indentified using multivariate analysis. Prognosis of patients with HCC⩽2 cm accompanied by MI was compared to that of patients with HCC⩽2 cm without MI.
Results: Forty-three patients with HCC⩽2 cm had MI (28.9%). Three independent predictors of the MI were revealed: invasive gross type (simple nodular type with extranodular growth or confluent multinodular type), des-γ-carboxy prothrombin (DCP) ⩾100 mAU/ml, and poorly differentiated. The sensitivity of DCP>100 mAU/ml for MI in HCC⩽2 cm of 53.5% (23/43 cases) was not very high, but its positive predictive value of 79.3% (23/29 cases) was relatively high. The sensitivity of preoperative imaging diagnosis for invasive gross type in HCC⩽2 cm was low 30.0% (6/20 cases), but the positive predictive value was relatively high 66.7% (6/9). Disease-free survival rates of patients with HCC⩽2 cm with MI were significantly worse than those for HCC⩽2 cm without MI (3-year; 44% vs. 72%). This disadvantage of disease-free survival rate of patients with HCC⩽2 cm with MI could be dissolved by hepatic resection with a wide tumor margin ⩾5 mm (p = 0.04).
Conclusion: Even in cases of HCC⩽2 cm, patients who are suspected of having invasive gross type tumors in preoperative imaging diagnosis or who have a high DCP level (⩾100 mAU/ml) are at risks for MI. Therefore, in such patients, hepatic resection with a wide tumor margin should be recommended.
No conflict of interest.

992 POSTER

Predictive value of plasma D-dimer for asymptomatic metastasis in cancer patients

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Background: Plasma D-dimer levels are high in patients with advanced tumors and can be used to predict the outcomes of cancer patients. At most advanced tumor stages, patients have asymptomatic metastasis, which contributes to early tumor recurrence after surgery. We hypothesize that plasma D-dimer can be used to identify patients with potential metastasis.
Methods: We first verified our hypothesis in different in vivo murine metastasis models (subcutaneous tumor, intraperitoneal metastasis and hematogenous metastasis), and we examined the plasma D-dimer levels using the enzyme-linked immunosorbent assay (ELISA) method. We then enrolled and examined plasma D-dimer levels by the latex-enhanced immunoturbidimetric assay (LEIA) method in 1268 primary cancer (1042 gastric cancer, 96 esophageal cancer, 50 lung cancer, 37 melanoma, 43 pancreatic cancer) patients in 3 cancer centers in northwestern China. We also followed 395 of 1042 gastric cancer patients at one cancer center to analyze the 2-year survival rate and early tumor recurrence.
Results: Among the three in vivo murine metastasis models, the plasma D-dimer level was extremely elevated in the hematogenous metastasis and intraperitoneal metastasis murine models but not in the subcutaneous tumor model and control group model. These results supported our previous hypothesis. In this large-scale clinical study, we found that plasma D-dimer levels were increased in distant metastasis, especially in patients with hematogenous metastasis. The cut-off value of the D-dimer levels was determined to be 1.5 mg/ml based on the ROC cure, and the sensitivity and specificity for predicting metastasis were 63.2% and 88.5%, respectively. In addition, patients with increased plasma D-dimer levels displayed early hematogenous-associated tumor recurrence and bad outcomes during the follow-up study.
Conclusion: Plasma D-dimer is a potential marker that is easy to measure at a low cost, and this marker can be considered for routine testing in cancer patients to predict asymptomatic metastasis.
No conflict of interest.

993 POSTER

Predictive role for pemetrexed sensitivity of thymidylate synthase expression in advanced cancer patients

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Background: High expression of thymidylate synthase (TS) in malignant cells has been proposed as a resistance mechanism to the antifolate pemetrexed. This study is aimed to evaluate the association of TS expression by a quantitative assessment in tumor cells with the efficacy of pemetrexed in patients with advanced non-small cell lung cancer, small cell lung cancer (SCLC) and mesothelioma.

Methods: 54 patients were studied: 40 stage IV NSCLC (26 adenocarcinomas, 11 large cell, and 3 squamous cell carcinoma), 3 SCLC and 11 mesothelioma. 21 patients received platins-pemetrexed as first line NSCLC, 20 pemetrexed in monotherapy as second and further lines and 3 carboplatin-pemetrexed fo extensive disease SCLC. RNA was obtained from FFPE tumor sections and the expression of TS was analyzed by RT-qPCR using appropriate mRNA specific primers and probes. TS levels was calibrated to expression in normal tissue.
Results: From 54 cases, TS expression was available in 32 cases, detecting overexpression in 23 (71.8%) and low expression in 9 (28.2%) patients. The response rate for patients with low TS expression was 0.63 compared with 0.15 in patients with overexpression ($p = 0.015$). A significant benefit in time to progression was observed in patients with low expression (median TTP 12 vs. 2 months respectively, $p = 0.002$), whereas did not impact on overall survival (median OS 20 vs. 19 months respectively, $p = 0.595$).
Conclusions: TS overexpression in tumor is associated with a reduced response to pemetrexed-containing chemotherapy and might be used as a predictive biomarker in advanced lung and mesothelioma cancer patients.
No conflict of interest.

994 POSTER

Predictive impact for bevacizumab of VEGF-A 165 family of isoforms in patients with non-squamous non-small cell lung cancer (NSCLC)

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Background: Bevacizumab is a recombinant monoclonal humanized antibody against vascular endothelial growth factor (VEGF) that improves Time to Progression (TTP) in patients with advanced non-squamous NSCLC, but currently no proven predictive markers exist. The VEGF-A 165 splice variant has been described as the most abundant and active isoform in cancer, where exon 8 modifications generates two family of isoforms with opposite *in vivo* effects, one pro-angiogenic (VEGF 165a) and other anti-angiogenic (VEGF 165b). The objective of this study is to explore the predictive role of $VEGF_{165}$a and $VEGF_{165}$b isoforms in patients with non-squamous NSCLC treated with a doublet of platin plus bevacizumab.
Methods: 22 patients were included (20 adenocarcinomas and 2 large cell carcinomas): 5 received carboplatin–taxol–bevacizumab, 14 carboplatin–taxotere–bevacizumab and 3 cisplatin–gemcitabine–bevacizumab. RNA was obtained from routine clinical samples and $VEGF_{165}$a and $VEGF_{165}$b expression was analyzed by RT-qPCR. Individual $VEGF_{165}$a and $VEGF_{165}$b family of isoforms expression was calibrated to normal tissue and the ratio between both isoforms was calculated.
Results: $VEGF_{165}$a overexpression was detected in 14 (63.6%) cases and $VEGF_{165}$b overexpression in 15 (68.2%) tumors. A predominant expression of the pro-angiogenic $VEGF_{165}$a in tumor was correlated with a significant benefit compared with cases with a predominant $VEGF_{165}$b expression (median TTP, 15 vs. 8 months respectively, $p = 0.005$). However, the expression of these isoforms did not impact on Individual overexpression of these isoforms was not associated with benefit to bevacizumab therapy ($p = 0.933$ and 0.166) or overall survival ($p = 0.477$).
Conclusion: The overexpression of $VEGF_{165}$a isoforms associated with a low expression of $VEGF_{165}$b was correlated with a clinical benefit to bevacizumab therapy in stage IV non-squamous NSCLC patients, supporting a potential use as predictive biomarkers.
No conflict of interest.

995 POSTER

Risk factors of thrombotic microangiopathy in patients treated by antiangiogenics in phase I trials

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Background: Antiangiogenics are effective treatments for several advanced cancers. Thrombotic microangiopathy (TMA) is a well known vascular and renal side effect of these drugs and such adverse event may limit its use. No risk factor of TMA has been described so far. Our objective was to assess the association of high blood pressure (HBP) and other prognostic factors with TMA.
Methods: Our retrospective study included data on all patients recruited from 2010 to 2012 at Gustave Roussy Institute in phase I trials evaluating antiangiogenesic drugs. The definition of TMA was clinical or histological. Patients with and without TMA were compared according to HBP defined as superior to 140 and/or 90 mmHg, sex, age, body mass index, history of antiangiogenic therapy, history of nephrectomy, various biological results, using a multivariable logistic regression model.
Results: Among the 56 patients exposed to antiangiogenic therapy, TMA occurred in 17 patients (30%). The diagnosis of TMA was histologically confirmed in 10 (59%) of 17 patients and schizocytes were present in one patient.
Proportion of women (59%), median age (57 years), history of partial or total nephrectomy (7%) and exposure to bevacizumab for more than 6 months (38%) did not differ in patients with or without TMA. Median level of fibrinogen in g/L was lower in patients with TMA (3.9) than in patients without TMA (5.1, $p = 0.0108$). In the multivariable analysis, TMA was associated with fibrinogen level (OR= 2.27 (95% CI=1.22; 4.35)) and with a clear trend was observed with history of treated hypertension (OR= 3.35(95% CI=0.73;15.34)). Analysis of data on sarcopenia and HBP characterization are on-going.
Conclusion: In our population antiangiogenic, TMA is only correlated with low level of fibrinogen at baseline. However, patients with a history of HBP exhibit a trend to present a higher risk of TMA. Further studies are warranted in order to better select the population eligible to antiangiogenic treatment.
No conflict of interest.

996 POSTER

RRM1 protein expression heterogeneity between diagnostic biopsies and resection specimens and changes in expression during carboplatin and paclitaxel treatment in non-small cell lung cancer

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Background: It is of interest if potentially predictive biomarkers such as RRM1 expression changes during chemotherapy if they are to be used for deciding treatment beyond first line.
Materials and Methods: RRM1 immunohistochemistry was performed on tumor samples from a total of 118 NSCLC patients T1−4N0−2M0. Samples from 65 patients, among which 53 had paired samples from before and after paclitaxel and carboplatin and 53 patients which had not been treated with chemotherapy, were included.
Results: No change in RRM1 expression was observed between paired samples of primary tumors in the NAC-group ($p = 0.524$) nor in the OP-group ($p = 0.171$). A mean H-score decreased of 0.2 in both groups ($p = 0.905$). RRM1 expression was higher after chemotherapy than before in N2-node metastases ($p = 0.010$). A discordant RRM1 expression (low vs. high) was observed in 32% paired diagnostic and subsequent resection specimen in the OP-group.
Conclusion: The substantial discordance between paired samples emphasizes the need of sufficient tumor tissue in biopsies when evaluating RRM1 expression. No change in RRM1 expression was observed in primary tumors but RRM1 was increased in N2-lymph node metastases following chemotherapy. Potential post-chemotherapy changes in RRM1 expression may be considered when basing treatment decisions beyond first line on RRM1 expression.
No conflict of interest.

997 POSTER

Significance of smudge cell on blood smear in chronic lymphocytic leukemia patients: A prospective single institutional study from India

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Background: Smudge cells are ruptured lymphocytes seen on routine blood smears of chronic lymphocytic leukemia (CLL) patients. We evaluated significance of smudge cells percentage on a blood smear in CLL patients.
Methods: We calculated smudge cell percentages (ratio of smudged to intact cells plus smudged lymphocyte) on blood smears of 175 consecutive untreated CLL patients registered at I.R.C.H, AIIMS, New Delhi over a period of 5 years (2006–2010).
Results: There were 130 males and 45 females. The median age was 59 years (30−88). Median absolute lymphocyte count was 40 $X10^9$/L. Clinical Rai stage distribution was: stage 0−5%, stage I − 25%, stage II − 40%, stage III −10 % and stage IV − 20%. The median smudge cells percentage was 28% (4% −76%). There was no correlation of proportion of smudge cells with age, sex, lymphocyte count, lymphocyte doubling time, beta 2 microglobulin, organomegaly, ZAP 70 + or CD 38 + CLL patients, but there was significant correlation with stage of disease. Median smudge cell

percentage in stage 0 & I −36% (12−76), stage II- 30% (12−61) and stage III&IV-20% (4−51) [p < 0.001]. Eighty five patients of early stage (0, I &II) patients required treatment during follow up [65% required treatment with smudge cell <30%, against 35% patients requiring treatment with smudge cells >30%, p = 0.01]. The percentage of smudge cells as a continuous variable correlated with OS [HR 0.96, p < 0.001]. The 5-year survival rate was 51% for patients with 30% or less smudge cells compared with 76% for patients with more than 30% of smudge cells. Median OS was 4.8 years with median follow up period of 3.6 years. Smudge cells percentage (<30% vs. >30%) had significant association with OS [HR 0.97, 95% CI (0.62–1.21), p = 0.001)].
Conclusions: Simple and inexpensive detection of smudge cells on blood smears on routine diagnostic test useful in predicting progression free and OS in CLL patients and may be beneficial in countries with limited recourses.
No conflict of interest.

998 POSTER

Circulating endothelial cells and dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) parameters as predictive biomarkers for survival benefit in patients with advanced non-small cell lung cancer (NSCLC) treated with sorafenib and metronomic oral vinorelbine

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Background: Biomarkers to predict benefit from anti-angiogenic therapy are still lacking. RECIST response criteria are inadequate for accurate evaluation of response. Sorafenib and metronomic oral vinorelbine combination was explored in this study and changes in blood and DCE-MRI parameters were investigated as potential predictive biomarkers of benefit.
Material and Methods: Eligible patients with advanced NSCLC who failed multiple prior lines of palliative chemotherapy were recruited to 3 successive cohorts. Each cohort was given a fixed metronomic (thrice a week) dose of oral vinorelbine at 60 mg/week, 90 mg/week, and 120 mg/week respectively. Each patient within each cohort received a starting dose of sorafenib at 200 mg bid for 4 weeks. In the absence of dose-limiting toxicities, the dose of sorafenib would be escalated to 400 mg bid for 4 weeks, 600 mg bid for 4 weeks and finally 800 mg bid. Biomarkers measured serially include DCE-MRI parameters, circulating endothelial cells (CECs) and circulating endothelial progenitor cells (CEPs), and plasma thrombospondin-1 level (TSP-1). The following DCE parameters were analyzed: blood flow(F), permeability surface area product(PS), fractional intravascular blood volume (v1), and extracellular-extravascular volume (v2).
Results: 46 evaluable patients were analysed. There were 5 partial responders (10.9%) and 22 with stable disease lasting at least 4 months (47.8%). Evaluation for biomarker response was performed only for the first 2 cycles of treatment due to the subsequent high attrition rate. There was no significant change in the biomarker parameters between the 3 cohorts. Collective analyses of the 3 cohorts demonstrated a significant near-universal decline in CEP, TSP and PS, and a significant increase in V2 after 2 cycles of treatment. These parameters however, were not predictive of survival benefit. Using multivariate modeling, high baseline or rise in CEC and lower baseline V1 predicted for improved overall survival(OS), while a low baseline or a decline in F predicted for improved progression-free survival (PFS).
Conclusions: Sorafenib and metronomic oral vinorelbine is active in advanced NSCLC. Baseline levels and changes in DCE parameters (F and V1) and CEC may be useful predictive biomarkers for survival benefit with this anti-angiogenic regimen.
No conflict of interest.

999 POSTER

Class-III-β-tubulin expression levels remains unchanged during carboplatin and paclitaxel treatment in non-small-cell lung cancer

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Introduction: Class-III-beta-tubulin (TUBB3) is a tubulin isoform involved in microtubule formation during mitosis. Its expression may be a potential predictive factor for outcome in non-small cell lung cancer during microtuble interfering cytotoxic treatments such as vinca alcaloids and taxanes. We investigated for changes in TUBB3 expression during neoadjuvant chemotherapy including taxanes, which may be of interest if future choice of chemotherapy is to be based on TUBB3 expression. If the biomarker expression changes during chemotherapy, biopsies before initiation of chemotherapy beyond 1st line may be required. Thus, the aim was to explore on TUBB3 expression heterogeneity and changes during chemotherapy.
Materials and Methods: TUBB3 expression immunohistochemístry on diagnostic biopsies and on available subsequent resection specimens in 65 non-small cell lung cancer (NSCLC) patients stage T1−3N0−2 (NAC-group). These patients received preoperative carboplatin and paclitaxel. Another group of 53 NSCLC patients stage T1−4N0−1 were treated with surgery alone without preceding chemotherapy (OP-group). Paired samples of diagnostic and resection specimens were compared in order to evaluate for changes in TUBB3 expression.
Results: No statistically significant change in TUBB3 expression was observed between initial diagnostic biopsies and subsequent surgical resections of primary tumors in either the OP-group (p = 0.124) or the NAC-group (p = 0.414). When dichotomized into high and low TUBB3 expression, discordance between diagnostic biopsies and resection specimens of the primary tumors occured in 22% and 40% in the OP-group and NAC-group, respectively (p = 0.169). Changes in TUBB3 expression were not associated with prognosis but significantly more patients having low TUBB3 expression experienced down-staging during neoadjuvant chemotherapy compared to patients having high TUBB3 expression (p = 0.0220).
Conclusion: We observed a high degree of discordance of TUBB3 expression between paired serial tumor samples, which likely reflects intratumoral heterogeneity. This emphasizes a need for sufficient tumor tissue in order for stratification of patients based on TUBB3 expression. However, there were no significant changes in TUBB3 expression after neoadjuvant carboplatin and paclitaxel chemotherapy, suggesting no need for rebiopsy in case of need for second line chemotherapy with microtubule interfering cytotoxic treatments. Low TUBB3 expression predicts down-staging during neoadjuvant chemotherapy.
No conflict of interest.

1000 POSTER

Expression of progesterone receptor membrane component-1 in non-small cell lung cancer

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Background: The progesterone receptor membrane component-1 (Pgrmc1) protein is upregulated in cancer, and it is required for tumor cell proliferation, motility and tumor formation in vivo. Inhibition of Pgrmc1 suppressed the growth of lung, breast and cervical cancer cell lines. Recent studies in vitro have shown that one of the reasons of platinum resistance can be overexpression of the Pgrmc1. Taking in account that treatment of non-small cell lung cancer (NSCLC) is based on platinum included chemotherapy and its efficacy is not satisfactory because of tumor resistance, we have proposed this resistance mechanism dealing with Pgrmc1expressin in cancer patients. To answer the question we have studied level and frequency of Pgrmc1expression in NSCLC tissues.
Materials and Methods: NSCLC surgical biopsy specimens of smoking male patients with squamous cell carcinoma (40) and adenocarcinoma (20) were analyzed by flowcytometry. Single-cell suspensions obtained from the tumors were incubated with primary rabbit polyclonal IgG to Pgrmc1 antibodies (Abcam) overnight and with secondary FIT?-conjugated goat polyclonal to rabbit IgG antibodies (Abcam) for 1.5 h. Mean number of specifically stained cells were analyzed by WinMDI software and Kolmogorov-Smirnov statistical approach. Pgrmc1 expression was estimated as ratio of the specific parameter to the same isotype one. Two indexes of Pgrmc1 expression were used: high level − Pgrmc1was revealed in 20−50% of the cells, low − less than in 20%.
Results: 1. Pgrmc1 expression (specific fluorescence more than in 10% of the cells) was revealed in 70% of NSCLC patients. High level (29.9±8.1%) was in 36% of the tumors, 67% of which were adenocarcinomas. Low level (14.8±2.4%) was in 64% of the tumors, 81% of which were squamous cell carcinomas. 2. In squamous cell carcinomas mean Pgrmc1 level was 15%, but in adenocarcinomas − 1.7 times higher (26%, p = 0.013). 3. In squamous cell carcinoma patients low Pgrmc1 level was revealed in 81% of cases, but high − in 19% only. In contrast, in adenocarcinoma patients high Pgrmc1 level was revealed in 67%, but low − in 33% only.

Conclusion: Pgrmc1 expression was revealed in the majority of NSCLC patients. In adenocarcinomas mean Pgrmc1 level and frequency of high level of Pgrmc1 expression were about 2−3 times higher than in squamous cell carcinomas. Taking into account our results and clinical observations that squamous histologic features as compared with adenocarcinomas is factor associated with improved survival platinum included chemotherapy, we believe that Pgrmc1 could be predictive marker of platinum resistance in NSCLC patients. Supported by Russian Foundation for Basic Research (Grants 13−04–01004-a, 12−04–00028-a).
No conflict of interest.

1001 POSTER

Clinical and pathological correlation of the activated form of the progesterone receptor (PR) in breast cancer (BC)

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Background: Ligand binding of the PR in normal tissue causes the formation of discrete transcriptionally active subnuclear foci. The presence of these activated PRs (APR's) in post menopausal patients with BC and endometrial cancer suggests that the PR is activated by pathways requiring minimal or no PR ligand or is constitutively active. The goal of this study is to correlate the APR status in BC biopsies to any clinical and/or pathological relationships. APRpos was defined as any tumor with more than 5% APR cells.
Methods: 303 archived BC biopsies were analyzed for standard HES, ER, PR and Ki67. Clinical and pathology data was obtained from patient (pts) records. APR status (PR nuclear morphology) was determined with distinct antibodies for the PR A & B isoforms and the nuclear morphology patterns were analyzed at $\times$1000 magnification. The APR determination by PRA & PRB was combined as appropriate for the analysis.
Results: Average age was 58 (17−89). Histology: ductal 85%, lobular 13%, other 2%. 86% ERpos and 83% were either PRApos or PRBpos; 7% were only ERpos, 7% were only PRApos or PRBpos. All but 3 PRpos pts had received antiestrogens. Staging: I 50%, II 43%, III 6%, IV 1%. Tumor grade; I: 24%, II: 51%, III: 25%. Median follow up was 31 months. Local or distant progression (PD) was observed in 19% of the pts. APR status was positive in 22%, negative in 61%, and PRneg 17% of the biopsies. PD was not associated with PR status ($p = 0.68$). With DFS defined as time to PD or death with a 5 year cut off, PRpos was superior to PRneg (HR = 0.3, $p = 0.002$). DFS (5 year cut off) was superior for APRpos vs APRneg (HR = 0.58, $p = 0.48$). In univariate analyses, APRpos was associated with higher tumor grade ($p = 0.001$). No association was found between APR status and age, stage of disease, Ki67 or HER2 status.
Conclusions: Although there was an association with higher tumor grade, the APR status was not clearly linked or associated with other clinical characteristics, markers for proliferation, ER or PR positivity, disease stage; indicating that APR cannot be predicted by routine clinical data or pathological testing. Further work on the APR is warranted, as this biomarker may be able to determine which patients could benefit from antiprogestin treatment.
Conflict of interest: *Ownership: Invivis Pharmaceuticals, Arno Therapeutics*

1002 POSTER

Clinical and pathological correlation of the activated form of the progesterone receptor (APR) in endometrial cancer (EC)

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Background: Ligand binding of the progesterone receptor (PR) in normal tissue causes the formation of discrete subnuclear foci, which are known to be transcriptionally active (APR). The presence of APR's in menopausal EC and breast cancer suggest that the PR is constitutively active or activated by pathways requiring minimal or no PR ligand. The goal of this study is to determine the APR status in EC and to describe any clinical or pathological relationships with the ultimate goal to develop a companion diagnostic predicting the efficacy of anti-progestins in patients with EC.
Methods: 72 archived 1º ECs were processed with standard IHC for estrogen receptor (ER) and PR & proliferation (Ki67). APR was determined using antibodies specific to the A and B isoforms of the PR (PRA and PRB) and evaluating nuclear morphology. Pathology and clinical information was collected from patients' records.
Results: Histology; endometrioid 78%, clear cell 8%, serous/papillary 7%, other 7%. 2 PR nuclear distribution patterns were observed: an aggregated pattern (A) indicative of APR, and a diffuse or finely granular pattern (D), indicative of an inactivated PR. This resulted in three tumor phenotypes: A cells only, D cells only, and a mix of A + D cells (AD). For endometrioid cancers, 84% and 68%, respectively, were PRpos or ERpos. APR was present with PRA in 33% and PRB in 37%, and 48% either PRA or PRB. The mean age was 65 in both the APRpos/neg groups. APR status was not associated with Ki67 expression, tumor grade, lymphatic or vascular invasion or FIGO stage, progression of disease or death, but was associated with lower ER positivity. 8 progressions were observed and not associated with APR status. More deaths from any cause were observed in the PRB APRneg group.
Conclusions: Lack of association with clinical characteristics suggests APR status is distributed across clinical sub-groups of EC and cannot be predicted by routine clinical or pathological testing. The small number of progressions/deaths does not allow APR to be tested as a prognostic variable. Further work on a larger cohort is warranted, as this biomarker may be able to select patients who may have increased benefit/risk ratio of antiprogestin treatment.
Conflict of interest: *Advisory board: Arno Therapeutics*

1003 POSTER

Cholesterol and its esters as serum biomarkers in malignant obstructive jaundice: A single step 1H NMR metabonomic approach

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Introduction: In obstructive jaundice (OBJ), composition of bile and cholesterol metabolism changes drastically with growing severity towards malignancy. The timely diagnosis of underlying malignancy with OBJ is complex, as malignant tumors are often asymptomatic in their earlier course and thus preclude its curative resection. The complex regional anatomy of hepatopancreatobiliary system confounds the recognition of potentially resectable lesion and hinders the pre-operative histological confirmation of malignancy. Therefore, objectives of the present study include: (i) identification of the variations in low molecular weight metabolites of serum under the pathological state of benign OBJ and hepatopancreatobiliary malignancy induced obstructive jaundice from normal conditions, (ii) to explore the role of serum cholesterol (Chol) and cholesterol esters (CE) and their relative ratio estimation in sera of benign and malignant OBJ with the help of H NMR spectroscopy and, (iii) the evaluation of status of bile acids, cholesterol and choline containing compounds in bile and their contribution towards differentiating between malignant and benign OBJ.
Material and Methods: Serum and bile specimens from benign OBJ patients ($n = 28$), malignant OBJ patients ($n = 36$) and serum of healthy controls ($n = 57$) were analysed by H NMR spectroscopy. Relative- and semi-quantitation of serum metabolites viz. isobutyrate, lactate, alanine, acetone, glutamine, creatine, threonine and 1-methylhistidine, total cholesterol (tCho), cholesterol (Chol) and cholesterol ester (CE) were performed. In bile, total bile acids (BA), cholesterol, phosphatidylcholine (PC) and glycerophosphatidylcholine (GPC) were quantified. The effect of benign and malignant OBJ on small metabolites and lipids was analysed by non-parametric Mann-Whitney U test.
Results: Serum levels of isobutyrate, alanine, acetone, glutamine, threonine and 1-methylhistidine were significantly lower in both classes OBJ patients and glutamine levels were further lowered in malignant OBJ. Serum Chol and CE were significantly altered in healthy control, malignant and benign OBJ. Malignant OBJ had significantly decreased levels of tCho, Chol/CE and lipid content when compared with benign OBJ.
Conclusions: The single step estimation of alterations in serum Chol and CE may have potential for early and differential diagnosis of malignant and benign OBJ. This may augment the novel insights in local and systemic effects of OBJ patients.
No conflict of interest.

1004 POSTER

Circulating tumor cells counts in advanced and metastatic colorectal cancer by immunomagnetic labeling: Results reflect the reality?

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Background: According to Jemal et al. (2011), colorectal cancer (CRC) was the third most commonly diagnosed cancer in men in the world, and the second in women in 2008. The first strategy for treatment is complete resection of the lesion. However, some patients experience recurrence, believed to be due to residual micrometastases. Traditional diagnostic methods are unable to detect CTCs present in these sites and released into the circulation. Our objective was to count and correlate CTCs levels and MRP-5 (multidrug resistance associated protein 5) expression with progression free survival (PFS).
Materials and Methods: Prospective study made by blood collection of patients with metastatic or advanced CRC. Blood was collected before the beggining of chemotherapy and after 60 days, in accordance with image exams. The enrichment of CTCs was made by direct immunomagnectic labeling of positive cytokeratin (CK) cells. These cells were permeabilized and labeled with antibody against pan- CK conjugated to ficoeritrin to identify epithelial cells. Leucocytes were identified by anti-CD45 antibody. CTCs were analysed by immunofluorescence and by light microscope and quantified by 8 mL of blood. The protein expression of CTCs was analysed after blood filtration by ISET (Isolation by Size of Epithelial Tumor Cells). Blood was collected in EDTA tubes and diluted in buffer for filtration. Then, membranes were stored at −20°C until analysis. After incubation with antibodies (MRP-5), the membranes were counterstained with DAB. PFS curves were made by Kaplan Meier method and the difference between curves were analysed by log-rank.
Results: There were included 16 patients treated with FOLFOX or FOLFORI and bevacizumab. The median age was 63.5 years (30−81). The majority of patients was men (62.5%) and included at stage IV (68.7%). The PFS after the treatment was observed by image exams and showed a media of 6.14 months (0.79–8.55 months). The median CTCs numbers detected in these patients were 23.5 CTCs/8 mL at baseline. Patients with lowest levels of CTCs (above the median) showed worse PFS (4.15 months) in relation to those with higher levels of CTCs (7.78 months, $p = 0.037$). The same was true for the CTCs counts in the first follow-up (4.20 $\times$ 7.73 months, $p = 0.047$, respectively). Only 11 patients were analysed for MRP-5 protein expression and no correlation was observed between this expression and PFS.
Conclusion: Although our CTCs counts seems conflicting, the lowest counts found in patients with worst PFS can be explained by the inhibition of tumor angiogenesis by bevacizumab, which may lead to hypoxia, invasive cell behaviour and epithelial mesenchymal transition (EMT), as postulated by Gazzaniga et al. (2011). As the method used was based on epithelial markers, it is possible that these patients with poorest PFS were under EMT. The expression of EMT and endothelial cells markers in CTCs filtered on ISET are under investigation in our lab.
No conflict of interest.

1005 POSTER

Quantitative assessment of lymph vascular space invasion (LVSI) provides important prognostic information in node-negative breast cancer patients

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Background: The prognostic value of lymph vascular space invasion (LVSI) has been in investigated in multiple studies, some of which have demonstrated an association of this phenomenon with disease-free survival. Clear definitive criteria and optimal determination of this parameter remain unclear, especially whether some sort of quantification of LVSI is clinically relevant.
Materials and Methods: EORTC trial 10854 investigated the efficacy of perioperative chemotherapy in 2795 patients with T1-T3, N0−2 and M0 breast cancer. A subset of 427 node-negative breast carcinomas from premenopausal patients from this trial were selected and scored for LVSI. The number of LVSI foci were counted and the cell number was determined in the largest tumor embolus within the lymph vessels. These two parameters were multiplied in order to calculate the LVSI tumor burden (LVSI-TB). The optimal cut-off for this parameter was calculated in a discovery set and tested in a validation set. This parameter was also compared to simple quantitation of the number of LVSI foci regarding the sensitivity and specificity for identifying patients with disease relapse.
Results: Tumors with a single LVSI focus are not at increased risk for disease relapse (HR 1.423, 95% CI 0.762–2.656) which indicates that quantitation of LVSI is necessary. The LVSI-TB had the highest sensitivity and specificity for performing quantitative LVSI assessment compared to simple determination of the number of LVSI foci. This parameter was independently associated with disease-free survival in the validation set (HR 2.366, 95% CI 1.369–4.090, $P = 0.002$) in multivariate analysis and provided prognostic information in both the low- and high-risk node-negative breast cancer groups ($P<0.001$ and $P = 0.007$ respectively).
Conclusion: In order to optimally implement determination of LVSI into the standard clinical care for breast cancer patients, this parameter needs to be quantified. This study shows that the determination of the number of LVSI foci multiplied by the number of tumor cells in the largest tumor embolus provides the most reliable quantitative assessment of this parameter.
No conflict of interest.

1006 POSTER

Facilitates chromatin transcription (FACT) complex as a marker and target of aggressive poorly differentiated cancers

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Background: The Facilitates Chromatin Transcription (FACT) is involved in chromatin remodeling during transcription, replication and DNA repair and was considered to be aubiquitously expressed complex that had no known associations with any disease. However, we discovered that FACT is expressed in very limited number of cells of the adult mammalian organism, mostly presented by stem and undifferentiated cells (Garcia, 2011). Moreover a novel anti-cancer agents, Curaxins, entered recently Phase I clinical trials, exert tumor cell killing though inhibition of FACT function (Gasparian, 2011). The goal of this study was to elucidate what role FACT plays in cancer.
Material and Methods: We assessed expression of FACT in normal and cancerous tissues of different organs on mRNA (>20,000 samples) and protein (>800 samples) levels to evaluate the correlation between FACT expression and clinical features of different cancers. We also ran *in vitro* and *in vivo* experiments to evaluate how modulation of FACT levels affects tumorigenic transformation and tumor cell properties. Finally we obtained genome wide distribution of FACT using ChIP-seq to identify genes which transcription requires FACT assistance.
Results: FACT expression is significantly higher in tumors of patients with poor overall survival (all cancers, breast cancer (BC), NSCLC), higher incidence of metastasis (BC, NSCLC, RCC) and the presence of other markers associated with poor prognosis (BC, NSCLC, colon cancer). Ectopic expression of FACT in normal cells does not drive transformation, but increases efficiency of oncogene-driven transformation. Conversely a reduction of FACT level, using a RNAi approach, reduces transformation efficiency and interferes with tumor, but not normal cell growth.
Genome wide analysis revealed non-random FACT distribution in tumor cells with significant enrichment over the bodies of genes regulated by transcriptional factors associated with cancer (Myc, AP1-, ets-families, YY1), stress response (NF-kB, HSF1, HIF1a) and pluripotent cell state (Oct3/4, Myc, Hox family). This pattern suggests selective assistance of FACT to the transcription of genes involved in cancer and early development.
Conclusion: FACT is an attractive target and marker of poorly differentiated aggressive cancers based on its role as an accelerator of oncogenic transformation through selective chromatin remodeling of genes involved in cancer stress response and maintenance of pluripotent cell state.
No conflict of interest.

1007 POSTER

Combined use of estrogen receptor status and TP53 mutation status regulated gene expression data to predict risk of relapse in neoadjuvant chemotherapy treated breast cancer patients

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Background: Breast cancers (bc) carry a complex repertoire of nucleic acid variations including polymorphisms, germline and somatic mutations that can influence gene expression and the clinical behavior of the disease. In the present study we aimed to identify a gene signature driven by *TP53* mutations and to assess its clinical relevance in ER-positive and ER-negative bc.
Methods: Bc data containing *TP53* mutation status and gene expression (for 22,277 genes) derived from five independent datasets were used (n = 695; ER+ n = 511 and ER− n = 184). The gene expression data was obtained using Affymetrix HGU133A microarrays. The raw array data was normalized in the R environment using the affy Bioconductor package. In this discovery cohort, ROC analysis was performed for each gene separately and the genes were ranked by their achieved AUC values. Kaplan–Meier analysis was performed by employing an updated version of our online available KM-plotter using 635 neoadjuvant chemotherapy-treated patients − none of these patients was included in the discovery cohort. Statistical significance was set at $p < 0.01$. *In vitro* assay with specific inhibitors against selected kinases were performed.
Results: Single genes were highly capable to discriminate *TP53* mutant and wild type tumors as well as patients with high and low risk of relapse in ER positive patients. The combination of multiple genes did not significantly improve classification. Among the most significant genes were: TTK (AUC = 0.82), *CDC20* (0.804), *STC2* (0.780), *CDCA8* (0.780), *CCNB2* (0.800) and *MYBL2* (0.79). All of the top *TP53*-regulated genes correlated to survival as well. Identical analysis in ER negative tumors did not reveal any gene associated with survival. Notably, TTK inhibitor (SP600125) was used in 2 TP53 mutated bc cell lines, MDA-MB-231 (ER−) and T47D (ER+) with a significant reduction in cell proliferation and increase in cell death, particularly in the T47D.
Discussion: By using a new statistical approach, we identified *TP53*-mutation driven genes highly correlated to shorter survival in ER-positive chemotherapy-treated breast cancer patients. We identified an important kinase, TTK, regulated by mutant TP53. Inhibition of TTK caused a significant cell death in ER+/TP53 mutated bc cells.
No conflict of interest.

1008 POSTER

Prognostic role of neutrophil to lymphocyte ratio (nlr) in solid tumors: A systematic review and meta-analysis

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Background: Inflammation may play an important role in cancer progression, and a high NLR has been reported to be a poor prognostic indicator in several malignancies. However, the exact magnitude of the prognostic impact of this readily available and inexpensive potential biomarker remains unclear.
Methods: A systematic review of electronic databases was conducted to identify publications exploring the association of blood NLR and overall survival (OS) in all solid tumors. Data from studies reporting a hazard ratio (HR) and 95% confidence interval (CI) or a *P*-value were pooled in a meta-analysis. The pooled HRs for OS by disease group and by extent of disease (non-metastatic versus metastatic versus mixed) were computed using inverse-variance and random-effect modeling.
Results: 68 studies comprising 31,026 patients were included in the analysis. 50 (74%) of the studies were published in 2011 or later and 21 (31%) reported on metastatic disease alone. The median cut-off for high NLR was 4.0 (range 1.9−5.0). Overall, NLR above the cut-off was associated with a HR for OS of 1.68 (95% CI 1.57–1.80, $P<0.001$). The magnitude of effect on OS was non-significantly greater in lower gastrointestinal (GI) and genitourinary tumors compared to other cancer sites (*P* for subgroup difference = 0.10, table). Compared with patients with non-metastatic disease, high NLR was associated with a differentially worse survival in those with metastatic cancer (*P* for subgroup difference = 0.004, table).

	Studies (N)	Patients (N)	Median cut-off NLR	HR for OS	95% CI	*P*-value
Site						
Upper GI	21	5429	3.3	1.59	1.39–1.83	<0.001
Lower GI	17	4542	5.0	2.00	1.59–2.53	<0.001
Lung	10	1977	3.9	1.53	1.31–1.80	<0.001
Genitourinary	8	2379	3.0	2.15	1.71–2.69	<0.001
Gynecological	3	1488	2.6	1.48	0.98–2.23	0.06
Other	9	15211	4.0	1.67	1.45–1.93	<0.001
Stage						
Non-metastatic	19	3981	4.8	1.39	1.24–1.56	<0.001
Mixed	28	20744	4.0	1.68	1.52–1.87	<0.001
Metastatic	21	6301	3.5	1.83	1.64–2.04	<0.001

Conclusion: A high NLR is associated with an adverse OS in many solid tumors. The magnitude of association of high NLR with worse OS is greater for metastatic than for non-metastatic disease. The addition of NLR to established prognostic scores warrants further investigation.
No conflict of interest.

1009 POSTER

PD-1+ immune cell infiltration inversely correlates with survival of patients with operable breast cancer

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Background: Programmed death-1 (PD-1), a coinhibitory checkpoint receptor, is mainly expressed on functionally 'exhausted' $CD8^+$ T cells, dampening the host antitumour immune response. We evaluated the ratio between effective and regulatory T cells (Tregs), and PD-1 expression as prognostic factors for breast cancer patients.
Material and Methods: A series of 218 newly diagnosed invasive breast cancer patients who had undergone primary surgery at Ruijin Hospital between 2004 and 2008 were identified. The influence of $CD8^+$ cytotoxic T lymphocytes (CTLs), $FOXP3^+$ (Treg cell marker), and $PD\text{-}1^+$ immune cell counts on prognosis was analysed utilising immunohistochemistry.
Results: A total of 208 breast tumours were examined after exclusion of 10 patients with uninformative slides. No correlation between $CD8^+$ cells and clinicopathologic variables were demonstrated, while both $PD\text{-}1^+$ immune cells and $FOXP3^+$ Tregs counts were significantly associated with unfavourable prognostic factors. In univariate analysis, high tumour infiltrating $PD\text{-}1^+$ cell counts were correlated with significantly shorter overall survival (OS) (p = 0.004, log rank = 9.55), with a hazard ratio of 3.29 (95% CI, 1.48–7.32). However, multivariate analysis showed PD-1 expression not to be independently associated with OS (HR = 2.37; 95% CI, 0.99–5.65; p = 0.051).
Conclusions: Tumour progression was seen with higher PD-1 expression on previously functional immune cells and more aggressive cancers harboured increased Tregs. Our results suggest a prognostic value of the $PD\text{-}1^+$ immune cell population in breast cancer patients. Targeting the PD-1 pathway as well as depletion of Tregs may be a feasible approach to treat patients with breast cancer.
No conflict of interest.

1010 POSTER

Protein biomarker signature for risk classification of hormone receptor positive breast cancer identified by reverse phase protein array based tumor profiling

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Background: Around 70% of breast cancer cases belong to the luminal intrinsic molecular subtype, characterized by hormone receptor overexpression. This subtype can be further divided into luminal A and luminal B, which is commonly used as surrogate for good and bad prognosis, respectively. The classification is crucial for therapy decision as patients of the luminal B subtype are at higher risk of recurrence and require chemo-endocrine therapy, contrasting low risk patients who do not benefit from chemotherapy. However, accurate definition of low and high risk luminal breast cancer has remained a challenge so far. Thus, the objective of this study was the identification of a robust protein biomarker signature to facilitate the risk classification of luminal breast cancer.
Materials and Methods: Reverse phase protein arrays (RPPA) were applied to quantify over 120 breast cancer relevant target proteins of hormone receptor positive breast cancer tumor samples. Subsequently, we used a novel bioinformatics workflow combining a bootstrap approach with three different classification methods for biomarker selection. To validate our RPPA derived results we have applied Western blot, immunohistochemistry, and mRNA profiling.
Results: Our results confirm that markers for cell proliferation are prominent factors to distinguish between low and high risk tumors with Ki-67, TOP2A, and PCNA appearing among the top hits. However, NDKA, RPS6, and caveolin-1 were selected as prime candidates. Comparably to Ki-67, NDKA and RPS6 were expressed at an elevated level in high risk tumors whereas caveolin-1 was observed to be downregulated.
Conclusions: We have identified a protein biomarker signature (consisting of caveolin-1, NDKA, RPS6, and Ki-67) using RPPA based tumor profiling with the potential to facilitate the risk of recurrence classification in luminal breast cancer. In addition, we present RPPA as promising experimental platform for the identification of biomarkers in clinical samples.
No conflict of interest.

1011 POSTER

Generation of a potent uPAR-antagonist by forced-proximity engineering of the receptor binding domains of urokinase and vitronectin

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Background: Extensive in vitro, in vivo and clinical evidence suggest that urokinase-type plasminogen activator receptor (uPAR) plays important functions in wide range of pathological processes including tumor growth, invasion and metastasis, inflammatory diseases and viral infections. Drugs interfering effectively with uPAR-function may therefore provide novel therapeutical regimens in a variety of pathological conditions. We here describe the conception, construction and validation of a novel type of inhibitor of the uPAR.
Material and Methods: *a)* Inspection of the crystal structure of the ternary complex between uPAR, the aminoterminal fragment of urokinase-type plasminogen activator uPA (growth factor-like domain, GFD) and the somatomedin B domain (SMB) of vitronectin (VN) reveals that the peptide backbone of uPA and VN are closely located. In particular Lys48 in uPA and Pro42 in VN are only distant 18Å. Connecting residues 1−48 of uPA (i.e. GFD) and 1−42 of VN (i.e. SMB) to a common scaffold, via their C-termini, is thus predicted to generate a chimera. To join GFD and SMB onto a common scaffold the constant region (Fc) of human IgG was chosen to form stable dimers (named uPAR-lock).
b) To evaluate the activity of uPAR-lock in inhibiting uPAR-signalling in live cells we quantified cell adhesion to VN coated wells by impedance measurements using a real-time cell analyser.
Results: *a)* Potent uPAR inhibitor was generated by forced proximity engineering. The uPAR binding domains of uPA and VN are natural and specific inhibitors of uPA and VN binding to uPAR and resulted in uPAR-lock.
b) uPAR-lock is a potent inhibitor of uPAR function. Addition of uPA induced a rapid and strong increase in the adhesion of 293/uPAR cells. Importantly, the treatment with uPAR-lock completely abrogates the increase in 293/uPAR cell adhesion induced by uPA addition. These data clearly showing that uPAR-lock is a potent and specific inhibitor of uPA induced, uPAR mediated, cell adhesion to VN.
Conclusions: The generated inhibitor (uPAR-lock) is a hetero-bivalent uPAR-ligand containing the receptor binding domains of the extracellular protease uPA and the Extracellular matrix protein VN positioned in close proximity on a common scaffold. Binding of uPAR-lock to uPAR results in a complex where the binding sites for both uPA and VN are occupied contemporarily and efficiently, thus blocking both the proteolytic and signalling activities of the receptor.
No conflict of interest.

1012 POSTER

Increased body mass index shortens telomeres through elevated C-reactive protein

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Rationale: Obesity is associated with decreasing telomere length (TL). The cause of this association is unknown.
Objectives: By measuring leukocyte TL, body mass index (BMI) and C-reactive protein (CRP) in 45069 individuals, we tested the hypothesis that increased BMI causes TL shortening, and that low-grade inflammation contributes through elevated CRP. Using the three obesity-associated polymorphisms rs9939609, rs17782313, and rs6548238, and the CRP promoter polymorphism rs3091244 in instrumental variable analyses, we estimated the causal associations between BMI and TL and between CRP and TL.
Findings: In multivariable adjusted observational analyses, TL decreased with 5 base pairs (bp) (95% confidence interval −7; −3) per unit increase in BMI, and further adjustment for CRP attenuated this association to −2 bp (−4; 0.1). In accordance, instrumental variable analysis showed a causal non-significant TL shortening of 6 bp (−37; 25) per unit increase in BMI. Furthermore, in observational analyses TL decreased with 10 bp (−17; −3) for a doubling in CRP, supported by the instrumental variable analyses showing a causal decrease of 66 bp (−124; −7).
Conclusions: The association between increasing BMI and decreasing TL may be causal, and possibly mediated through elevated CRP: elevated CRP *per se* is a causal determinant of TL shortening.
No conflict of interest.

1013 POSTER

Pooled analysis of two phase III studies provides prognostic indicators for clinical out-come after catumaxomab treatment for malignant ascites

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Background: For identification of factors with potential impact on efficacy of catumaxomab (CATU) in patients (pts) with malignant ascites data from two phase III studies (IP-REM-AC-01 and CASIMAS) were used for a meta-analysis.
Materials and Methods: All randomized pts of both studies were included: 389 pts treated with CATU plus paracentesis and 88 control pts (paracentesis only). Efficacy parameters were overall survival (OS), puncture-free survival (PuFS) and time to first puncture (TTPu). Karnofsky Index (KI), total serum protein (protein), presence/absence of distant metastases (metastases) and number of prior chemotherapies (prior CTX) at inclusion were analysed as potential prognostic factors for the treatment effect of CATU.
Results: Pts treated with CATU showed a significant prolongation of PuFS (44 vs 11 d, $p < 0.0001$), TTPu (88 vs 13 d, $p < 0.0001$) and OS (88 vs 68 d, $p = 0.007$) compared to control.
CATU treated pts with a KI of 80–100 at inclusion had a significantly better OS and improved PuFS compared to those with a KI of 60−79 (120 vs 57 d, $p < 0.001$ and 55 vs 27 d, $p < 0.001$, respectively). TTPu was not improved (88 vs 96 d, $p = 0.186$). Linear Cox regression of KI as a co-variable showed a significantly positive impact of high KI on CATU efficacy for OS (HR 0.97, $p < 0.001$) and PuFS (HR 0.98, $p < 0.001$) but not for TTPu (HR 0.99, $p = 0.054$).
Cox regression analysis of the presence of distant metastases and low (< normal) total serum protein on CATU efficacy showed a negative impact on

OS (metastases: HR 1.43; p < 0.001; protein: HR 1.39, p = 0.002), PuFS (metastases: HR 1.37, p = 0.003; protein: HR 1.45, p < 0.001) and TTPu (metastases: HR 1.28, p = 0.069; protein: HR 1.41, p = 0.011).
Median number of prior CTX was 3. Pts with >3 prior CTX had a reduced treatment effect of CATU compared to those with 1 or 3 prior CTX. Overall, significant treatment effects on ascites (PuFS and TTPu) were observed in all subgroups for all factors; however, significant effects on OS were only found in pts with KI 80–100, with no distant metastases, with ⩾ normal total serum protein and with 3 prior CTX.
Conclusion: Karnofsky Index, distant metastases, total serum protein and number of prior CTX at screening were identified as factors having a significant impact on OS in CATU-treated pts and better prognostic pts compared to controls. In contrast, the effect of CATU on ascites control was observed in all subgroups irrespective of whether the pts were in the good or poor prognostic group.
Conflict of interest: *Advisory board: Fresenius Biotech GmbH. Corporate-sponsored research: Fresenius Biotech GmbH. Other substantive relationships: Employee Fresenius Biotech GmbH*

1014 POSTER

A new IDH1/2 PCR assay for one-step detection of 12 IDH1 and IDH2 mutations in glioma

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Background: Isocitrate dehydrogenase (IDH) mutation status is a strong diagnostic and prognostic marker in glioma which will probably be introduced in the WHO classification system. Current screening for IDH mutations is performed with an IHC assay specific for IDH1 R132H, the most frequent mutation; subsequent sequencing is recommended when IHC is negative or equivocal. A qPCR assay was designed to detect in one single step, IDH1R132H and 11 rare IDH1/2 mutations in FFPE samples. This study describes development, analytical performance and validation of this new assay.
Material and Methods: PCR Clamping was used to detect IDH1 R132H and 11 additional mutations (5 IDH1 R132, 1 IDH1 R100, 5 IDH2 R172). ARMS was combined to selectively identify IDH1 R132H/R132C and IDH2 R172K. Limit of detection (LOD) (minimum % mutant DNA detected in a WT DNA background) was determined using five low positive samples per mutation (n = 5x30 measurements/mutation). FFPE glioma samples (n = 170) were retrospectively collected from 3 independent sources. The assay was validated on samples meeting assay requirements (<10 yrs, $\geqslant$50 mm^2, $\geqslant$40% tumor cells) comparing PCR IDH status to IHC (mIDH1 R132H) and bidirectional sequencing. Additionally, to better document minor mutations, synthetic samples for the 11 minor mutations (30% and 45% mut DNA in WT DNA) were tested.
Results: Assay sensitivity varied across mutations with LOD <5% for 11/12 mutations (mean=3.3%). From the first 120 clinical samples analyzed, 103 were <10 yrs (48/103 glioblastomas). IDH status was successfully obtained by PCR for these 103 samples. All IHC positive cases were concordantly identified as R132H by PCR (n = 45). One R132H case detected by PCR was negative by IHC (negative concordance 98%). PCR additionally detected 9 rare mutations (8 IDH1, 1 IDH2). Moreover, the kit produced 100% correct results on the synthetic samples with rare mutations.
Conclusions: The one-step IDH1/2 PCR assay showed a 100% technical success rate and is more sensitive than published references for bidirectional sequencing. Positive concordance with IHC detection for IDH1 R132H was 100%. Complete validation results including sequencing data (to be presented at the meeting) will further document the value of this new assay to screen in one step for 12 IDH12 mutations.
Conflict of interest: *Ownership: No. Advisory board: No. Board of directors: No. Corporate-sponsored research: No. Other substantive relationships: HG, CP, FM, AC, and HPSP are full time employees of QIAGEN Marseille*

1015 POSTER

Plasma testosterone in the general population, cancer prognosis and cancer risk

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Background: Testosterone is an important anabolic hormone in humans and, i*n vitro*, testosterone stimulates growth of lung and colon cancer cells. We tested the hypothesis that increased plasma testosterone associates with increased risk of cancer and with increased risk of early death after cancer in the general population.
Material and Methods: Plasma testosterone was measured in 8771 20−94 year old men and women who participated in a prospective study of the general population. Participants were included in 1981−83 and followed for up to 30 years.
Results: During follow-up, 1140 men and 809 women developed cancer. For risk of early death after cancer and after adjustment for age at diagnosis, tumour stage at diagnosis, and time since blood-sampling, the hazard ratios in men were 1.30 (95% confidence interval 1.03–1.65) for the 2nd quintile, 1.31 (1.02–1.67) for the 3rd quintile, 1.52 (1.19–1.93) for the 4th quintile, and 1.52 (1.20–1.91) for the 5th quintile, versus the 1st quintile. In women, corresponding hazard ratios were 1.09 (0.81–1.46), 1.17 (0.86–1.59), 1.03 (0.76–1.39), and 1.80 (1.32–2.46). For risk of any cancer for a doubling in testosterone levels, multifactorially adjusted hazard ratios were 1.07 (0.98–1.18) in men and 1.06 (0.93–1.22) in women. For both men and women, a doubling of testosterone levels was not associated with risk of any individual cancer type.
Conclusions: In this prospective study of 8771 men and women from the general population followed for up to 30 years, increased testosterone levels were associated with a 30−80% increased risk of early death after cancer, but with unchanged risk of incident cancer.
No conflict of interest.

1016 POSTER

Expression of cancer stem cell (CSC) markers in primary tumors (PT) and matched lymph node metastases (LNM) in breast cancer patients

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Background: Breast cancer is characterized by high intra-tumor heterogeneity, with multiple cell populations differing in metastatic potential. CSCs, representing a minor subset of cells, play a critical role in breast cancer initiation, progression, metastasis and drug resistance. However, their status in LNM remains unclear. We evaluated in PT and in matched LNM protein levels of CSC markers: CD44 and ALDH1, and epithelial–mesenchymal transition (EMT) markers: E-cadherin and vimentin. The results were correlated with clinicopathological data, overall (OS) and disease-free survival (DFS).
Material and Methods: We examined formalin-fixed paraffin-embedded samples from PT and matched LNM from 42 stage II−III breast cancer patients. Protein expression was measured by immunohistochemistry on tissue microarrays. For CD44 and ALDH1 staining intensity (scored as: 0-negative, 1-weak, 2-intermediate, 3-strong) and percentage of positively stained cells (0–100%) were multiplied to count the expression score. For E-cadherin and vimentin $\geqslant$10% of stained cells defined a positive result. Results were considered concordant if PT and LNM were both positive or both negative. Concordance was measured by Cohen's kappa coefficient (κ), with κ value equal 1 indicating perfect agreement. DFS and OS were compared using F-Cox test. Hazard ratios (HRs) with 95% confidence intervals (95% CI) were computed using Cox regression analysis.
Results: Median expression score of CD44 was significantly higher in LNM compared to PT (p = 0.04). Status of ALDH1 and CD44 between PT and LNM was discordant in 16/42 (38%) and 7/27 (26%) of cases, respectively (κ=0.24 and κ=0.5), with only negative-to-positive conversion for CD44. Status of E-cadherin was fully concordant (κ=1), and of vimentin has changed in 7% (3/40, κ=0.63). CD44 positive status correlated with vimentin expression (p = 0.03). Increased expression of CD44 in LNM was strongly associated with shorter OS (HR 8.4, 95% CI 1.04–67.6, p = 0.001) and DFS (HR 9.6, 95% CI 1.2–76.7, p = 0.0005), whereas its expression in PT had no prognostic impact. Status of ALDH1 and vimentin in both PT and LNM did not correlate with OS and DFS.
Conclusions: Compared to PT, LNM are enriched in cells with CSC markers, suggesting that phenotype of these aggressive cell subpopulations might easier be captured in LNM than in PT. High level of CD44 in LNM confers worse prognosis, confirming the correlation of CSC-phenotype with aggressive disease behavior.
No conflict of interest.

1017 POSTER

HER3 expression in primary colorectal cancer and corresponding lymph node metastases

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Background: To evaluate the prognostic value of the epidermal growth factor receptor HER3 and to elucidate heterogeneity of HER3 expression in primary colorectal cancer (CRC) and corresponding lymph node metastases.
Material and Methods: HER3 expression was analyzed immunohistochemically (IHC) in primary tumors and in corresponding lymph node metastases from 236 patients with stage II and III CRC. In 58 primary tumors, fluorescence in situ hybridization (FISH) detection was performed.
Results: HER3 was detected at high frequency in the cellmembrane. Seventy per cent of the primary tumors were categorized with high HER3 expression compared to 75% in the lymph nodes metastases. HER3 expression in the primary tumor was an independent prognostic factor for overall survival in the entire group of patients ($p = 0.026$) and in the subgroup of patients with colon cancer stage II ($p = 0.030$). A high HER3 expression in the primary tumor was associated with worse clinical outcome. The expression of HER3 was homogenous within the tumor ($p < 0.0001$) and correlated with the HER3 expression in corresponding lymph node metastases ($p < 0.0001$). No gene amplification with respect to HER3 was seen in primary tumors using FISH analysis.
Conclusion: High HER3 expression was found in about 70% of the primary CRC tumors and corresponding lymph node metastases. HER3 expression in the tumor was an independent prognostic factor where a high HER3 expression was associated with worse clinical outcome. There was correlation in HER3 expression between primary tumors and corresponding lymph node metastases.
No conflict of interest.

1018 POSTER

Can we accurately report PTEN status in advanced colorectal cancer?

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Background: The tumour suppressor gene PTEN is considered to have a potential role as a biomarker for anti-EGFR therapy in CRC, although results are inconsistent and there is debate as to the optimal method of reporting low PTEN expression/loss of function. Immunohistochemistry (IHC) is frequently used, although other methods have also been reported (Fluorescence in situ hybridisation and mutation status). PTEN status also appears to vary between primary and secondary tumour samples, further complicating interpretation of the data. Our group has used the Taqman® copy number assay (CNA) previously and here we report results of a subgroup of patients from the AGITG/MAX trial PTEN analysis exploring the concordance between pathologists assessment of PTEN IHC expression, and the relationship of Taqman CNA result and IHC.
Methods: Genomic DNA was extracted from FFPE tissue sections. The Taqman PTEN CNA was performed using 5 ng DNA in quadruplicate PCR. The results are calculated as a ratio relative to a 2-copy control using the 2-ΔΔCt method (Rotorgene software), and multiplied by 2 to give the copy number. Loss of PTEN was defined as $\leqslant$1.5 copies, no loss was >1.5 copies. IHC was performed on 60 tissue arrays and then assessed by two blinded Pathologists. Scoring was 0, 1+, 2+, 3+ for PTEN IHC expression. The two pathologists were compared directly for an IHC concordance rate, and then the scores were grouped and majority score used for IHC v Taqman CNA.
Results: Tissue arrays were analysed for PTEN staining by IHC. 95% of tissue arrays were from the primary CRC. Three were found to have no residual tissue present on the array. 18 of 57 (31.6%) had a score of zero, ie loss of PTEN expression based on IHC. Concordance of IHC PTEN loss (0 v 1+, 2+, 3+) was 63% (36/57) when comparing two pathologists. Using majority score for IHC from the two pathologists, for the 18 specimens with IHC loss of expression, 12 (66.7%) had copy number loss by Taqman. Furthermore the rate of IHC PTEN loss was 44% of those with copy number loss (12/27). There was no evidence that PTEN loss in this small subset measured by low copy number or IHC negativity was prognostic for RR, PFS or OS.
Conclusion: PTEN loss based on IHC is not directly associated with PTEN copy number loss, suggesting that there are other mechanisms such as mutation or promoter methylation, leading to loss of IHC expression. Conversely loss of just 1 PTEN allele may still allow compensatory up-regulation of PTEN to normal levels. This supports the concept that various mechanisms may lead ultimately to loss of PTEN expression. PTEN assessment by IHC alone however remains unreliable based on the lack of concordance between pathologists and robust validation will be required before routine use.
No conflict of interest.

1019 POSTER

The protective role of the vagus nerve in cancer

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Background: The evolution of tumors is multifactorial and complex. Recent research shows however, that not only do microenvironmental factors play pivotal roles in carcinogenesis, but so does the autonomic nervous system. The vagus nerve is thought to have protective roles in cancer since it reduces inflammation, oxidative stress and sympathetic activity. Vagotomized tumor-bearing animals show greater metastasis, and in contrast, activating the vagus nerve by a medication was found to reduce tumors and their metastases. In a series of retrospective studies we conducted, higher heart rate variability (HRV), a non-invasive index of vagal nerve activity, was found to predict reduced tumor burden and longer survival times, independent of important confounders including stage and treatment. Furthermore, finding modifiable prognostic factors paves the way for new treatments, which is crucial in advanced pancreatic cancer.
Methods: A 'historical prospective' study in N = 272 patients with advanced pancreatic cancer was performed. HRV was obtained retroactively from ECGs near diagnosis, and some other confounders such as age and treatments were obtained from the medical charts. Levels of C-reactive protein (CRP) were also measured as an inflammatory marker. Overall survival and survival date were obtained from medical charts and the national registry.
Results: In a Cox regression, higher initial HRV (>20 msec) significantly predicted lower risk of death, independent of confounders including age and cancer treatments. This relationship was mediated (explained) by CRP levels. Importantly, in patients who lived only one month or less from diagnosis, HRV was unrelated to CRP, while in patients surviving longer, HRV was significantly inversely related to CRP ($r = -0.20$, $p < 0.05$), suggesting that neuroimmuno-modulation let patients survive longer. Finally, chemotherapy doses increased overall survival only when vagal nerve activity was low, while patients with high vagal nerve activity survived longer, even without chemotherapy.
Conclusion: These results support vagal nerve protection in a fatal cancer, and propose that the mechanism may involve neuroimmunomodulation. Vagal nerve activity may also determine in whom certain treatments are effective and necessary.
No conflict of interest.

1020 POSTER

Prognostic value of Tubedown-100 in patients with breast cancer

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Background: Tubedown-100, also known as NAA15 and NARG1, is a large protein initially found to express at high level in testis tissues and proliferative neuronal tissues. It has been found to be expressed in certain cancer cells including thyroid cancer and lymphoma cells. Although Tubedown-100 has been indicated in the regulation of apoptosis, its biological role in cells including cancer cells remains unknown. It clinical implication in cancer is not known. In the present study, we aimed to investigate the pattern of expression of this molecule in human breast cancer and the potential prognostic value in the patients.
Materials and Methods: The levels of Tubedown-100 gene transcripts were determined using quantitative transcript analysis and PCR analysis. Human breast cancer cell lines MCF-7 and MDA MB-231 were used. Anti- Tubedown-100 transgenes were constructed and used to regulate the expression of Tubedown-100 in breast cancer cells. (cell growth and apoptosis were evaluated on the cells with differential expression of Tubedown-100) A cohort of human breast cancer tissues (n = 127) were

tested for the levels of Tubedown-100 gene transcript. Patient's clinical, pathological and outcome results were analysed against the levels of Tubedown-100.
Results: MCF-7 and MDA MB-231 cells expressed Tubedown-100 gene transcripts. Knockdown of Tubedown-100 gene in both cells resulted in cells with significantly increased growth rate and motile and adhesive to matrix (P<0.001). The Tubedown-100 knockdown cells did not have a significant difference in apoptosis compared with control cells. Levels of Tubedown-100 transcript were significantly lower in tumours from patients with a predicted poor prognosis compared with those with good prognosis (p = 0.038), although there were no significant links with tumour grade. Perhaps the most interesting observation is that levels in patients who developed distant metastasis and who died of breast cancer related complications had significantly lower levels than those who remained disease free (p = 0.016 and p = 0.022, respectively). This is reflected a significantly shorter overall survival time in patients with low levels of Tubedown-100 than those with high level.
Conclusions: It is concluded that Tubedown-100 is aberrantly expressed in patients with breast cancer and the levels are linked with the prognosis of the patients. Tubedown-100 thus is a potential prognostic indicator in patients with breast cancer.
No conflict of interest.

1021 POSTER

Expression of aquaporin 5 and its polymorphism predicts survival in patients with early breast cancer

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Background: Our previous study showed the association of aquaporin 5 (AQP5) up-regulation with cancer proliferation and migration in hormone-responsive breast cancer cell lines and with unfavorable prognosis in patients with breast cancer. Accordingly, we analyzed the prognostic impact of AQP5 expression and polymorphisms in a large number of patients with early breast cancer (EBC).
Materials and Methods: AQP5 expression was investigated based on the immunohistochemistry of tissue microarray specimens from 609 EBC patients who underwent surgery between 2003 and 2008. We scored the staining intensity (IS) and percentage of positive tumor cells (PC). The genomic DNA was extracted from paraffin-embedded tumor-free tissue and then genotyped for 3 polymorphisms (rs3736309, rs1964676, and rs74091167) using the Sequenom Mass array system.
Results: Among the 3 polymorphisms, AQP5 overexpression (IS + PC $\geqslant$6) was correlated with AQP5 rs74091167 GG genotype. AQP5 overexpression and AQP5 rs74091167 was significantly associated with disease-free survival (DFS; P <0.001 and P = 0.021, respectively). Moreover, a multivariate survival analysis revealed that AQP5 overexpression and the GG genotype of AQP5 rs74091167 were significantly associated with DFS (HR = 2.026, 95% CI 1.058–3.881, P = 0.030; HR = 0.377, 95% CI 0.179–0.793, P = 0.010, respectively), which was prominent in patients with an ER/PgR-positive tumor.
Conclusions: Consistent with our previous study of breast cancer cell lines, AQP5 expression and AQP5 rs74091167 variant can be considered as a prognostic marker in patients with EBC after curative surgery. In the future, functional relevance of this variant needs to be clarified.
No conflict of interest.

1022 POSTER

Significance of S100A7 and S100A4 expression as a prognostic biomarker for oral squamous cell carcinoma

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Oral cancer is a leading cause of cancer death worldwide. The goal of cancer-screening program is to detect tumors at early stage, enough that treatment is likely to be successful. Moreover, the screening tool must be sufficiently noninvasive and inexpensive to allow widespread applicability. A substance secreted by tumor tissue, not secreted by non-tumor tissue, and easily and cheaply detectable in saliva, serum or urine is, therefore, an ideal biomarker because the cancer is detected specifically and non-invasively. The aim of the study was to investigate the expression pattern of calcium- binding proteins S100A7 and S100A4 for patients with oral squamous cell carcinoma. The S100 Calcium binding protein family consists of at least 25 different types of low molecular weight proteins (9−13 kDa), which are characterized by two calcium-binding sites of the EF-hand type conformation and located on a cluster on human chromosome 1q21. Psoriasin (S100A7) is a member of the S100 gene family in the early stages of tumor genesis S100A7 is highly expressed in ductal carcinoma *in-situ*, but S100A7 is often up regulated in adjacent invasive carcinoma.S100A7 is thus also associated with altered and abnormal pathways of epithelial cell differentiation. The prognostic significance of S100A4 as potential biomarker for oral Cancer. The nuclear S100A4 in TNM (Tumor Node Metastasis) stage indicates the proper early diagnosis in the OSCC.S100A4 promotes metastasis and is involved in several steps of the metastatic cascade, including cell motility, invasion and angiogenesis. Disruption of calcium signaling pathways has been implicated as a central mechanism in tumor genesis and specifically in the process of invasion and metastasis The protein biomarker expression in the OSCC human tissue specimens and matching normal oral tissues from 20 patients were examined. Expression of the protein and mRNA were analyzed by Western blot, RT PCR and IFC/IHC in the human oral cancer tissue comparison with adjacent normal tissue Increased expression at mRNA level was observed in OSCC samples by quantitative real-time RT-PCR.Moreover, significantly increased mRNA ratios between malignant and normal samples were observed. From this we can predict that over expression of S100A7 and S100A4 that epithelial cells undergoing abnormal differentiation and tumor genesis, this could be the potential early detection bio-marker to prevent cancer progression and will show new direction in early stage cancer treatment.
No conflict of interest.

1023 POSTER

CRNDE (a novel marker of poor prognosis in patients with cancer) encodes the CRNDEP protein, a component of stress granules

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Background: The *CRNDE* gene, currently known as non-protein coding, has been found to negatively affect prognosis in patients with colorectal and ovarian carcinomas when overexpressed in cancer at mRNA level. Identification of a protein product encoded by this gene may be important due to its potential role in cancer prognosis and prospective usage in ovarian cancer screening.
Material and Methods: The study was performed on RNA samples isolated from normal endometrium, ovarian cancer and HeLa cells. 5' RACE/3' RACE techniques and reverse transcription PCR followed by nested PCR were employed to identify complete splice variants of the *CRNDE* gene. Next, based on bioinformatics analyses, the most promising open reading frame (ORF) was chosen and cloned into five expression vectors. These vectors were used to elicit overexpression of the hypothetical peptide in bacteria (pQE30, pET201) and HeLa cells (pCDNA3.1(+)). They were also utilised in cellular localisation studies under a fluorescence microscope (pEGFP-N1, pDsRed Monomer-C1). In addition, a polyclonal antibody against the peptide was developed in rabbits. It was used in western blot hybridisation and immunohistochemical experiments.
Results: The 5' RACE and 3' RACE experiments revealed two different splice variants of *CRNDE*. Additional PCR experiments, inspired by the results of other research teams, proved the existence of several other splice variants of *CRNDE*. Some of them seemed to be tissue-specific, but the variant recognised here as protein-coding was ubiquitous. This shortened variant encodes the CRNDEP peptide, consisting of 84 amino acids. This peptide localises to stress granules in HeLa cells, and its upregulation stimulates the formation of these granules. Given these results and the outcome of bioinformatics analyses, CRNDEP seems to exhibit oxidase activity, thus enhancing risk of oxidative stress when overexpressed. The presence of CRNDEP in the variety of human tissues was confirmed by our team with the use of immunohistochemical methods. The existence of a protein product encoded by the *CRNDE* gene has never been reported before in the literature.
Conclusions: *CRNDE* emerges as a protein-coding gene. The product of this gene, the CRNDEP peptide, was identified herein as a component of stress granules, and its overexpression seems to stimulate the formation of these granules.
No conflict of interest.

1024 POSTER

The CRNDE, VAV2 and CEBPA genes as new negative prognostic factors in ovarian cancer patients

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Background: Ovarian cancer is the leading cause of death from gynaecological malignancies. Mortality in this disease is exceptionally high due to the absence of specific symptoms at early phases and the lack of good screening methods. The majority of patients are diagnosed at late stages, characterised by poor prognosis. Identification of new molecular prognostic markers, potential targets of molecular therapy, may facilitate the fight against this neoplasm.
Material and Methods: The genes examined in this study were selected based on the results of preceding gene expression microarrays. The prognostic value of their expression at mRNA level was evaluated in ovarian cancer patients treated with either cisplatin and cyclophosphamide (the PC regimen, N = 32) or taxanes and cisplatin (the TP regimen, N = 74). *HGPRT* was chosen experimentally as a reference gene. In qPCR reactions, inventoried TaqMan assays (Life Technologies) were used, except for the *CRNDE* gene, expression of which was evaluated with two personally designed TaqMan assays, specific to two different splice variants. The amount of genomic DNA contamination was assessed and taken into account if necessary (i.e., for *CEBPA*, an intronless gene). The results were analysed statistically using univariate and multivariate Cox proportional hazards models.
Results: Elevated mRNA expression of *CRNDE* (two different splice variants), *VAV2* and *CEBPA* genes negatively influenced prognosis by significantly increasing risk of death and/or recurrence. For *CEBPA*, this association was mainly observed in a group of patients treated with PC. The clinical significance of *VAV2* overexpression seemed to be related to the TP treatment, though a negative impact of upregulation was also visible in the group of all patients analysed. Overexpression of *CRNDE* negatively affected prognosis without clear discrimination between the chemotherapies administered. In addition, some clinical associations of *CRNDE* seemed to depend on TP53 accumulation status.
Conclusions: Considering the Real-Time qPCR results, the *CRNDE*, *VAV2* and *CEBPA* genes emerged as novel cancer-promoting factors and potential molecular markers in ovarian cancer patients. The clinical meaning of their protein products should be further evaluated in a bigger, well characterised group of tumours through immunohistochemical staining.
No conflict of interest.

1025 POSTER

Characteristics of the relation between epithelial–mesenchymal transition and proliferative activity in breast carcinomas

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Background: Metastases in distant sites are the leading cause of death from breast cancer. One of the most important features of this process is epithelial–mesenchymal transition (EMT), the key marker of which is vimentin − a protein of intermediate filaments of cytoskeleton. EMT is a final stage of tumour dedifferentiation and is started by a row of signalling mechanisms responsible for adhesion and proliferation of tumour cells. The aim of the research was to study interplay between the level of proliferation of breast carcinoma tissue, detected by a proliferative index Ki-67, and realisation of EMT.
Material and Methods: 129 cases of breast carcinoma were studied. Vimentin in the tumour cells was detected by monoclonal antibodies Monoclonal Mouse Anti-Swine Vimentin (DAKO, Denmark). For detection of the cell proliferation index antibodies Mouse Anti-Human KI-67 Antigen (DAKO, Denmark) were used. Immunohistochemical tests were made in autostainer 'DAKO' (Denmark) with the use of Dako Wash Buffer, visualisation system Dako EnVision+Dual Link System-HRP, chromogen Dako Liquid DAB+ Substrate Chromogen System (DAKO, Denmark). Test evaluation was made with the microscope 'Zeiss Ymager M' (Germany). A criterion of positive expression of vimentin in the tumour cells was presence of strong cytoplasmic staining. Proliferative activity of the investigated tumour was evaluated by the percentage ratio between the stained nuclei of breast carcinoma cells and the unstained ones.
Results: A weak positive correlation between vimentin expression and Ki-67 level was found ($r = 0.39$; $p < 0.05$). Due to heterogeneity of the group of analysed carcinomas all the cases were divided into immunohistochemical subtypes: luminal A subtype − 39 cases (30.2%), luminal B (Her2-) subtype − 36 cases (27.9%), luminal B (Her2+) subtype − 15 cases (11.6%), Her-2 subtype − 15 cases (11.6%), basal-like subtype − 24 cases (18.6%). We found a strong positive correlation between proliferative activity of a tumour and vimentin expression in Her-2 positive and basal-like subtypes ($r = 0.85$; $p < 0.05$; $r = 0.87$; $p < 0.05$ respectively). A weak negative correlation was found for cases from luminal A subtype ($r = -0.38$; $p < 0.05$). For other subtypes a fairly significant correlation between studied parameters was not found.
Conclusions: EMT mainly occurs in breast carcinomas with a high level of proliferation that reflects on the correlation between the presence of the vimentin expression and a high level of Ki-67, distinctive for basal-like and Her-2+ subtypes, associated with poor prognosis and a high risk of distant metastases development.
No conflict of interest.

1026 POSTER

Prognostic significance of heme oxygenase-1, S100A4 and syndecan-1 expression in primary non-muscle invasive bladder cancers

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Background: The prognosis of non-muscle invasive bladder cancer (NMIBC) is variable and significant proportions of patients undergo tumor recurrence and progression despite clinically complete transurethral resection. We have examined whether altered protein expression for three potential biomarkers, which are associated with different BC carcinogenesis pathway and have been studied by limited number of studies, could predict tumor recurrence and progression in patients with primary NMIBC.
Materials and Methods: The study included 109 patients who were diagnosed with primary NMIBC after clinically complete transurethral resection between 2000 and 2008 at our institute. After extensive and critical literature review regarding prognostic molecular markers based on immunohistochemistry and cDNA microarray in NMIBC, three molecular markers including heme oxygenase (HO-1), S100A4 and syndecan-1 (SYND1) were selected. Protein expression was analyzed by immunohistochemistry, and the immunoreactivity for each biomarker was evaluated using a semi-quantitative scoring system for both the intensity of the stain and the percentage of positive neoplastic cells. Survival analysis was performed using Kaplan–Meier curves and Cox regression to determine the effect of each marker on recurrence-free survival (RFS) and progression-free survival (PFS).
Results: The altered expressions for each marker were noted in 36 patients (33.0%) for HO-1, 40 (36.7%) for S100A4 and 69 (63.3%) for SYND1, respectively. Abnormal expressions of HO-1 and S100A4 were significantly correlated with higher T stage and grade, whereas SYND1 alteration was significantly with lower T stage and grade (all $p < 0.001$). On multivariate analysis including clinicopathological parameters and biomarkers, the three biomarkers were significant predictors for RFS while HO-1 and S100A4 were significant predictors for PFS. A combination analysis of three markers showed that patients with multiple ($\geqslant 2$) marker alteration was associated with significantly lower 5-year RFS (43.0%) and PFS (64.0%) rates than patients with none or single marker alteration (RFS: 78.1%, $p = 0.003$; PFS: 97.0%, $p < 0.001$). In protein-protein interaction analysis using BisoGenet, there were large protein network among the three markers.
Conclusions: Our findings indicate that immunohistochemical analysis for HO-1, S100A4 and SYND1 may be useful in predicting tumor recurrence and progression, thus planning treatment strategies in NMIBC.
No conflict of interest.

1027 POSTER

Role of C-reactive protein in advanced cancer prognostication

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Background: CRP, a non-specific marker of inflammation may help cancer prognostication. CRP is secreted by liver due to interleukin-1 (IL-1), IL-6 and tumor necrosis factor (TNF). It has been linked to shorter survival in some cancers. We examined associations between CRP levels and prognosis in solid tumors.
Material and Methods: Retrospective study of electronic medical records (EMR). Multiple CRP levels at a tertiary cancer center reviewed (2006–2011). Hematological cancer diagnoses excluded. Survival defined from the date with highest CRP to date of death. CRP reported as median (25^{th}, 75^{th} percentile). CRP reference range 0−10 mg/L.
Results: N = 6809 with solid tumors identified. 56% males. 83% Caucasian, 15% African American. Common cancers − genitourinary (GU) 29%, breast

14%, gastrointestinal (GI) 14%, lung 7%. Highest CRP for GI, GU, lung, breast = 8 (2, 15); 6 (2, 15); 3 (1, 8); 2 (1, 5) respectively. Median survival (months) = 13 (8, 30); 18 (11, 33); 16 (8, 27) and 25 (15, 41) respectively.
Conclusions: 1. Higher median CRP in GI, GU, lung and breast cancers.
2. Higher CRP associated with shorter prognosis across primary sites (even within reference range).
3. Inverse relationship between absolute CRP values and survival.
4. High CRP, an adverse prognostic indicator in most solid tumors.
No conflict of interest.

1028 POSTER

Atypical spitzoid melanocytic tumors versus spitzoid melanoma: Diagnostic and prognostic assessment by FISH analysis

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Background: The aim of our study was to evaluate whether molecular alterations detected by Fluorescence In Situ Hybridization (FISH) could be helpful in differentiating Atypical Melanocytic Spitzoid Tumors (AST) from Spitzoid Melanoma (SM) and performing risk assessment particularly for AST in order to a correct management of the patients.
Material and Methods: The study included 61 AST and 32 SM retrived from the files of the Department of Pathology-Istituto Nazionale Tumori-Milan from January 2010 up to March 2013. All cases were reviewed by two expert pathologists and analyzed by FISH technique using the 4-probe multicolour FISH DNA kit (Visys/Abbott Molecular®) targeting RREB1 (6p25), MYB (6q23), CCND1 (11q13) and CEP6. Sentinel lymph node biopsy (SLNB) was performed in 8 AST and 24 SM.
Results: Positive FISH result was found in 27 of 61 AST (44.6%) and 20 of 32 SM (62.5%). Gain of both CCND1 and RREB1 was the most common molecular alteration in AST (23%) and SM (75%). In AST series 4 (50%) out of 8 patients had metastatic involvement of sentinel node, 3 of them with positive FISH result. In SM series 7 (29%) out of 24 patients had metastatic involvement of sentinel node, 4 of them with positive FISH result. Furthermore molecular analysis of nonmetastasizing cases show that 1 of 4 AST (25%) and 10 of 17 SM (58.8%) had also positive FISH result. All patients affected by AST or SM with positive SLNB were alive with no evidence of disease at last follow-up.
Conclusions: Our study shows that FISH analysis is not really helpful in differential diagnosis of AST versus SM because we found positive FISH result in both lesions (AST 44.6% versus SM 62.5%) with the same molecular alteration (CCND1 and RREB1) as the most common. Furthermore we cannot use it as prognostic tool because of positive FISH result in both metastasizing and not metastasizing AST and SM. To validate the utility of FISH analysis for the differential diagnosis and risk assessment of AST versus SM a larger sample of cases of both series with prolonged follow-up need to be evaluated and tested by a broader spectrum of FISH probes.
No conflict of interest.

1029 POSTER

Evidence of cathepsin K (CTSK) in the aggressive development and invasion of pituitary adenomas

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Background: CTSK, cathepsin K, is a member of cysteine proteinases and has been found to be highly expressed in muscle and skeletal tissues. It has been indicated in the degradation of extracellular matrix and in particular protein component of bone matrix and that CTSK knockout mice has abnormalities in bone development and functions and resulted in increased fragility of bones. Pituitary adenomas are mostly benign with or without active endocrine functions. Located in the fossa of sphenoid bone, sella turcica, one of the key features of the pituitary adenomas is the invasion and destruction of the surrounding bones in the sella fossa. However, biological and molecular events involved in the destruction of sella fossa remains unclear. In the present study, we investigated expression of CTSK in pituitary adenomas with particular reference to invasion and destruction of sella fossa.
Materials and Methods: Pituitary adenomas were freshly collected immediately after surgery. Histological, radiological and biochemical analyses were carried out to provide clinical classification (Knosp's method) and to establish the endocrine status of the tumours. Expression of CTSK in pituitary tumours was determined using quantitative gene transcript analysis and analysed against tumour grade, invasion, Knosp grade, endocrine nature. Statistical analyses were conducted using Mann-Whitney U test and Kruskall-Walis method.
Results: Pituitary tumours which had invaded sphenoid sinus had a higher level of CTSK compare with those without invasion (median 14.8 vs 25.7). Likewise, using the Knosp classification, Stage 3 and 4 tumours which had signs of invasion showed high levels of CTSK than Knosp 0, 1 and 2 tumours (medians 25.7 vs 14.8). These links were independent of the size of tumours. It was interesting to observe that TSH-, gonadotrophin- and ACTH-secreting tumours had high levels of CTSK than endocrine-inactive tumours (70.1, 53.9 and 46.2 vs 20.9 respectively) and tumours secreting PRL and GH had lower levels (3.02 and 4.0 respectively). Finally, it was noteworthy that pituitary tumours with internal haemorrhage had lower levels of CTSK than those without haemorrhage (25.70 vs 4.0, $p < 0.05$), suggesting that CTSK is an unlikely candidate for this clinical condition.
Conclusions: It is concluded that Cathepsin K, an proteinase commonly involved in the regulation of bone absorption and bone pathology is over-expressed in pituitary adenomas which have aggressive pattern toward its surrounding bone tissues. This provides new direction in the understanding of the biology of pituitary tumours and their progression.
No conflict of interest.

Proffered Papers Session (Sat, 28 Sep) **Radiobiology/Radiation/PhysicsRadiotherapy Techniques**

1050 ORAL

Targeting hypoxia to enhance the anti-tumour effect of a stereotactic radiation schedule

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Background: Hypoxia in tumours is well known to reduce the efficacy of radiation therapy. Recent studies suggest that such hypoxia may play a more significant role when radiation is given as large doses/fraction. The aim of this study was to use clinically relevant approaches for eliminating hypoxia to see if they could improve tumour response to a stereotactic radiation schedule.
Material and Methods: A C3H mammary carcinoma grown in the right rear foot of female CDF1 mice was used in all experiments. Treatments were performed in restrained non-anaesthetised animals when tumours had reached 200 mm^3 in size. Tumours were locally irradiated (230 kV x-rays) with 3 x 15 Gy (each fraction given with an interval of 2−3 days over a one week period). Hypoxic modification was achieved by intraperitoneally (i.p.) injecting the radiation sensitizer nimorazole (200 mg/kg), combining the oxygen modifiers nicotinamide (120 mg/kg; i.p.) and carbogen (95% O_2 + 5% CO_2) breathing, using the hypoxic cytotoxin hyperthermia (41.5^{O}C; 1-hour), or injecting the vascular disrupting agent OXi4503 (10 mg/kg; i.p.). Three days after the final irradiation the tumours were subjected to a clamped top-up dose which involved giving graded radiation doses with the tumour bearing leg clamped for 5 minutes before and during irradiation. The percentage of mice in each treatment group showing local tumour control 90 days after irradiating was recorded and the TCD50 values (radiation dose to control 50% of tumours) estimated from the clamped top-up radiation dose response curves. A Chi-squared test ($p < 0.05$) was used to determine significant differences between the TCD50 values.
Results: The clamped top-up TCD50 value (with 95% confidence intervals) following 3 x 15 Gy was 30 Gy (23−38). This was significantly reduced to 6 Gy (3−10) when nicotinamide (injected 20 minutes prior to irradiation) and carbogen breathing (starting 5 minutes before radiation and continued during each radiation period) were combined; to 9 Gy (5−17) by heating tumours 4-hours after each radiation treatment; and 12 Gy (8−19) if OXi4503 was injected 1 hour after each irradiation. The value obtained when nimorazole was injected 30 minutes prior to irradiation is currently under analysis.
Conclusions: Targeting hypoxia is a very effective method for improving the efficacy of radiation given in a stereotactic schedule. This enhancement also seemed to be relatively independent of the hypoxic modifier used.
Supported by grants from the Danish Cancer Society and the Danish Council for Independent Research: Medical Sciences.
No conflict of interest.

1051 ORAL

EGFR-amplification correlates with response to combined treatment of fractionated irradiation and EGFR-inhibition in HNSCC tumour xenografts

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Background: With the aim to identify potential biomarkers for the improvement of local tumour control by simultaneous EGFR inhibition during fractionated irradiation, 10 different HNSCC tumour xenografts are evaluated for local tumour control after irradiation with or without EGFR inhibition, while simultaneously investigating factors that might influence the response. Results of the first 5 tumour models are already published (Gurtner et al., Radiother Oncol 2011 (99):323–330) and revealed a correlation between EGFR-amplification (EGFR-CEP-7 ratio) and response to combined treatment of irradiation and EGFR-Inhibition with cetuximab. Here we present an update of the data on a total of 8 tumour models and a comparison of EGFR gene amplified versus non-amplified tumours.
Material and Methods: For evaluation of local tumour control dose 50% (TCD_{50}) 120 days after treatment tumours were treated with fractionated irradiation (RT) (30f/6 weeks) alone or combined with application of the monoclonal EGFR-antibody cetuximab (1 mg, weekly, i.p.). For tumour growth delay and relative tumor volume cetuximab was applied alone (once d0 or 4x d0, d2, d5, d7). Results were compared with molecular data on fluorescense-in situ-hybridisation (FISH) and immunohistochemistry.
Results: A significant improvement of local tumour control could be observed for the combined treatment of RT and cetuximab compared to RT alone in all 3 tumours harbouring an EGFR gene amplification. The enhancement ratios for the TCD_{50} after irradiation alone versus irradiation plus cetuximab were 2.0 (CAL-33), >40 (UT-SCC-14) and >44 (UT-SCC-8). In only 2 of the 5 tumour models without EGFR gene amplification local tumour control was improved by simultaneous Cetuximab application.
Conclusion: EGFR gene amplification appears as a promising biomarker for prediction of the improvement of local tumour control by combined fractionated irradiation and Cetuximab treatment. However, using this biomarker alone would result in some false-negative predictions, as also the group of non-amplified tumours contains some responder models. Thus, further biomarker evaluation is warranted to improve the validity especially in the latter subgroup of tumours.
Supported by Deutsche Forschungsgemeinschaft (DFG-PAK190).
No conflict of interest.

1052 ORAL

Myeloid cells as a novel determinant of hypoxic radioresponse in colorectal cancer cells through L-arginine turnover

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Introduction: Tumor-associated myeloid cells may undergo antitumor M1 or protumor M2 polarization linked to the alternative L-arginine turnover through inducible nitric oxide synthase (iNOS) and arginase-1 (ARG) respectively. The former pathway is known to result in production of nitric oxide (NO), a potent inhibitor of mitochondrial respiration. This study explored the ability of M1 versus M2 macrophages to affect radioresponse of colorectal cancer (CRC) cells in a model of metabolic hypoxia, and screened the iNOS/ARG signature of mouse and human tumor-associated myeloid cells.
Material and Methods: Mouse peritoneal macrophages were polarized to M1 and M2 types by exposure to IFN-γ/LPS or IL-4 respectively, and profiled by RT-PCR. CRC cells and macrophages were placed in a tissue-mimetic co-culture system (TMCS), wherein metabolic hypoxia was induced under limited oxygen diffusion. Oxygen depletion was assessed by fluorescence, and hypoxic radioresponse to 0−12 Gy by colony formation assay. ARG+ myeloid cells were phenotyped by FACS in colon CT26 mouse tumors and in 10 rectal cancer patients.
Results: M1 stimuli increased in macrophages the mRNA levels of iNOS, IL-6, IL-12α and IL-12β by 49700, 220, 260 and 740-fold respectively, and NO/nitrite output above 40 μM. M2 macrophages showed the up-regulation of ARG, Ym1, Fizz1 and CCL17 by 20, 499, 118 and 72-fold respectively, and no iNOS activation. In the TMCS, M2 macrophages significantly contributed to oxygen consumption and hypoxic radioprotection in CRC cells up to 2.5-fold, as compared with aerobic cells. Contrasting, M1 macrophages were able to uniformly restore impaired radioresponse of mouse CT26 and human DLD-1, HT29, HCT116, and SW480 CRC cells through NO-induced arrest of oxygen consumption resulting in oxygen sparing. The radiosensitizing effect was entirely attributed to iNOS+ macrophages since all CRC cell lines failed to activate the iNOS/NO pathway in the presence of M1 stimuli. In CT26 tumor-bearing mice, the myeloid $CD11b^+Gr\text{-}1^+$ subset underwent M2-type polarization marked by ARG activation. In cancer patients, whole blood CD15+ granulocytes displayed ARG overexpression and accelerated L-arginine turnover (up to 3-times), as compared with healthy donors.
Conclusions: CRC is associated with the predominant expansion of ARG+ myeloid cells that feature radioprotective properties and compete for L-arginine, thereby compromising the radiosensitizing potential of iNOS+ myeloid cells.
No conflict of interest.

1053 ORAL

A validated score predicting short survival (death within 30 days) after palliative radiotherapy: Better health economics and less overtreatment

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Background: Radiotherapy (RT) might palliate symptoms from incurable cancer. Its use should be tailored to prognosis and avoided in the terminal phase of disease. Survival prediction is challenging and recent reports have disclosed overutilization of RT during the final 30 days of life. Decision aids predicting short survival might help to avoid overtreatment.
Material and Methods: Uni- and multivariate analyses of factors predicting use of RT during the final 30 days of life for all palliative RT courses (metastatic or non-metastatic) administered at Nordland Hospital between 20.06.2007 (opening of radiation oncology unit) and 31.12.2009. Development of a predictive model by recursive partitioning analysis (RPA) and independent validation of its performance in patients treated during 2010 and 2011.
Results: We analysed 579 palliative RT courses given in the time period 2007–2009. Of these, 25 (4%) remained incomplete (typically because of clinical deterioration). Median survival was 6.3 months. In 53 cases (9%) RT was administered in the final 30 days of life. In univariate analysis, 19 factors were significantly associated with this endpoint. Multivariate analysis confirmed performance status (PS), primary tumour type, liver metastases, known disease progression outside the actual RT volume(s), steroid use, opioid analgesic use, serum haemoglobin, c-reactive protein and albumin levels as independent predictors for use of RT in the final 30 days of life. RPA resulted in a model consisting of 6 parameters (low haemoglobin, opioid analgesic use, ECOG PS 3−4, known progressive disease, steroid use, lung (small or non-small cell) or bladder cancer), which correctly identified 75% of RT courses administered during the final 30 days of life. Maximum survival of patients fulfilling all criteria was 69 days. Death within 40 days occurred in 83%. In the independent validation data set (2010–2011) these figures were 74% (30 days), 84% (40 days) and 100% (92 days).
Conclusions: Assigning the right patient to the right palliative approach is challenging. Based on our results, we suggest that patients with lung or bladder cancer with ECOG PS 3−4, low haemoglobin, progressive disease outside the actual RT volume, and on steroids and opioids are at high risk of dying shortly after initiation of RT. Our model facilitates decision making (best supportive care versus RT) and is the first decision aid specifically addressing RT in the final 30 days of life.
No conflict of interest.

1054 ORAL

Reduction of heart dose during left breast cancer radiotherapy: comparison between respiratory gating RT and IMRT

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Background: Breast conserving surgery and post-operative whole breast radiotherapy (RT) have proved to reduce local recurrence and improve survival of early stage breast cancer patients. It has also been demonstrated that long-term survivors have a significantly higher risk of cardiac death as a consequence of heart irradiation during left breast tangential RT. Novel technologies, such as prospective respiratory gating RT (PGRT) and intensity modulated radiotherapy (IMRT), provide a chance to reduce heart doses. This study compares the cardiac dose delivered by a standard 3D conformal tangential radiotherapy (CRT) to that delivered by PGRT or a 5 fields-IMRT.

Material and Methods: Patients with early left breast cancer, referred for adjuvant radiotherapy to our Institution, were enrolled in this study. For each patient, two simulation CT-scans were acquired: the first during free breathing and the second on prospective gating during deep inspiration breath-hold. The scans were monitored by the Varian RPM^{TM} respiratory gating system. For each patient, three treatment plans were performed: a 3D-CRT plan and an IMRT plan, based each on the free-breathing scan, and a PGRT plan based on the deep inspiration breath-hold scan. Mean heart dose (MHD), heart V_{25} and mean dose to the controlateral breast were evaluated. Dose-volume histograms were compared by the Friedman test.
Results: 44 patients were enrolled. Median age was 52 years (range 34−76), the mean breathing period was 4.3s (range 2–12.9), and the mean 4DCT scanning time was 12.5 s (range 10–16.5). Overall patients' compliance to respiratory gating technique was good. The median MHD was 3 Gy (range 1.22–7.38) in the CRT plans, 1.9 Gy (range 0.50–3.60) in the PGRT plans and 4.13 Gy (1.12−8.5) in IMRT plans ($p < 0.001$). The mean heart V_{25} was 1.06% (range 0−9.7), 0% (range 0−2.7) and 0.1% (range 0–5.82) for CRT, PGRT and IMRT plans, respectively ($p < 0.001$). Mean and maximum doses to the controlateral breast was 0.79 Gy (range 0.02−2) and 6.97 Gy (range 0.25–13.8) for the PGRT plans, and 1.98 Gy (0.05–5.38) and 9.39 Gy (range 3.73–20.57) for the IMRT plans ($p < 0.001$).
Conclusions: In this study the prospective gating tangential RT to left breast proved to offer the better dose sparing of heart, with also a lower irradiation of the controlateral breast.
No conflict of interest.

1055 ORAL

Present and future radiation therapy infrastructure in Europe: a wake up call to cut the mustard?

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Background: Radiation therapy (RT) is required in 50% of newly diagnosed cancer patients and 25% of those previously irradiated. The present status of teletherapy (TRT) units in 33 countries of Europe was recently published. To further look into a complete RT scenario with TRT and brachytherapy (BRT) units and manpower − radiation oncologist (RO), medical physicist (MP) and radiotherapy technologist (RTT) as exists today and projected needs till 2020, a comprehensive analysis for European countries was carried out.
Material and Methods: Data for 40 European countries, whose individual cancer incidences, equipments and manpower were available in the databases of GLOBOCAN and DIRAC were analysed. Norms recommended by IAEA and ESTRO-QUARTS were used to ascertain the adequacy of RT facility for each country.
Results: The combined outcome of these countries is summarized in the table.

Parameter	Total	Range (min to max)
Cancer incidence[2]	3,377,743	1,378 to 493,853
RT needed	2,111,089	861 to 308,658
TRT listed[3]	3,638	2, 529
TRT required	4,691	2, 686
Deficit in TRT	1,053	−283 to 59
BRT listed[3]	700	0 to 94
BRT required	1,055	1 to 154
Deficit in BRT	355	−95 to 7
RO listed[3]	7,399	2 to 1,218
RO required	7,037	3 to 1,029
Deficit in RO	Nil	−501 to 488
MP listed[3]	3,823	2 to 744
MP required	5,278	2 to 722
Deficit in MP	1455	−504 to 46
RTT listed[3]	13,213	4 to 4,241
RTT required	14,074	6 to 2,058
Deficit in RTT	860	−1,728 to 2,809

[2] http://globocan.iarc.fr

[3] http://www-naweb.iaea.org/nahu/dirac/default.asp

Additional number of TRT units, BRT units, RO, MP and RTT required by 2020 are 1661, 492, 550, 2138, and 2685 respectively.
Conclusions: None of the 40 countries have presently an all inclusive recommended number of RT units and manpower. While in some, the deficiencies are marginal, in others, a gross lack or imbalance of either manpower or treatment units or both were detected. This could lead to long RT waiting list, inadequate implementation of specialized RT techniques like IMRT, possibility of compromise on quality of RT and in some cases to even resort to 'fill in the RT waiting list' by chemotherapy. All these could seriously affect the treatment outcomes and nullify the efforts of early detection and treatment. Thus, in view of the imminent rise in cancer incidence during the next decade and the projected needs, adequate steps are highly desirable at individual country level or jointly to provide optimal RT access to all patients.
No conflict of interest.

Society Session (Sun, 29 Sep)
European Society for Therapeutic Radiology and Oncology (ESTRO)

1056 ORAL

VARIAN AWARD: Prediction of normal tissue morbidity in radiotherapy of prostate cancer using motion-inclusive dose distributions

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Background: In radiotherapy (RT) of prostate cancer the key organs at risk (ORs) − the rectum and the bladder − display considerable motion, which may influence the dose/volume parameters predicting for morbidity. In this study we compare motion-inclusive doses to planned doses for the rectum and the bladder and explore their associations with prospectively recorded morbidity.
Material and Methods: This study included 38 prostate cancer patients treated with hypo-fractionated image-guided intensity-modulated RT that had an average of nine (7−10) repeat CT scans acquired during treatment. These scans were registered to the respective treatment planning CT (pCT), based on rigid registration (translations) on intra-prostatic fiducial gold markers, followed by a new dose calculation on the repeat CT geometry. One motion-inclusive dose distribution was assessed for each patient and structure (rectum, rectum wall, bladder and bladder wall) by averaging over the, on average nine, motion-inclusive dose-volume histograms. The pCT volumes, the treatment course averaged volumes as well as the planned and motion-inclusive dose distributions were associated with acute and late morbidity (morbidity cut-off: $\geqslant$ Grade 2) using logistic regression.
Results: Acute rectal morbidity (observed in 11 (29%) patients) was significantly (p£0.05) associated with smaller treatment course averaged rectal volumes (population median: 75 vs. 94 cm^{-3}). Furthermore the motion-inclusive rectal wall volume receiving doses close to the prescription dose (2 Gy-equivalent dose of 76 Gy (a/b=3 Gy)) was also significantly associated with this morbidity end-point.
Conclusions: To the best of our knowledge, this study is the first to show that motion-inclusive DVH parameters are better predictors than DVH parameters based on the 'static' planning CT along. Both findings of the study are plausible − smaller rectal volumes are likely to be related to a more stable portion of this organ being located in the high-dose volume high and a high-dose relation with morbidity is in agreement with the QUANTEC study − increasing the credibility of the findings despite the modest patient number. This study indicates that the deviations between planned and delivered dose/volume parameters − caused by internal organ motion − should be accounted for to improve the ability to predict morbidity following RT.
No conflict of interest.

1057 ORAL

ACCURAY AWARD: Targeting radiation resistance in p53 mutant tumours

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Background: Increasing our understanding of how resistance to treatment occurs, helps us develop more efficient and personalised therapeutic regimes for cancer patients. Through molecular dissection of events that drive tumour initiation and progression, we have uncovered a functional connection between the most frequent oncogenic mutations that are likely to contribute to therapeutic resistance in 30% of all human tumours. Mutations activating the 'AKT/PI3K' signalling pathway and inactivation of

the '*TP53*' tumour suppressor gene are common mechanisms that cancer cells require to proliferate and escape pre-programmed cell death. Tumours employ many strategies to inactivate p53; however sequence mutations that result in mutant p53 protein (p53mut) are most often observed. p53mut tumours not only fail to respond to DNA damaging therapy, but are also described to promote therapeutic resistance by dominant negative suppression of p53 dependent promoter activity. We find that in combination these events lead to therapeutic resistance that is reversible by the AKT clinical candidate, MK-2206 and the PI3K inhibitor PI-103.
Methods: Using a combination of *in vivo* and *in vitro* techniques we have tracked the molecular mechanism for AKT mediated resistance to treatment in solid tumours. This has helped us to simultaneously derive potential biomarkers that could highlight where the greatest efficacy may be achieved in clinical practise.
Results: We demonstrate that AKT inhibition promotes reduced levels of p53mut in tumour cells via a novel regulation of the 'tumour suppressor' p14ARF and promotes re-engagement of cell cycle arrest, senescence and increased sensitivity to ionising radiation in both *in vivo* and *in vitro* systems. We also show that PI3K/AKT inhibitors- and as proof of concept, the clinical candidate AKT inhibitor, MK-2206, and PI3K inhibitor, PI-103, are effective in treatment of mice with therapeutically resistant tumours with elevated AKT and carrying p53mut.
Conclusions: We show that targeting the PI3K/AKT pathway sensitise xenografts carrying p53 mutations to DNA damaging therapy. We have also been identifying potential molecular markers to select the cohort of patient most likely to benefit best from this treatment.
No conflict of interest.

Poster Session (Mon, 30 Sep)
Radiobiology/Radiation/PhysicsRadiotherapy Techniques

1058 POSTER

CBCT-based internal gross tumor volume definition for radiotherapy of of non-small-cell lung cancer: Comparison with target volumes based on three-dimensional CT and four-dimensional CT

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Background: To evaluate the amount of respiration information included in CBCT and investigate the use of CBCT c-ombined with 3DCT and 4DCT in the definition of target volumes.
Materials and Methods: Thirty-first patients with NSCLC sequentially underwent 3DCT and 4DCT simulation scans of the thorax during free breathing. A 3D conformal treatment plan was created based on 3DCT. The first CBCT was performed and registered to the planning CT using the bony anatomy registration. All contours were performed by a radiation oncologist using the same contouring protocol. GTV-3D and GTV-50 were contoured based on 3DCT and end-expiration phase (50% phase) of 4DCT. Internal GTVs (IGTV-MIP and IGTV-CBCT) were contoured based on maximum intensity projection (MIP) of 4DCT and CBCT. The differences in the position, size, and degree of inclusion (DI) of different volumes were compared.
Results: The mean size ratio of GTV-3D, GTV-50, IGTV-MIP to IGTV-CBCT were 0.77 ± 0.18, 0.84 ± 0.2, 1.1 ± 0.26 respectively for tumors in the upper lobe and 0.67 ± 0.11, 0.65 ± 0.18, 1.17 ± 0.27 respectively for tumors in the middle and lower lobe. The motion vector showed a significant correlation to the ratio of GTV-50 to IGTV-CBCT ($r = -0.45$, $p = 0.012$) for all the patients. DIs of GTV-3D, GTV-50, IGTV-MIP in IGTV-CBCT were 0.65 ± 0.27, 0.65 ± 0.2 and 0.62 ± 0.2, while DIs of IGTV-CBCT in GTV-3D, GTV-50, IGTV-MIP were 0.47 ± 0.2, 0.49 ± 0.2 and 0.67 ± 0.19 respectively.
Conclusion: The tumor motion included in CBCT is significantly larger than 3DCT and end-expiration phase of 4DCT, but less than 4DCT MIP. CBCT can include the respiration motion information well compared to 4DCT MIP. The use of 3DCT registered to CBCT, or 4DCT registered to CBCT based on bony anatomy in radiotherapy may result in a severe target miss, which should be focused on when we perform adaptive radiotherapy and rectify treatment planning.
No conflict of interest.

1059 POSTER

Comparison of internal target volumes defined on three-dimensional CT, four-dimensional CT and cone-beam CT images of non-small-cell lung cancer

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Background: To compare positional and volumetric differences of internal target volumes defined on three-dimensional CT (3DCT), four-dimensional CT (4DCT) and cone-beam CT (CBCT) images of non-small-cell lung cancer.
Materials and Methods: Thirty-first patients with NSCLC sequentially underwent 3DCT and 4DCT simulation scans of the thorax during free breathing. A 3D conformal treatment plan was created based on 3DCT. The first CBCT was performed and registered to the planning CT using the bony anatomy registration. All contours were performed by a radiation oncologist using the same contouring protocol. GTVs were contoured based on 3DCT, maximum intensity projection (MIP) of 4DCT and CBCT. CTV3D, ITVMIP and ITVCBCT were defined with a 7 mm margin accounting for microscopic disease. ITV10 mm and ITV5 mm were defined based on CTV3D. ITV10 mm with a 5 mm margin in LR, AP directions and 10 mm in CC direction; ITV5 mm with an isotropic internal margin (IM) of 5 mm. The differences in the position, size, Dice's similarity coefficient (DSC) and inclusion relation of different volumes were compared.
Results: The median size ratio of ITV10 mm, ITV5 mm, ITVMIP to ITVCBCT were 2.33, 1.88, 1.03 respectively for tumors in the upper lobe and 2.13, 1.76, 1.1 respectively for tumors in the middle-lower lobe. The median DSC of ITV10 mm, ITV5 mm, ITVMIP and ITVCBCT were 0.6, 0.66 and 0.83 for all patients. The median percentage of ITVCBCT not included in ITV10 mm, ITV5 mm, ITVMIP were 0.1%, 1.63% and 15.21% respectively, while the median percentage of ITV10 mm, ITV5 mm, ITVMIP not included in ITVCBCT were 57.08%, 48.89%, 20.04%. The median percentage of ITVCBCT not included in ITV5 mm were 1.24% for tumors in the upper lobe and 5.8% for tumors in the middle-lower lobe ($p = 0.404$).
Conclusion: The individual ITV derived from 4DCT can't encompass the ITV from CBCT effectively, and using 4DCT ITV in radiotherapy may result in a target miss. The ITVs derived from 3DCT with istropic margins can encompass the CBCT ITV, but the size of 3DCT ITVs was far greater than the CBCT ITV. It is feasible to generate the 3DCT ITV with an isotropic IM of 5 mm for tumors in the middle-lower lobe.
No conflict of interest.

1060 POSTER

A correlation study on target displacement and its influencing factors of primary thoracic esophageal cancer during radiotherapy based on repeated four-dimensional CT scan

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Background: To investigate the correlation between the motion of gross tumor volume(GTV)and the tumor volume, length, the largest diameter of lesion in CT image with enhanced four dimensional computed tomography (4DCT) scanning during fractionated radiotherapy.
Material and Methods: Thirty-two patients with thoracic segment esophageal carcinoma were divided into upper (9 patients), middle (14 patients) and distal (9 patients) esophageal tumors, enhanced 4DCT were performed after every ten fractions. The gross tumor volume (GTV) were delineated by the same radiotherapist on each of the 10 4DCT phase, the displacements in left-right (LR), anterior-posterior (AP), senior-inferiors (SI) directions and three-dimensional vector were calculated, the tumor length and the largest diameter of lesion were also calculated. Then, investigate the correlation between the motion of GTV and the tumor volume, length, the largest diameter of lesion for every fraction.
Results: The correlation were not significantly between the motion of GTV and the tumor volume for the first positioning, the tenth fraction and the thirtieth fraction; but the correlation was significantly to the distal segment for the twentieth fraction in the LR direction ($r = 0.731$,$P = 0.040$). The correlation were not significantly between the motion of GTV and the tumor length for the first positioning, the tenth fraction and the thirtieth fraction; but the correlation was significantly to the upper and distal segment for the twentieth fraction in the SI direction($r = 0.714$,$p = 0.031$;$r = 0.646$,$p = 0.044$), the correlation was also significantly to the distal segment for the twentieth fraction in the LR direction($r = 0.765$,$p = 0.027$). The correlation were significantly between the motion of GTV and the largest diameter of lesion to all patients for the first positioning in LR, SI and three-dimensional vector ($r = 0.373$,$p = 0.036$;$r = 0.377$,$p = 0.033$;$r = 0.415$,$p = 0.018$), but the correlation were not significantly for the tenth fraction, the twentieth and the thirtieth fraction.

Conclusion:s There have an correlation between the primary tumor displacements and the tumor volume, length and the largest diameter of lesion during the radiotherapy, but the appearance of time and the degree of correlation were different.
No conflict of interest.

1061 POSTER

Research of primary thoracic esophageal tumor volume variance during radiotherapy based on reduplicated four-dimensional CT scan

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Background: To investigate the volume variation of primary thoracic esophagus carcinoma with enhanced four dimensional computed tomography (4DCT) scanning during fractionated radiotherapy.
Material and Methods: Thirty-two patients with thoracic segment esophageal carcinoma were divided into upper (9 patients), middle (14 patients) and distal (9 patients) esophageal tumors, enhanced 4DCT were performed after every ten fractions. The gross tumor volume (GTV) were delineated by the same radiotherapist on each of the 10 4DCT phase, $IGTV_{MIP}$ was the contour delineated from the maximum intensity projection (MIP), all 10 GTVs were combined to form $IGTV_{10}$, GTV_{mean} was the average of all 10 phases of each GTV.
Results: The majority of the GTV_{mean}, $IGTV_{MIP}$ and $IGTV_{10}$ were decreased with increasing fractions during radiotherapy based on repeated 4DCT scanning, but the volume change was different in different positions or different fractions. GTV_{mean} increased by 4.20–39.42% (1.31–7.44 cm^3) at the tenth fraction for 21.87% (7/32) patients, and the differences were significant ($t = -4.753$, $P = 0.003$). Except the upper esophageal tumors, statistical significance were existed in GTV_{mean}, $IGTV_{MIP}$ and $IGTV_{10}$ for all patients between the twentieth fraction and the first positioning (all $P<0.05$).
Conclusions: Repeated 4DCT scanning could not only observed the volume variance of primary tumor GTV without motion information, but also observed IGTV volume change. For primary middle and distal esophageal cancer, the best time to reset position should be selected at twentieth fraction when the primary tumor target volume changed significantly, and it was preferable to guide target correction and planning modification.
No conflict of interest.

1062 POSTER

Radionuclide therapy in cancer patients with bone metastases

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Aim: We submit our experience in the application of radionuclides for therapy of bone metastases of cancer patients with different foci of appearance of the cancer process: breast cancer, prostate cancer, lung cancer and others.
Material and Method: In 167 patients with bone metastases we used 32-P in 71 patients and 89-Sr in 96 patients. 93 are women and 74 are men; 90 women are with cancer of the breast, 52- with prostate cancer, 24 are with lung cancer and 1 with renal cell carcinoma. All patients are observed for side effects when an application of a radiopharmaceutical is done-32-P per os and 89-Sr intravenous, as well as for the changes of haemoglobin, leucocyte and thrombocyte count.
Results: One months after the radionuclide therapy we observed a significant reduction of the leucocyte and thrombocyte count in the group accepted 32-P ($t = 3.83$, $p < 0.05$; $t = 5.29$, $p < 0.001$). For the group, where 89-Sr is applied we did not calculate statistically significant decrease of the tested indicators mentioned above. At the same time the basic reason for which the radionuclides are applied- pain, decreases in intensity and patients return to their normal activity.This is more typical for patients with cancer of the breast and prostate cancer.
Discussion: The serious symptom 'pain' is influenced by the not so high applied activity of 2 mCi of 32-P speaks in favour of the use of this radiophar-maceutic, although there is a resistance among authors of its application with regard to myelosuppression. According to our observations it is light, the blood indicators restore quickly even without special therapy and patients can take the advantage of this additional method to overcome pain syndrome. The intravenous applicaton of 89-Sr in activity of 4 mCi also influences pain in a very good way, but the price per patient is high and all patients wait for an reimbursement from the health insurance. This is a significant factor for wider use. The use of 32-P is cheaper but the delivery stopped and for the moment we can use only 89-Sr.
Conclusion: The application of 32-P and 89-Sr is additional possibility for the treatment of pain due to bone metastases of cancer patients- easy and effective especially for those that are not treated effectively after local irradiation. The myelosuppressive effect is not statistically significant and both isotopes can be used successfully in the treatment of pain in cancer patients.
No conflict of interest.

1063 POSTER

Influence of radiotherapy on frequency of sister chromatid exchange, micronuclei and binuclear cells in breast cancer patients

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Purpose: Sister chromatid exchange (SCE) is a mutual segment exchange which occurs between two chromatids of sister chromosome that does not change the structure of the chromosome morphologically. Micronucleus (MN) is round objects stemming from nucleus and located in cytoplasm outside the main nucleus. Few studies have previously analyzed the effect of chemotherapy or radiotherapy on SCE or MN frequencies in breast cancer patients. The aim of this study was to evaluate any cytogenetic change in SCE, MN and binuclear cell (BNC) of peripheral blood lymphocytes in breast cancer patients treated with postoperative radiation therapy (RT).
Material and Methods: Frequency of the SCE, MN and BNC were examined in 22 breast cancer patients received RT and 10 healthy individuals. All parameters were measured before (RT-a), at the completion of (RT-b) and three months after the completion of (RT-c) RT. Median patient age was 47.5 (range: 29−58), and 13 (59%) were pre-menopausal, 9 (41%) were post-menopausal. Median RT dose was 50 Gy (range: 50−66). Eighteen (82%) patients received chemotherapy in addition to radiotherapy.
Results: A significant difference emerged in SCE ($p = 0.008$) and MN ($p = 0.004$) between RT-a and control groups. No statistical difference observed in BNC frequencies in breast cancer patients compared to control group.
Compared to the control group there was a significant increase in SCE frequencies in RT-b ($p = 0.008$) and RT-c ($p = 0.005$). There was also a significant increase in SCE frequencies in RT-b ($p = 0.001$) and RT-c ($p = 0.001$) values compared to RT-a measurements. There was not any statistically significant difference in the SCE frequencies between RT-b and RT-c measurements.
The frequencies of MN were also significantly higher in RT-b ($p = 0.005$) and RT-c ($p = 0.005$) than in control group. The MN frequencies were significantly increased in the RT-b compared to RT-a ($p = 0.001$). However, there was not any statistically significant difference in MN frequency between RT-a and RT-c measurements. MN levels decreased to pre-RT levels three months after completion of treatment.
No significant difference in BNC was observed between control group and any study group values.
MN decreased significantly at RT-c compared to RT-b ($p = 0.001$). No statistically significant difference was observed in MN frequencies between RT-a and RT-c (Table).
Conclusion: Increasing MN and SCE frequencies following radiotherapy is an expected situation. Decrease in MN frequency at 3-month after the completion of RT suggests that expected repair continues. Persistent SCE at the same period suggests that recovery in SCE has not completed yet and a longer period of time is needed.
No conflict of interest.

1064 POSTER

Unilobar transarterial radioembolization versus portal vein embolization for induction of contralateral liver hypertrophy in patients with secondary liver malignancies − a matched-pair analysis

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Background: Selected patients with liver malignancies can be cured by surgical resection. In case of a small-sized future liver remnant (FLR), portal vein embolization (PVE) of the tumour-bearing liver is used to induce hypertrophy of the contralateral lobe but leaves the tumour untreated and may even stimulate tumour growth. Unilobar transarterial radioembolization using Y90-labelled resin microspheres (RE) treats the tumour in the embolized lobe, reducing the risk of tumour progression, and has also been demonstrated to produce hypertrophy of the contralateral lobe. However, contralateral hypertrophy induction with these two modalities has never been compared directly. We performed a matched-pair analysis to compare the capacity for contralateral hypertrophy induction of PVE vs. RE.

Methods: Patients with secondary liver malignancies limited to the right lobe who were treated by right-lobar PVE (n = 141) or RE (n = 35) were matched according to the following criteria known to have an impact on liver regeneration following PVE: (i) Baseline FLR/Total liver volume ratio, (ii) prior platinum-containing chemotherapy, (iii) inclusion of liver segment 4 in the treatment, and (iv) baseline platelet count.The relative change in FLR volume from baseline to follow-up 4−6 weeks after treatment was calculated and compared between treatment groups using a one-way ANOVA.
Results: 21 fully matched pairs of patients were identified. After matching, minor differences between the PVE and RE groups were still seen in the interval between treatment and follow-up imaging, embolized liver volume, body weight, prevalence of colorectal cancer as the primary cancer site, and number of prior chemotherapy lines; however, covariate testing revealed none of these factors to have an impact on relative volume change in the contralateral liver lobe, indicating that the criteria used for matching resulted in two well comparable cohorts of PVE and RE patients. Baseline and post-treatment FLR volume as well as relative change in FLR volume before/after treatment are shown in table. The increase in FLR volume from baseline to follow-up was significant with both modalities but PVE produced significantly more FLR volume gain than RE (68.7 vs. 34.2%, p < 0.001). None of the RE patients demonstrated tumor progression in the embolized lobe at follow-up imaging.

	RE		PVE		
	Mean	SD	Mean	SD	
FLR baseline (mL)	246.1	115.6	287.1	84.3	
FLR post treatment (mL)	317.8	141.1	474.9	143.5	
Change from baseline (%)	+34.2	28.6	+68.7	39.0	<0.001
p(change from baseline within treatment)	<0.001		<0.001		

Conclusions: Our study shows for the first time that unilateral RE is inferior to PVE in terms of contralateral hypertrophy induction. However, contralateral hypertrophy induced by RE is substantial and RE minimizes the risk of tumour progression in the treated lobe, possibly making it a suitable modality for selected patients who need preoperative FLR hypertrophy induction and whose liver tumours are at risk of becoming locally unresectable in case of progression.
Conflict of interest: *Other substantive relationships: B. Garlipp has received lecture fees from SIRTEX Medical Ltd., J. Ricke has received lecture fees and research funding from SIRTEX Medical Ltd.*

1065 POSTER

Predictive nomogram for heterotopic ossification following radiation prophylaxis of traumatic acetabular fractures

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Purpose: To report clinically predictive model for heterotopic ossification (HO) in patients (pts) who have undergone surgical repair and radiation (RT) prophylaxis after traumatic acetabular fracture (TAF).
Methods: Between 1995 and 2010, 737 pts were eligible to our study. All underwent surgery followed by prophylactic post-operative RT after TAF. All pts received a single fraction of 7 Gy within 72 hours from surgery, prescribed to mid-plan without bone shielding. The data collected on each patient (24 categories in all) included: age, gender, race/ethnicity, body mass index (BMI), type of injury, time between injury and surgery, time between surgery and RT, use of indomethacin, NSAIDs, and narcotic, hip fracture, Brooker grade, etc.
Results: A logistic regression model was constructed and internally validated with bootstrapping techniques. Statistically significant predictors for HO were age, BMI, narcotic use, time interval between surgery and RT, and bilateral vs. unilateral acetabular fracture. The parameters in the final model were: age (coefficient=0.0211, standard deviation (SD)=0.0069, p = 0.0021), BMI (coefficient=0.0766, SD=0.0180, p < 0.0001), surgery to RT in days (coefficient = 0.1379, SD = 0.0968, p = 0.1546), bilateral vs. unilateral fracture (coefficient = −0.8683, SD = 0.3381, p = 0.0102), narcotic use (coefficient=0.7078, SD=0.2354, p = 0.0026). The area under the 'receiver operating characteristic' curve (AUC) for the predicted probability of HO was 0.731 (95% CI 0.70–0.76). The model calibrated well and demonstrated adequate discriminative ability.
Conclusion: This predictive nomogram provides a precise algorithm to predict the risk of HO. Prophylactic RT is an effective modality for HO prevention, however, patients' age should be wisely considered because of scattered RT dose to the reproductive organs (ovaries and testicles) and the risk of RT induced malignancies.
No conflict of interest.

1066 POSTER

Combination of topotecan and chronomodulated radiotherapy for treatment of xenografted human nasopharyngeal carcinoma

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Background: Nasopharyngeal carcinoma (NPC) is a malignant disease of the head/neck region and radiotherapy is the predominant treatment strategy. Here we reported a novel therapeutic strategy by combination of topotecan (TPT) and chronomodulated radiotherapy for NPC.
Materials and Methods: After a uniform biological rhythm was built through a light/dark cycle (LD 12:12). A xenografted NPC model was established by subcutaneous injection of poorly differentiated human NPC cells (CNE-2) to BALB/c (nu/nu) nude mice. Then the mice were separately administrated with: TPT (10 mg/kg), radiotherapy (RT), and TPT+RT, the anti-tumor effect was evaluated by analysis of tumor re-growth delay, the expressions of pimonidazole hydrochloride (HP-1), phosphorylated H2AX (γ-H2AX), DNA-topoisomerase I (Top I), cell cycle and apoptotic at 3, 9, 15, 21HALO (HALO means hours after light onset). The tumor-loaded mice without any treatment were used as the control.
Results: All therapeutic protocols showed the obvious tumor growth delay compared to the control at the same time point. In which, TPT+RT had the best tumor inhibitory effect and existed a remarkable increase in γ-H2AX expression and decrease in HP-1. For four time points, TPT+RT group at 15HALO showed the best inhibitory effect on tumor re-growth. The results revealed tumor hypoxia and DNA damage response varied in a time-dependent manner. The expression of Top I also showed obvious circadian rhythms with higher level at 15HALO and lower at 3HALO. Flow cytometry also appeared same trend of an increased apoptosis index and decreased proportion of S-phase cells (P<0.05).
Conclusions: Our study confirmed that combination of TPT and chronomodulated radiotherapy could enhance the radiosensitivity of xenografted NPC. TPT+RT group at 15HALO had the best therapeutic effect. The chronomodulated radiosensitization mechanisms of TPT might be related to many factors: tumor hypoxic state, cell cycle and apoptosis, DNA damage and the circadian rhythm of Top I.
No conflict of interest.

1067 POSTER

Treatment of glomus tumours with fractionated stereotactic radiation therapy and tomotherapy

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Background: Glomus are uncommon benign tumours. Treatment options are resection and radiotherapy. These tumours usually were treated using conventional RT 3D with 10−15 mm margins. Technical innovation allows to cover target volume with narrow margins. Since 2002 in our institution we use fractionated stereotactic radiation therapy (FSRT) in these tumours.
We analyze local control, clinical response and toxicity in patients treated with new techniques.
Methods and Materials: Between March 2002 and January 2013, 16 glomus were treated. 13 patients with FSRT and 3 with tomotherapy. Median follow-up was 31 months (range: 6−66.5).
Median age was 60 years (range: 46−81). 12 women and 4 men. Most common symptoms were tinnitus (13 patients) and injury lower cranial nerves (9 patients). Location: 87.5% jugular and tympanic. 93.8% unilateral. 43.8 % had surgical resection previously. Median glomus size was 30 mm (range: 10−70) and median target volume was 21.3 cc (range 6.37–464.2).
Median margins added to the gross tumour volume (GTV) to generate planning target volume (PTV) was 3 mm (range 2−10). The median total dose was 50.4 Gy (1.8 Gy per fraction) at 95% PTV coverage.
Median conformity index in FSRT was 1.2 (range: 1.18–1.47).
Results: No patients developed exacerbated symptoms or new neurological complications.
50% improved tinnitus and hearing.
No cases of clinical or radiological progression were identified.
63.7% of tumours were stable and 37.3% showed size reduction.
Conclusion: FSRT and tomotherapy are effective and safe therapies for patients with glomus. High local control rates associated with very low incidence of side effects were achieved. This treatment may be used in many patients as an alternative to surgical resection.
No conflict of interest.

1068 POSTER

Hypersensitivity of cancer cells derived from human thyroid, cervical and breast carcinomas to triptolide and its combination with radiation

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Background: Many human carcinomas are highly resistant to chemotherapy and radiotherapy; therefore, development of approaches to better therapeutic targeting such tumors is of paramount importance. In the present work, we examined the effects of triptolide (a diterpenoid triepoxide from the Chinese herb *Tripterygium wilfordii* exhibiting anticancer activity), as a mono-agent or in combination with gamma-radiation, on human carcinoma cells of different origin.
Materials and Methods: Three tumor cell lines (1) FRO (derived from human anaplastic thyroid carcinoma), (2) HeLa (derived from human cervical carcinoma) and (3) MCF-7 (derived from human breast carcinoma) were here studied. In the comparative experiments, human normal (non-tumor) epithelium cell lines 293 and HBL-100 were used as well. The cell death/survival was assessed in MTT-test, annexin-V staining and clonogenic assays. The expression of certain cell survival- and apoptosis-related proteins was explored by serial immunoblotting.
Results: We have established that the above three carcinoma cell lines are extremely sensitive to very low (0.5−5 nM) concentrations of triptolide and its combinations with low doses (2−5 Gy) of irradiation. This hypersensitivity was usually manifested in the suppressed cell proliferation, massive apoptotic cell death and sharply (100–10000-fold) impaired clonogenicity following the (co)treatment. As for the molecular basis of such enhanced cytotoxicity, the simultaneous inhibition of NF-kappaB- and Akt-mediated cytoprotective pathways in the cancer cells treated with triptolide seems to promote apoptosis that may be aggravated by such an apoptotic stimulus as radiation exposure. Besides, the known ability of triptolide to inhibit the HSF1-dependent expression of cytoprotective heat shock proteins (e.g. Hsp70 and Hsp27) may also help to kill the cancer cells treated with the drug. Importantly, when the above normal (non-tumor) cells were (co)treated by the same way, they exhibited the significantly less sensitivity as compared with the carcinoma cells.
Conclusions: The present findings allow us to hope that clinically achievable and tolerable concentrations of triptolide in the organism of patients will exert therapeutic effects upon carcinoma tumors and/or improve the outcome of anticancer radiotherapy.
No conflict of interest.

1069 POSTER

Quantitative evaluation of online correction shifts between bone and soft tissue matching for gated and non-gated stereotactic body radiation therapy (SBRT) treatments

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Purpose: To compare the use of setup marks on skin versus setup marks on immobilization device for patient positioning for SBRT. To determine the magnitude and frequency of online correction shifts between bone and soft tissue.
Methods: A retrospective study of two hundred and seven fractions of lung SBRT treatments was performed, of which one hundred and three were non-gated (group I) and one hundred and four were gated treatments (group II).
The first part of the study compared cone beam computed tomography (CBCT) localization using bone landmarks with reference to setup marks either on the patient or the immobilization device (BodyFix) in the anterior-posterior (AP), left-right (LR) and superior-inferior (SI) directions. The second part of the study evaluated if fluoroscopic localisation for moving tumours was influenced by change in tumour motion, baseline tumour position or if the internal target volume (ITV) created from treatment planning 4DCT was appropriate. Analysis of total tumour excursion was performed using CBCT for each fraction.
Results: The first part of the study demonstrated that the setup marks on the localization device yielded lower magnitude shifts in the AP and SI directions when using CBCT guided bone matching. Initial results show that 12% of gated treatments and 24% of non-gated treatments required soft tissue matching. Analysis of Group I and II showed that the ITV created from the initial 4DCT motion was adequate. The majority of soft-tissue moves were due to a change in baseline position of the tumour. An analysis of individual patients whose tumour motion was outside the norm (3 mm) will be presented. Data table 1 shows the number of total fractions and number of soft tissue shifts for gated and non gated treatments.

Table 1. The number of fractions of gated and non gated treatments where soft tissue shifts were performed. The number of shifts outside 0.3 cm is also presented.

	# Fractions	Ant	post	Sup	inf	Right	left
Gated	104	2	3	3	4	1	6
Soft tissue >0.3 cm		0	3	0	1	0	4
Non Gated	103	10	6	10	5	9	3
Soft tissue >0.3 cm		6	0	2	3	0	1

Conclusion: Based on this analysis, setup marks are placed on the immobilization (BodyFix) device for all SBRT treatments in our department. Our current motion analysis method has proven to be sufficient for creating ITVs. From our experience we have found that in most cases there may be no difference between online CBCT bone matching and soft tissue. However, the use of soft tissue verification and tumour motion using fluoroscopy is recommended on a daily basis.
No conflict of interest.

1070 POSTER

Comparison of target definition by 4DCT and 3DCT, the addition of asymmetric margins, or the addition of traditional margins for esophageal cancer

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Background: To investigate the 4DCT based planning target volume (PTV) definition compared to conventional PTV definition and PTV definition using asymmetrical margins for thoracic primary esophageal cancer.
Materials and Methods: Forty-three patients with esophageal cancer underwent 3DCT and 4DCT simulation scans during free breathing. The motion of primary tumors located in the proximal (group A), mid- (group B), and distal (group C) thoracic esophagus were obtained from the 4DCT scans. PTV3D was defined on 3DCT using the tumor motion measured based on 4DCT; PTVconv was defined on 3DCT using a 1.0 cm margin to CTV; PTV4D was defined as the union of the target volume contoured on the 10 phases of 4DCT images. PTV centroid position, volumetric differences and dice similarity coefficient (DSC) were evaluated.
Results: The median centroid shifts between PTV3D and PTV4D, PTVconv and PTV4D in the three dimensional directions were all less than 0.3 cm for the three groups. The median size ratio of PTV4D to PTV3D was 0.80, 0.88, 0.71 for group A, B and C, and for PTV4D to PTVconv was 0.67, 0.73, 0.76 respectively ($\chi 2 = -3.18, -2.98, -3.06$; $P = 0.001, 0.003, 0.002$). The DSC were 0.87, 0.90, 0.81 between PTV4D and PTV3D, with 0.80, 0.84, 0.83 between the PTV4D and PTVconv ($\chi 2 = -3.18, -2.98, -3.06$; $P = 0.001, 0.003, 0.002$). The difference between degree of inclusion of PTV4D in PTV3D and PTV4D in PTVconv was all less than 2%. Compared with PTVconv, PTV3D decreased 11.81% and 11.86% of irradiated normal tissue in group A and B respectively, but increased 2.93% for group C.
Conclusions: For proximal and mid- esophageal cancer, 3DCT-based PTV using asymmetrical margins provides a good coverage of PTV4D, meanwhile for distal esophageal cancer, 3DCT-based PTV using conventional margins provides an ideal conformity with PTV4D.
No conflict of interest.

1071 POSTER

Diffusion-weighted magnetic resonance imaging in radiotherapy: Do not forget about geometric distortion

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Background: Due to its high soft tissue contrast, MRI is commonly used in radiotherapy. Higher field strengths give higher signal-to-noise ratios and thus improved tissue contrast. Diffusion-weighted (DW) MRI enables measurement of the apparent diffusion coefficient (ADC) of the water in the field of view (FOV). Low ADCs are associated with higher cell densities and malignancy so DW MRI could improve tumour delineation. The most frequently used DW MRI technique comprises a single-shot, spin-echo

echo-planar imaging sequence. However, echo-planar images suffer from geometrical image distortions due to the relatively long gradient echo train. In theory, the incidence of these distortions increases as the field strength rises.
Material and Methods: We investigated two 3-T systems (a GE Discovery MR 750® and a Philips Achieva®) and two 1.5-T MRI systems (a Philips Intera® and a GE Signa HD®) with phased array coils. Distortion was assessed for a morphologic turbo spin-echo (TSE) T2-weighted sequence (contiguous axial slice thickness: 5 mm; matrix: 512x512; FOV: 30 cm) and DW sequences using different diffusion weightings (B values of 600, 1000 and 2000 sec/mm^2; matrix: 256x256; FOV: 30 cm). Acquisition characteristics with the phased array coil were the same for all MRI systems and distortion was measured on each ADC map. The geometric distortion was measured using a cylindrical MRI 3D Geometry Phantom® filled with an aqueous solution (dimensions: 21 x 22 x 23 cm; hole spacing: 1.5 cm; hole diameter: 0.3 cm; 196, 196 and 140 holes in the x, y and z plates, respectively). The deviation between the markers' theoretical and measured positions yielded the distortion as a function of distance to the center of the FOV. The results were compared in the Student's t-test and the threshold for statistical significance was set to $p < 0.05$. The statistical analysis was performed with SPSS software.
Results: For the two 1.5 T MRI scanners, the median ($\pm$ standard deviation (SD)) distortions on TSE T2 images were 1.2$\pm$0.3 mm, 2.4$\pm$5.2 mm and 3.2$\pm$5.4 mm at 35, 70 and 100 mm from the center of the FOV, respectively. These values were respectively 1.8$\pm$1.1 mm, 2.9$\pm$5.1 mm and 6.1$\pm$5.5 mm in ADC B600 images and 1.6$\pm$0.4 mm, 4.3$\pm$5.3 mm and 8.4$\pm$5.4 mm in ADC B1000 images.
For the two 3 T MRI scanners, the median$\pm$SD distortions on TSE T2 images were 0.2$\pm$0.1 mm, 0.7$\pm$6.7 mm and 0.9$\pm$7.2 mm at 35, 70 and 100 mm from the center of the FOV, respectively. These values were respectively 4.2$\pm$3.7 mm, 20.1$\pm$7.6 mm and 31.2$\pm$5 mm in ADC B600 images and 1.9$\pm$2.8 mm, 18.1$\pm$4.5 mm and 25$\pm$4.3 mm in ADC B1000 images. Distortion was significantly greater in 3 T scanners than in 1.5 T MRI scanners ($p < 0.01$) for DW images but not for T2 sequences. The B2000, B1000 and B600 distortions were all significantly different ($p < 0.01$).
Conclusion: Distortion is much greater in DW MRI than in morphological MRI and must be carefully assessed and corrected before it can be integrated into radiotherapy planning. The development of higher gradients and/or readout-segmented echo-planar imaging is probably a promising approach.
No conflict of interest.

1072 POSTER

A preliminary study of bone marrow metabolic response after pelvic radiation on 18F-FDG PET-CT: Correlation with hematologic toxicity

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Background: The relationship between metabolic decrease and radiation dose in irradiation field has not been revealed. The aim of this study is to evaluate the impact of pelvic radiation on bone marrow (BM) metabolic response using 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) and hematologic toxicity according to metabolic change.
Material and Methods: We analyzed 19 gynecologic patients treated radiotherapy with or without chemotherapy. The patients underwent baseline 18F-FDG-PET before treatment, immediate and delayed 18F-FDG-PET after treatment. Pelvic bone marrow (BM) was defined as the region extending from the iliac crests to the ischial tuberosity. On the 18F-FDG-PET, the 0.8 cm $\times$ 0.8 cm sized round region of interest (ROI) was drawn in each 10, 20, 30, and $\geqslant$40 Gy (V10, V20, V30, and V40, respectively) irradiated volume, and in the control (the first lumbar spine (L1)). Each ROI was divided by that of the liver for metabolic correction. The correlation between BM metabolic change of each dose regions, BM dose-volume metrics and hematologic nadirs (hemoglobin (Hb), white blood cell (WBC), platelet (PLT), and absolute neutrophil count (ANC)) were evaluated.
Results: The median age was 66 years old. All the patients were uterine cervical cancer except two (endometrial cancer, uterine leiomyosarcoma). The median radiation dose to pelvis was 45 Gy (range, 19.8 Gy-60.4 Gy). In comparison with pre-treatment 18F-FDG-PET, the metabolic change in the immediate 18F-FDG-PET was 29.54%, 33.43%, 36.60%, 37.41% and in the delayed 18F-FDG-PET was 31.04%, 41.73%, 44.38%, 27.71% (V10, V20, V30, V40, respectively). The metabolism of the L1 was not affected according to the hematologic change. The relationship between interval metabolic changes of V10−40 on the immediate, delayed 18F-FDG-PET and radiation dose were significant according to the linear regression model (immediate t=4.992, p<0.005, delayed t=2.167, p = 0.034). Percent hematologic changes were 15.49%, 50.96%, 39.77%, 45.21% (Hb, WBC, PLT, and ANC, respectively). Hematologic changes were not correlated with immediate and delayed metabolic response significantly.
Conclusions: The metabolic change of pelvic BM after radiotherapy was linearly correlated with irradiated dose, however, was not connected with hematologic alteration.
No conflict of interest.

1073 POSTER

Assessment of esophageal tumor motion and impact uncertainties using four-dimensional computed tomography

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Background: To access the three-dimensional motion caused by respiration and its influencing factors for radiotherapy of the thoracic primary esophageal cancer.
Methods: Sixty-five patients with esophageal cancer underwent 3DCT and 4DCT simulation scans during free breathing. The amplitude was calculated as the maximum difference between any of the 10 phases. The distance between the GTV upper/lower edges and the interesting target (carina, lower edge of aortic, the apes of the doms of the diaphragms) were measured. The motion of different thoracic groups was measured.
Results: The centroid motion of GTV were (0.15$\pm$0.10) cm, (0.12$\pm$0.15) cm, (0.34$\pm$0.15)cm in lateral(LR), anteroposterior (AP) and superioinferior (SI) directions, respectively. There were no relationship between GTV motion and patient gender, age and body mass index(BMI)($p > 0.05$). Tumor in the lower thorax had a lager displacement in LR and AP directions than tumor in the upper and mid- thorax($p = 0.036$, 0.014). Squamous carcinoma exhibited smaller motion than adenocarcinoma in all the three dimensional directions. A significant difference between the motion of the tumors with different length, and no significant difference was found in the motion of these locations in the absence or presence of the enlarged nodes. There is a negative correlation between the GTV movement and the distance between the GTV upper/lower edges and carina.
Conclusions: The greatest motion was seen in the SI direction for the thoracic esophageal cancer during free breathing. Appropriate site-specific internal target volume expansion should be consulted the tumor location and histologic type, and correlated with the distance between the GTV upper/lower edges and carina. The recommend margins might be applicable to patients with or without involved nodes.
No conflict of interest.

1074 POSTER

Comparison of the thoracic esophagus position and volume between quiet end-inspiration and end-expiration three dimensional CT assisted with active breathing control and corresponding phases in four dimensional CT

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Background: To compare the position, volume and matching index (MI) of the thoracic esophagus between quiet end-inspiration and end-expiration three dimensional CT (3DCT) assisted with active breathing control (ABC) and the corresponding phases in four dimensional CT (4DCT).
Material and Methods: Eleven patients with peripheral lung cancer underwent 4DCT simulation scan and 3DCT simulation scans in end-inspiratory hold (CT_{EIH}) and end-expiratory hold (CT_{EEH}) in succession. The 4DCT images from each respiratory cycle were sorted into 10 phases: the 0% phase was defined as end-inspiratory phase (CT_0), while the 50% phase was defined as end-expiratory phase (CT_{50}). The proximal, mid- and distal thoracic esophaguses were delineated separately on CT_0, CT_{50}, CT_{EIH} and CT_{EEH} images.
Results: In the X direction, the displacement differences of the proximal, mid- and distal thoracic esophaguses between CT_0 and CT_{EIH} were (−0.02$\pm$0.16)cm, (0.06$\pm$0.26)cm and (0.10$\pm$0.33)cm respectively, and in the Y direction, that were (0.04$\pm$0.24)cm, (0.04$\pm$0.12)cm and (0.08$\pm$0.15)cm respectively, and the displacement differences of the same direction were not statistically significant (all $P > 0.05$). In the X direction, the displacement differences of the proximal, mid- and distal thoracic esophaguses between CT_{50} and CT_{EEH} were (−0.02$\pm$0.24)cm, (0.12$\pm$0.37)cm and (0.26$\pm$0.33)cm respectively, and in the Y direction, that were (0.03$\pm$0.21)cm, (0.04$\pm$0.17)cm and (0.14$\pm$0.18)cm respectively, and the displacement differences of X and Y directions of proximal and mid-thoracic esophaguses between CT_{50} and CT_{EEH} were not statistically significant (all $P > 0.05$), while that of distal thoracic esophaguses between CT_{50} and CT_{EEH} were both statistically significant (both $P<0.05$). The volumes of the proximal, mid- and distal thoracic esophaguses were all

larger in CT_0 and CT_{50} than in CT_{EIH} and CT_{EEH}, but the differences between them were found both not statistically significant ($P > 0.05$). The MIs of the volumes of the proximal, mid- and distal thoracic esophaguses between CT_0 and CT_{EIH} were (0.50 ± 0.17), (0.50 ± 0.19) and (0.56 ± 0.08), and that between CT_{50} and CT_{EEH} were (0.50 ± 0.16), (0.47 ± 0.14) and (0.51 ± 0.15). The MI of each segment esophagus between CT_0 and CT_{EIH} was larger than that between CT_{50} and CT_{EEH} ($P > 0.05$).
Conclusions: The influence of breathing modes to the centroid positions of the proximal, mid-thoracic normal esophaguses were not significant. But there were spatial mismatches for any segment esophagus between two breathing modes.
No conflict of interest.

1075 POSTER

Low dose pre-irradiation and radio-adaptive response detected by MTT in HT29 and MRC5 cell lines

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Background: The effects of radio-adaptive response is the main interest of many studies. Adaptive response can lead to hypersensitivity or radioresistance. Both phenomena play important role in radiotherapy. The aim of this research was to examine the effects of low-dose pre-irradiation followed by two different irradiation regimes on metabolic activity in two cell lines: HT29 human colorectal adenocarcinoma and fetal fibroblasts MRC5 cell lines.
Material and Methods: The cell lines were pre-irradiated with 0.03 Gy, 0.05 Gy and 0.07 Gy and the control cell lines were not pre-irradiated. Both, control and pre-irradiated cells were irradiated two hours after priming dose and specially designed hyper- and hypofractionation regimes were applied. For the hyperfractionation the calculated doses were 1.3 Gy twice per day, with four hours period between daily fractions during four consecutive days. For the hypofractionation the calculated doses were 4.6 Gy on the first and fourth day, once per day, in order to obtain same overall treatment time as in hyperfractionation regime. The determined irradiation doses were estimated as biological equivalent (BED) to four-day treatment with 2 Gy fraction. Cell survival was tested by MTT. STATISTICA 10.0 software was applied in data processing.
Results: In hyperfractionation regime the low-dose of 0.05 Gy led to a significantly induced radioresistance in MRC5 cells compared with non pre-irradiated control. Low doses of 0.03 Gy and 0.07 Gy significantly increased radioresistance in HT29 cell line compared with non pre-irradiated control and pre-irradiation dose of 0.05 Gy. Statistically significant decrease of metabolic activity in HT29, after 0.05 Gy priming dose was observed, compared with 0.03 Gy and 0.07 Gy priming doses. In hypofractionation regime after priming dose of 0.05 Gy, as in hyperfractionation regime, statistically significant increase of cell metabolic activity in MRC5 cells was observed. In HT29 cells 0.05 Gy and 0.07 Gy priming doses led to a significance decrease of metabolic activity compred with irradiated control.
Conclusions: In both regimes, the priming dose of 0.05 Gy followed by challenging dose after two hours, led to decrease of metabolic activity in human colorectal cancer cells, and at the same time had significant radioresistance effect on the metabolic activity of human fetal lung fibroblasts. These results represent promising effect of applied low-dose pre-irradiation followed by different irradiation regimes afterwards.
No conflict of interest.

1076 POSTER

Emodin enhances growth suppression of human hepatoma cells by irradiation via enhancement of apoptosis and inhibition of cyclin D1

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Background: The application of radiotherapy of hepatocellular carcinoma (HCC) is limited due to radioresistance in tumor and radiotoxicity in nontumorous liver. Therefore, study for radioresistance mechanism and improvement of killing effect of irradiation by therapeutic insult such as radiosensitizer etc. Emodin (1,3,8-trihydroxy-6-methylanthraquinone), a family of plant derived polyphenol has been proven to have anticancer properities. There is limited data about role of emodin as radiosensitizer in human hepatoma cell line. In this study, we examined the followings: (i) whether emodin attenuated radioresitance of hepatoma cell line, (ii) what was the mechanism of radiosensitization.
Material and Methods: Methods: Two human HCC cell lines were used in this study: HepG2, and Hep3B. They were exposed to four different manners; none (control), irradiation (10 Gy, one fraction), emodin (10 μM), and irradiation combined with emodin. Cells were then subjected to MTT assay (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a yellow tetrazole) and immunoblotting in 24 hours and 72 hours after exposure.
Results: The growth suppression of two cell lines was significantly more enhanced compared to control group in the same order as followings; combination group, emodin, and irradiation. Treatment with irradiation combined with emodin resulted in maximal upregulation of apoptotic signaling such as poly (ADP-ribose) polymerase (PARP) and caspase-9 and downregulation of proliferation signaling such as cyclin D1.
Conclusions: Emodin enhances the activity of irradiation in tumor growth suppression of human hepatoma cells via enhancement of PARP, caspase-9 and inhibition of cyclin D1. Therefore, our findings may provide new insights into understanding the pharamacological mechanism of emodin as radiosensitizer in HCC and may aid in the design of new therapeutic strategies for the radioresistant HCC.
No conflict of interest.

1077 POSTER

Endocrinological late effects after radiotherapy

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Background: Treatment for cancer might lead to hormonal dysfunctions. Aims of this cross-sectional study were to assess the prevalence of disturbances in four hormonal axes: Hypothalamic-pituitary (HP) − thyroid axis, HP-adrenal axis, HP-gonadal axis and Growth hormone (GH), and to analyze associations between disturbances and patient- and treatment-related variables. Here we report frequency of abnormal values for all axes and analyze variables related to the thyroid- and GH axes.
Material and Methods: Eligible patients aged $\geqslant$15 years at diagnosis were treated for lymphoma, plasmacytoma, multiple myeloma or carcinoma of the epipharynx region by radiotherapy to the head and neck region or total body irradiation, with or without chemotherapy, from 1980–2006. For each axis the hormonal function was dichotomized as normal or impaired according to reference values at the laboratory. Treatment data was obtained from the patient records, and the radiation dose to the pituitary and thyroid gland was estimated. Comparisons were performed by chi-square and t-tests with $p < 0.05$ considered statistically significant (two-sided).
Results: A total of 84 males and 57 females treated for lymphoma (HL=20, NHL=103), multiple myeloma (n = 5), plasmacytoma (n = 3) and carcinoma (n = 10) were included. Observation time was 15.8 (6.4) years, age at diagnosis was 43.4 (15.1) years and at age survey 59.2 (12.9) years (mean, SD). Forty-nine (37%) survivors had biochemical hypothyroidism, 35 (25%) had abnormal GH- and/or IGF-1 values and 2 had abnormal values in the adrenal axis. Forty (48%) men had impaired gonadal function and 10 (18%) women had premature menopause (<42 years).
Survivors with hypothyroidism had received a significantly higher dose to the thyroid gland and had significantly longer observation time than those with normal thyroid function [mean 29.8 Gy (SD 16.5) vs 12.9 Gy (SD 15.8) $p < 0.001$, mean 18.3 years (SD 6.2) vs 14.1 years (SD 6.2), $p < 0.001$]. Survivors with abnormal levels in the GH-axis had received a non-significant higher radiation dose to the pituitary gland [mean 16.9 Gy (SD 18.3) vs mean 12.4 Gy (SD 11.9) ($p = 0.19$)]. There were no significant associations between gender and age at survey and abnormal levels in the GH axis and/or the thyroid axis.
Conclusions: Abnormal hormone values are frequent after radiotherapy to the head and neck region and should be measured in follow up. The clinical impact of failure in the GH axis needs further examinations.
No conflict of interest.

1078 POSTER

Do we need adaptive radiotherapy in head and neck cancer to decrease xerostomia?

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Background: Significant morphologic variations can be observed during the course of locally advanced head and neck cancer (HNC). The purposes of this study were:
– to estimate the difference between the planned dose and the actual delivered cumulative dose in the parotids (PG),
– to assess the benefit of a weekly replanning to spare the PGs.
Material and Methods: 11 patients (pts) with locally advanced HNC received IMRT to a total dose of 70 Gy. Each pt had one initial planning CT (CT0) and a weekly CT (wCT) during the treatment. The anatomical structures were manually segmented on each CT. The dose distribution corresponding to the pretreatment planning was calculated on each wCT. A new IMRT planning was also generated on each wCT, in order to spare the PGs at least as they were spared at the pretreatment planning. Each weekly dose distribution was reported on the CT0 by elastic registration. Two kinds of cumulative dose were therefore calculated on the CT0: one corresponding to the actual delivered dose and the other one to the weekly re-planned dose. The cumulative doses (with or without replanning) were compared with the planned dose for the PGs. The risk of xerostomia was estimated by the NTCP model (n = 1, m=0.4, TD50=39.9).
Results: The volume of the PGs decreased of an average of 33% [10−69 %] during the treatment. The average Dice score for the parotid registration was 0.93 (0.88–0.95). The dose in the PGs was increased in 62.5% of the PGs, by comparing the planned dose with the actual delivered dose. This increase was observed in 50% of the homo-lateral PG and 75% of the contra-lateral PGs. An increase of more than 3 Gy of the mean PG dose was observed in 31 % of PGs (up to 10 Gy for 1 PG),observed in 50% of pts and corresponding to an absolute average increase risk of xerostomia of 13% [6−24%]. A weekly replanning allows reducing the mean PGs dose at least at the same dose than at the pretreatment plan for more than 80% of the pts ($D_{mean\ Replan}$ = 31.3 Gy, $D_{mean\ initial}$ = 32.5 Gy, p = 0.013). Moreover, the doses in the CTV and PTV were not statistically different between the pre-treatment planning and the weekly re-planning.
Conclusion: A weekly re-planning can benefit significantly to one third of the PGs (and 50% of the pts), leading to decrease the absolute risk of xerostomia of at least 13%. An ongoing randomized IMRT trial comparing one planning to a weekly planning aims demonstrating the benefit on this adaptive radiotherapy strategy.
No conflict of interest.

1079 POSTER

Nodal PTV margin validation for head-and-neck cancer patients (HNC) treated with image-guided tomotherapy: Need of adaptive re planning?

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Background: Changes in dimension, shape and position of positive lymphnodes (PLs) in patients treated with image-guided RT for HNC may lead to dangerous geographical misses, especially in the case of concomitant boosting of PET PLs. Aim of this study was to assess the entity of the problem and to check if the margin (5 mm) used in our simultaneous-integrated-boost (SIB) approach with Helical Tomotherapy (HT) is appropriate.
Material and Methods: Thirty-seven HNC N2/N3 patients (pts) treated with SIB HT (delivering 54, 66 and 69 Gy in 30 fr on PTV(N), PTV($T+N^+$) and PTV of the PET-positive $T+N^+$) were considered. Regarding PLs position: 33, 7 and 2 PLs were respectively in levels II, III and V. For each patient, MVCTs taken at fr 1, 5, 10, 15, 20, 25 and 30 were matched with the planning kVCT (pl_kVCT) on bone anatomy (averaged on the treated volume). Three experts contoured 42 PLs of 30 pts on the pl_kVCT and all MVCTs (7 patients were excluded because PLs were not visible on MVCT). Intra-observer variability was assessed by blind re-delineation of 16 PLs. Volumes were normalized to fraction 1 MVCT and time-trend in volume change was assessed by Spearman's test. PLs displacement was assessed by the center of mass (CM) shift with respect to the 1st MVCT. For each PL, the % fraction of the union (UN) of all PL positions over the whole treatment that was missed by the clinical PTV (pl_kVCT PL contour+5 mm) was assessed. For pts with some missing, larger margins were tested to find UN coverage >99%.
Results: PLs were sufficiently well visible on MVCT: an acceptable intra-observer variability confirmed this impression (median DICE: 0.805±0.134). 27/42 PLs showed an average volume reduction of 70% (range: 27−94%), with significant time trend (median Spearman ρ = −0.93; range −0.78÷-1.00; p < 0.05).
Larger 3D average CM shifts on the whole population were observed in the 2nd part of the treatment toward the midline (medial shift in the 1st and 2nd part: 0.1 vs 1.6 mm, Wilcoxon test p < 0.001). Only 7/42 PLs of 7/30 pts needed margins >5 mm: respectively 6 and 7 mm for n = 2; 8, 9 and 12 mm for n = 1.
Conclusions: Results show a significant, although small, residual error in the localization of PLs during IGRT for HNC. 64% PLs show a significant shrinkage. A margin of 5 mm covers all possible positions of PLs in about 80% of pts, extending to 93−97% with a margin of 8−9 mm. Interestingly, the shrinkage seems to counterbalance the shift of PLs due to deformations, more pronounced in the last fractions. Seeing these results, adaptive re-planning aiming to avoid to miss PLs should not be recommended (excepting very selected pts) also in the case of PET PLs boost.
No conflict of interest.

1080 POSTER

Evaluation of EPID based transit dosimetry on the implementation of In-vivo dosimetry and a step forward for dose guided adaptive radiation therapy

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Background: The common practice of In-vivo dosimetry using point detectors were very successful with conformal treatment techniques but could not be extended its usage effectively for modulated treatment techniques. To address the need for an efficient in-vivo dosimetry system for the modulated treatments, Edinburgh Cancer Centre collaborated with Math Resolutions, U.S.A, to develop a 'transit dosimetry' solution using Electronic portal imaging device [EPID] based data acquisition. The algorithm used in 'Dosimetry Check' software was extended to support transit dosimetry and was extensively tested. Further studies were performed to integrate cone beam CT based dose calculations using transit dosimetry.
Material and Methods: 6MV and 10MV clinical photon beams delivered from Varian Accelerators (Clinac 21EX, Novalis − Tx and Silhouette) and amorphous silicon based EPID [aSi 1000] systems mounted on these accelerators were used in this study. For conformal and fixed gantry dmlc based modulated techniques, transit images were acquired in 'integrated' acquisition mode and for volumetric modulated [RapidArc] deliveries, 'continuous' acquisition mode is used. All the patient treatments were planned using Eclipse [Varian, U.S.A] treatment planning system. Cone beam images were taken only for RapidArc treatment deliveries using Varian On-board Imager system [Ver.15].
The transit dose calculations were initially tested using beam deliveries on water equivalent slabs and compared with 0.6cc ion chamber based measurements. Reproducibility and sensitivity of the transit dosimetry process was tested using fixed gantry dynamic MLC based modulated deliveries on an anthropomorphic thoracic phantom.
Results: The water equivalent phantom based verifications agreed within +/− 3% with the treatment planning system and the ion chamber measured values. The reproducibility study using the anthropomorphic phantom resulted within the standard deviation of +/− 0.005%. The sensitivity study with a known manual shift of the phantom by 5.0 cm shift resulted 7% dose deviation.
The agreement of transit dosimetry based dose estimations at the isocentre for 325 clinical patients so far collected from different clinical sites treated with conformal techniques agreed with the treatment planning results within a mean value of +/− 4.0%. Larger deviations of the order of +/− 10% were observed from Ca. Breast treatments especially if the mono-isocentric technique is used. For H&N and Prostate RapidArc deliveries, the results were of similar magnitude with the independent verifications using ArcCheck diode array system [Sun Nuclear, U.S.A].
Conclusions: EPID based transit dosimetry using 'Dosimetry Check' software can be reliably used for in-vivo dosimetry purposes for all co-planar treatment techniques. The reliability of the cone beam based calculation highly depends on the reproducibility of the Hounsfield units and the registration process.
No conflict of interest.

1081 POSTER

Long-term risk of ischemic heart disease following Hodgkin lymphoma treatment

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Background: Hodgkin lymphoma (HL) is the prototype of a curable malignancy. However, treatment causes excess cardiovascular morbidity and mortality in long-term survivors. The objective of this study is to identify risk factors for ischemic heart disease (IHD), defined as myocardial infarction (MI) and angina pectoris (AP) (⩾grade 2 CTCAE4.0). We quantified separate and joint effects of radiation dose to the heart, anthracycline dose, other chemotherapeutic agents, lifestyle factors and established cardiovascular risk factors.
Methods: A nested case-control study was conducted in a cohort of 2201 5-year HL survivors who were treated in the Netherlands between 1965 and 1995. Cases with IHD were matched to controls with HL who did not develop IHD (ratio 1:2 at least) on sex, age, date of HL diagnosis and duration of follow-up. Detailed treatment information was collected from medical records. Radiation dose to the heart was based on the prescribed mediastinal dose reported in the radiotherapy charts. Conditional logistic regression was used for analyses.
Results: 180 cases with IHD were identified from the cohort and matched with 499 controls. Mediastinal radiotherapy (usually performed using parallel opposed fields) was associated with an increased risk of IHD (OR: 3.0, 95% CI: 1.7−5.4). A dose-response relationship was identified (OR per 10 Gy: 1.2, $p = 0.004$). As compared to patients who did not receive mediastinal irradiation, we observed increased risks of IHD for patients who received 20−34 Gy (OR: 2.1, 95% CI: 0.97–4.63), 35−39 Gy (OR: 2.0, 95% CI: 1.10–3.51) or ⩾40 Gy on the mediastinum (OR: 3.6, 95% CI: 1.94–6.77) ($p < 0.001$), after adjusting for smoking at HL diagnosis and the presence of cardiovascular risk factors at cut-off (Diabetes Mellitus type II, hypertension, hypercholesterolemia) or obesity at diagnosis or at cut-off. No associations or interactions were found with (anthracycline-containing) chemotherapy.
Conclusions: Mediastinal irradiation is associated with a dose-dependent increased risk of IHD in patients treated for Hodgkin lymphoma.
No conflict of interest.

1082 POSTER

Multidisciplinary management of small cell cancer of non-pulmonary origin

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Background: While small cell lung cancer is managed by chemotherapy generally followed by consolidative radiation therapy, management of a non-pulmonary primary is less clear. In contrast to pulmonary small cell, aggressive surgery for these primaries is often employed. We analysed treatment technique and outcome in a large cohort of these patients to better define the role of surgery, radiation and chemotherapy.
Materials and Methods: An IRB approved chart review of all primary small cell cancers of non-pulmonary origin returned 60 (65% male, mean age 67 years) histologically confirmed cases. A total of 52 were pure small cell and the remainder were mixed with adenocarcinoma (n = 3), transitional cell carcinoma (n = 2), sarcomatoid (n = 2) and squamous cell (n = 1). Primary tumour location was head and neck (n = 20), bladder (n = 8), rectum (n = 7), prostate (n = 6), cervix (n = 5), vagina (n = 4), oesophagus (n = 4) and 1 case each from: anus, axilla, breast, ovary, trachea and inguinal. Treatment varied by anatomic site, with 31 (52%) patients undergoing definitive surgery, 51 (85%) undergoing chemotherapy, and 100% undergoing radiation therapy to the primary and regional nodes. External beam radiation therapy (XRT) was intensity modulated or 3D in almost all cases with 20 (33%) also undergoing image guided radiation therapy. The mean XRT dose to the primary was 52.4 Gray.
Results: Treatment was well tolerated. Late morbidity (grade 1/2) included 3 cases of xerostomia and 1 case each of stricture, cystitis, urinary frequency and anal incontinence. Local control was maintained in the majority of patients. Failure was most commonly distant (bones, liver, brain) with only one patient developing lung metastasis. Only 30% of patients are alive at last follow-up. Univariate analysis of local control and survival revealed that chemotherapy ($p = 0.01$) and male gender ($p = 0.007$) were statistically significant variables. Type of surgery and extent of surgery (definitive versus biopsy) did not impact outcome.
Conclusions: Small cell cancer of non-pulmonary origin is aggressive with high rates of systemic spread and poor 5 year outcome. The major treatment factor impacting survival remains chemotherapy. The addition of radiation to chemotherapy allows for control of the primary tumour. The role of surgery is limited as no benefit to survival or local control was seen. Responders may undergo consolidative XRT to the primary site. Consideration for central nervous system prophylaxis by radiation is also suggested by these data, as this is a common site of failure.
No conflict of interest.

1083 POSTER

Patterns of tumor response after stereotactic radiosurgery for vestibular schwannoma

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Background: Stereotactic radiosurgery (SRS) is commonly used for the treatment of vestibular schwannoma. In this study, we evaluate the control rates and MRI changes after treatment with Linac based SRS.
Material and Methods: 27 consecutive patients treated with 12 to 14 Gy using LINAC based SRS at a single institution from 2007–2013 were analyzed. Baseline and post-treatment tumor volumes were assessed on T1 weighted contrast enhanced magnetic resonance imaging. Local control and changes in tumor volume were calculated.
Results: Median follow up time was 35.6 months (range 1.5–61.9) and median treatment tumor volume was 1.1 cc (range: 0.1−8.7 cc). Sixty three, 33, and 4% of patients had reduction, stable, and progression in the tumor volume at their last post treatment MRI, respectively. Median SRS treatment dose was 12 Gy (range: 8−14) treated to 100% of the PTV. Median Dmin was 99.6% (range: 60.9–100), and median Dmax was 124.2% (range: 108.7–148.5%). Median number of beams was 12 (range: 8−15). 42% developed an early transient increase in their post treatment tumor volume occurring 3 to 7 months after SRS. Additionally, 19% had late transient increase in their post treatment volumes occurring 26−37 months post SRS. 7% had both an early and late transient increase in their tumor volumes. Tumor volume, treatment dose, and Dmax did not correlate with MRI changes.
Conclusions: Early and late transient increases in tumor volume occur in a significant number of patients with vestibular schwannoma treated with SRS. It is important to continue to monitor these patients with follow up imaging to avoid mistaking them for treatment failures.
No conflict of interest.

1084 POSTER

Plasmon-induced photothermal effects of gold nanoparticles on human permanent cell line T-24

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Background: Gold nanoparticles (GNPs) have been extensively used in various biomedical applications due to their advantageous biocompatibility, excellent optical scattering and photothermal properties, high chemical, photo- and thermal stability in comparison with most of molecular absorbers. The plasmon resonance for gold nanoparticles (GNPs) is at ~520 nm. The aim of the present investigation was to elucidate the effect of spherical GNPs with diameter 40nm combined with laser irradiation on permanent human tumor cell line T-24 (transitional cell bladder carcinoma).
Materials and Methods: The permanent tumor cell line T-24 was cultured in DMEM, supplemented with 10% FCS, at standard conditions. The samples were irradiated with Nd-YAG laser system, at λ=532 nm, pulse duration τ p= 15 ns and repetition rate 1 Hz. Laser pulses with energies of 20.5 J, 21.5 J, 22.5 J and 23.5 J for 5 s and 10 s were used. The potential anti-tumor effect in vitro of GNPs and laser treatment on T-24 cells were studied by MTT assay. Apoptotic changes in cell morphology were investigated with Annexin V/Propidium iodide (PI) and DAPI staining.
Results: Cells treated with GNPs or laser irradiation alone showed no significant difference from the control. Significant inhibition of tumor cell growth was detected in samples, pre-treated with GNPs and laser

beam with energy 20.5 J for 5 and 10 s (76.19±5.81 and 71.29±7.01 respectively). Similar results were obtained after irradiation with energy 21.5 J for 5 s (71.07±7.06).
Induction of apoptosis in treated with GNPs and irradiated cells was studied using Annexin V-FITC/PI and DAPI staining. Well defined morphological features of apoptosis were observed in order to interpret the results from MTT cytotoxicity assay. The results were statistically significant.
Conclusions: Based on the results obtained the combination of GNPs 40 nm and laser treatment with different characteristics of the laser beam and time of influence resulted in localized heating and causing irreversible thermal cellular destruction. This approach could have potential application in clinical practice and in experimental models in vivo for local treatment of tumors.
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No conflict of interest.

1085 POSTER

When pain restricts symptomatic radiotherapy procedure

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Background: Irradiation treatment of various cancer processes in order to achieve symptomatic relief in the shortest time and with the least toxicity to maintain or increase the quality of life of patients. The ionizing radiation is a proven therapy for the treatment of pain due to bone metastases. The pain relief is achieved in 70−80% of patients using different fractionation schemes and total dose, occurs in 2−3 days, up to 2−4 weeks. However, what do we do when the pain suffered by these patients limits the tolerance requirements for the preparation and administration of radiotherapy? The aim of this study was to evaluate the efficiency of oral transmucosal fentanyl citrate (OTFC) as an analgesic for a highly specific subgroup of cancer patients.
Material and Methods: We analyzed the influence of predictable procedural breakthrough pain (set up, mobilization, treatment administration) in candidates for symptomatic radiotherapy and control pain with the use of oral transmucosal fentanyl citrate. From January 2007 to March 2013 we retrospectively reviewed 1995 patients indicating analgesic purposes radiotherapy, patients who didn't tolerate set up requirements and treatment time for breakthrough pain, and changes in use of OTFC.
Results: Between 2007–2009 the 11.63% (111) of patients requiring radiotherapy for analgesia (954), received OTFC before receiving radiotherapy, a 27.02% (30) who indicated OTFC not tolerated not set up. Between 2010 to March 2013, after evaluation the reasons for not proceeding tolerance of palliative radiotherapy, 24.68% (257) of these patients received OTFC (out of 1041 cases), all patients tolerated the procedure set up radiotherapy. The average score premedication with OTFC with procedural breakthrough pain according to VAS was 7.5 (range 5−10). The average score after use of OTFC was 1.8 (range 1−3). The 47% required a dose of 200 mg, 23% 400 μg, 600 μg 22%, and 8% 800 μg. No patients colds undesirable effects related to the use of OTFC.
Conclusions: We can recommend the ideal analgesic OTFC as its speed and safety for the treatment of breakthrough pain in Radiation Oncology procedural. It is easy and convenient administration of short duration, allowing tolerance and administration of radiation therapy. It is important consider predictable pain control but limiting. Give the patient independence, which they can take, even if you are away from home.
No conflict of interest.

1086 POSTER

Adjuvant hypofractionated radiation therapy for breast cancer: Long term results in a cohort of 80 Cases treated at the Department of Radiation Oncology of CHUOran

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Background: To evaluate the incidence of local recurrence (LR) and locoregional recurrence (LRR) and the toxicity results (acute and late) in a group of patients with breast cancer treated with a hypofractionated schedule of adjuvant radiotherapy after surgery.
Patients and Methods: From January to December 1998, 80 patients underwent radiotherapy treatment (telecobaltotherapy) after conservative (6%) and radical (94%) surgery at our department. The dose delivered was 36 Gy (3 Gy daily fraction). The boost dose was 15 Gy (3 Gy daily fraction) in conservative surgery. To score toxicity, we used the RTOG criteria (acute) and SOMA-LENT scale (late).
Results: With a median follow-up of 77 months (9 to 113 months), 7 patients had locoregional recurrences. The 8-year actuarial rates for local recurrence (LR) and LRR were 5.4% (±2.6%) and 9.5% (±3.4%), respectively. The 8-year overall survival rate was 74.3% (±8.1%). 72 patients (90%) were tolerated this hypofractionated schedule (grade 0). We found that 14 patients had grade ⩾ II late toxicity (17.5%). No patients developed grade IV late toxicity. On univariate analysis, the grade of SBR was influenced the LR and LRR ($p = 0.023$). The tumor size ($p = 0.038$), lymph node status ($p = 0.039$) and hormone receptor status ($p = 0.0001$) were influenced the OS. On multivariate analysis, we found that tumors classified T3−4 ($p = 0.028$; HR 3.999) and hormone receptor status ($p = 0.001$; HR 14.16) were independent factors on the OS.
Conclusion: This hypfractionated RT scheme is perfectly realizable (acceptable results in terms of local control and toxicity). It permitted a short course of treatment (<3 weeks), allowing a larger number of patients to be treated per year, with a reduction in cost to the health system. However, an important number of patients and a longer follow-up are necessary to better appreciate the efficacy and the cosmetic outcome of this scheme.
No conflict of interest.

1087 POSTER

Radiotherapy and prolongation of overall treatment time: a single center case report

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Background: The prescribed total radiation dose should be administered within a specific time; however, in clinical practice, unplanned treatment interruptions are inevitable for many reasons. This fact can have a detrimental effect on the tumour local control and patient's outcome. In this report we evaluate, in a single institution, the difference between the planned and the registered overall treatment time (OTT) of a different tumour sites, due to unplanned interruptions for various reasons.
Material and Methods: A total of 3936 patients (pts) were treated between 1990 and 2010 for breast, prostate, lung, head and neck (H&N) and pelvic malignancies with radical or adjuvant intent. Palliative or symptomatic treatments were excluded. Overall there were 1032 males and 2904 females with a mean age of 66 years. For all patients [treated with single fraction (F) of 1.8 to 2 Gy administered five times per week] we registered the total radiation dose, the number of fractions and the treatment's duration (in days); than for each group we evaluated the difference between the mean planned overall treatment time (number of fractions/5 multiplied for seven days of a week) and the mean duration of the treatment.
Results: The table shows the differences (in days) between mean planned and registered overall treatment time stratified by different tumour sites; the gap represents about 10% of planned OTT for all of the groups. Causes of prolongation of OTT could be various (holydays, machine breakdowns, toxicity and others), but we can't identify them in our computerized record. Moreover this case report don't correlate the prolongation of OTT with the therapeutic outcome.

Site	Pts	Gender (M/F)	Total dose	Dose/F (Gy)	Number of Fs	OTT (days) planned	OTT(days) observed	Difference (days)
Breast								
no boost	902	0/902	50 Gy	2	25	35	39	**4**
+ boost	1597	0/1597	60 Gy	2	30	42	47	**5**
Pelvis	219	67/152	45 Gy	1.8	25	35	38	**3**
Prostate	184	184/0	76 Gy	2	38	53	58	**5**
Lung	76	66/10	61.2 Gy	1.8	34	48	51	**3**
H&N								
no CT	741	494/247	58.7 Gy (mean)	1.8−2	31	43	46.5	**3.5**
+ CT	217	145/72	63.7 Gy (mean)	1.8−2	33.5	47	50	**3**

Conclusions: This is a simple picture of an unselected case report of patients treated at a single institution. Our results shows a moderate gap between planned and observed OTT. Efforts should be done to minimize the unforeseen prolongation of the overall treatment time through different methods for compensation (weekend treatments, increase number of daily fractions, increased dose per fraction, delivering extra fractions). In our centre, according with a codified internal protocol, we add a fraction on Saturday if unplanned break caused by machine breakdowns exceeds two consecutive days; we generally don't operate a compensation if the prolongation of the treatment is due to other causes (e.g. holydays, toxicity). If the break has occurred late in the schedule, we sometimes deliver one or more extra fractions.
No conflict of interest.

1088 POSTER

The impact of intensity modulated radiotherapy on skin dose for deep sited tumours

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Abstract: Background: The purpose of this study was to investigate the impact of IMRT on surface doses for brain, abdomen and pelvis deep located tumours treated with 6 MV photon and to evaluate the skin dose calculation accuracy of the XIO, 4.04 treatment planning system.
Materials: More investigations for the influences of IMRT on skin doses will increase its applications for many treatment sites. Measuring skin doses in real treatment situations will reduce the uncertainty of skin dose prediction. In this work a paediatric human phantom was covered by a layer of 1 mm bolus at three treatment sites and thermolumencent dosimeter TLD chips were inserted into the bolus at each treatment site before CT scan. Two different treatment plans (3-DCRT and IMRT) for each treatment sites were performed on XIO, 4.04 treatment planning system using superposition algorism.
Results: The results showed that the surface doses for 3DCRT were higher than the surface doses in IMRT by 1.6%, 2.5% and 3.2% for brain, abdomen and pelvis sites respectively. The results showed that there were good agreement between measured and calculated surface doses, where the calculated surface dose were 15.5% for brain tumour calculated with 3DCRT whereas the measured surface dose were 12.1%. For abdomen site the calculated surface dose for IMRT treatment plan was 16.5% whereas the measured surface dose was 12.6%.
Conclusions: The skin dose in IMRT for deep sited tumours is lower than in 3DCRT which is another advantage for the IMRT. The TLD readings showed that the difference between the calculated and measured point dose is negligible. The Superposition calculation algorism of the XIO, 4.04 treatment planning system modelled the superficial dose well.
No conflict of interest.

1089 POSTER

Development of pretreatment 'truly' patient-specific quality assurance procedure for stereotactic body radiotherapy using volumetric modulated arc radiotherapy

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Background: In stereotactic body radiotherapy (SBRT) using volumetric modulated arc therapy (VMAT), pretreatment patient-specific quality assurance (QA) is essential. But radiochromic films suitable for larger doses (10−25 Gy) than conventional fraction dose (~2 Gy) are hardly available now. In some institutions, VMAT-SBRT verification with radiochromic film have been performed by rescaling dose prescribed to be inside the optimal dose range from the calibration curve (c.g. ~2 Gy). This is not patient-specific QA. We have developed a new patient-specific QA procedure for VMAT-SBRT patient pretreatment verification.
Materials: Co-planar VMAT plans (one arc VMAT plans, the total dose 55 Gy in five fractions) were created in five patients, who have been already treated using breath-holding conventional seven non-coplanar static SBRT (55 Gy in five fractions). We constructed a script to export VMAT plan from Pinnacle^3 (Philips Medical Systems, Best, The Netherlands) and to divide it into three partial arcs VMAT plans and then to import the divided three arcs plan into Pinnacle^3. We compared digitally reconstructed radiographs (DRRs) of all control points, 2D/3D dose distribution and DVH parameters of targets and organs at risk (OARs) of original plans and divided plans. And then we performed gamma analysis on both plan with the DD-System (R-TEC. Inc., Tokyo, Japan) using 1 mm/1% with a dose threshold of 5%. We moreover divided the divided plans into three plans with one partial arc VMAT in Pinnacle^3 and performed patient-specific QA measurements for each partial arc plans as routinely performed in conventional fraction dose (e.g. 2 Gy).
Results: All original plans and divided plans are completely coincided on DRRs of all control points, 2D/3D dose distribution and DVH parameters of targets and OARs. Gamma analysis showed original plans and revised plans are perfectly matched. In all five patients, gamma evaluation of three plans with one partial arc VMAT plans showed more than 95 % of passing rate using 3 %/3 mm criteria.
Conclusions: New pretreatment 'truly' patient-specific QA procedure was developed using a script in Pinnacle^3. New procedure enables us true QA for VMAT-SBRT patient plans using the same procedures as ones in VMAT plan using conventional fraction doses.
No conflict of interest.

1090 POSTER

Quality improvement project streamlines workflow performance and results in improved access to cancer care

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Objectives: Our Team performed a work-flow performance quality improvement project in our Radiosurgery Center. Our primary endpoint was to decrease the mean time between initial consult and first radiosurgery treatment. Our goal was to determine our current performance level and then implement a systematic performance quality improvement process to streamline workflow through the center, which in turn would result in improved access to care, patient satisfaction, and clinical outcomes without compromising patient safety.
Methods: We retrospectively reviewed our workflow performance for 248 patients treated in 2010 using 15 metrics to evaluate delays in the workflow and identify variables we could modify to improve performance. We assigned times to each metric as a benchmark. Time limits were assigned to each step in the process. Our evaluation resulted in a goal of 23 days between consult and treatment. In 2011−12, we prospectively evaluated 539 patients using the above metrics to evaluate the effect of our interventions.
Results: In 2010, the Radiosurgery Center treated 248 patients; mean time between consultation and treatment was 36 days. Access to dedicated CT Simulation time was a cause for delay and for 2011 we increased dedicated slot times which reduced our mean time between consultation and start by 4.52 days to 31.48 days with 245 patients treated. We determined the largest barrier to care was insurance carrier approval. To improve the insurance approval process, our Radiation Oncologists developed site specific templates which provided specific carrier approval requirements depending on the type of radiosurgical intervention. Contouring of target volumes and treatment planning times were rigorously monitored and timelines were enforced for each step to prevent treatment planning delays. In 2012 we treated 294 patients and our mean time between consult and initial treatment dropped to 22.92 days, this was an 8.56 day improvement over 2011, and a 13 day improvement over 2010, while patient volume in the center increased by over 17%, between 2011 and 2012. Patient safety was monitored throughout the process to ensure there was no compromise in patient treatment from changes in the process.
Conclusion: This research demonstrates that proactive interventions can result in a significant reduction in time between consult and initial treatment. Improved access provides more agility within our center while allowing for scheduling flexibility to triage more acute lesions with expedited start times. Protected treatment planning time has been demonstrated to decrease the potential for errors in treatment plans while ensuring adequate quality assurance and plan review prior to treatment. This model is a low-cost high-yield example of the quality improvement process which could easily be adapted to fit many practice models and yield significant improvement in the delivery and access of safe patient care.
No conflict of interest.

1091 POSTER

Deliberated errors caused by shifts in an ionization chamber bidimensional array. How far can we get without realizing?

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Background: One of the issues we have to take into account about bidimensional ionization chamber arrays for IMRT pre-verification is the low spatial resolution and sample frequency. In this study we analyze PTW 2DARRAYSeven29® (2DARRAY) which consists of 729 ionization chambers with a center to center distance of 1 cm and a volume of 0.125 cm^3.
Our goal in this study is to find a pattern between systematic misalignments and the values of the gamma index criteria for IMRT verification. We also hope to determine if a spatial resolution of 1 cm is small enough to detect misalignments less or equal *to* 5 mm.
Materials and Methods: We carried out several deliberated shifts (±1 mm, ±3 mm and ±5 mm) in three orthogonal directions (head-feet, left-right and

up-down) on 2DARRAY placed inside PTW Octavius® Phantom (Octavius). Both of them were irradiated in a Siemens Oncor Impression® 6MV Linear Accelerator equipped with a 160 multileaf collimator. Previously, a real prostate plan was transferred on to 2DARRAY and Octavius CT and it was computed by Pinnacle® v9.2 Treatment Planning System without any shift, providing us with a reference dose map and a reference central chamber dose. We also measured the dose at the isocenter for 5x5, 10x10 and 20x20 cm^2 fields to check the constancy of the dose along the whole study. Finally, we compared the doses at the 2DARRAY central chamber and reference map doses computed by TPS to those measured in each shift using the 2DARRAY. The comparison between the reference dose map computed by TPS and 2DARRAY measured planar doses was performed by PTW Verisoft® Software drawing on a gamma index (3 mm, 3%, local dose).
Results: There is an agreement between the TPS reference dose in the central chamber and those obtained by 2DARRAY whatever the shift performed. In all cases the differences were less than 2.5%. However, we obtained unacceptable values for gamma index when shifts were greater than 1 mm. For 1 mm shifts, the drop in the gamma index was from 100% to 98.8%, the mean gamma index for 3 mm shifts was 81.1% and for 5 mm it was 70.4%.
Conclusions: Misalignments greater than 1 mm can be detected by map dose measured by 2DARRAY when using a gamma index criteria (3%, 3 mm, local dose) but no useful information is provided by dose at the 2DARRAY central chamber as we have a tolerance level of 3%. On the other hand, these results could be achieved once we had planned and verified about 30 prostate cases and the values of the gamma index were always approximate 100%.
No conflict of interest.

1092 POSTER

An approach to individualized tolerance level of patient-specific QA depending on treatment planning using dosimetric metrics

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Background: The aim of this study is to compare and evaluate the individualized tolerance levels of patient-specific DQA depending on the delivery techniques (IMRT vs VMAT) and treatment sites using a variety of dosimetric tools.
Material and Methods: Dosimetric QA (DQA) measurements were performed with (1) a point dose by an ion chamber, (2) 2D dose distribution by radiochromic film (EBT2) for an axial plane and an ion chamber array (Matrixx®) for a coronal plane, and (3) 3D dose distribution by a head-mounted ionchamber array (COMPASS®). The two criteria (2 mm/2% and 3 mm/3%) were used to analyze the gamma passing rate of 2D and 3D dose distributions. Several statistics were applied to analysis the normality of each group (IMRT, VMAT, Prostate, and H&N), significance between the comparisons (IMRT vs VMAT and Prostate vs H&N), and correlation between dosimetric tools. The concept of confidence limit was applied to approach to the tolerance levels.

Measurement		2D (Matrixx)	2D (Film)	3D w/Body	3D w/PTV
Point dose	*r*-value	−0.33	0.17	0.35	−0.32
	p-value	<0.05	0.29	<0.05	<0.05
	N	40	40	40	40
2D (Matrixx)	*r*-value		−0.11	−0.02	0.42
	p-value		0.49	0.89	<0.05
	N		40	40	40
2D (Film)	*r*-value			0.17	0.31
	p-value			0.30	0.05
	N			40	40
3D w/ Body	*r*-value				0.02
	p-value				0.90
	N				40

Results: The difference between IMRT and VMAT showed in the point dose, axial plane dose, coronal plane dose and 3D volume dose measurements. The difference between prostate and H&N showed in the axial plane dose, coronal plane dose, and 3D volume dose measurements. There was no the correlation between the dosimetric tools as shown in table.
Conclusions: 3D volumetric verification is required to assess the dose discrepancy in VMAT and the multi-institutional study is required to have confidence in the implementation of individualized tolerance level based on the approach and results in this study.
No conflict of interest.

1093 POSTER

Quality assurance in IMRT: A comparison between two-dimensional ionization chamber array and film dosimetry

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Background: Two dimensional ionization chamber arrays are an easy-handling and fast real-time method for pre-treatment verification in IMRT. However, spatial resolution can be an issue because the sample frequency in the Fourier domain must be at least 0.2 mm^{-1} (5 mm in coordinate space) when using 1 cm^2 beamlets. Commercial devices provide smaller resolutions PTW 2DARRAY Seven29® (2DARRAY): 0.1 mm^{-1}, Scanditronix Wellhofer IMRT Matrixx®: 0.13 mm^{-1} and Sun Nuclear Mapcheck2®: 0.14 mm^{-1}). Together with Merge 27® software, a 5 mm shift for 2DARRAY in orthogonal directions can provide a 5 mm spatial resolution map dose. Although this is not a good settlement as it triples the time for verification. The aim of this study is to check if 2DARRAY has a good gamma index agreement to Film dosimetry using Gafchromic® EBT2 when IMRT Step and shoot beamlets have a minimum area of 4 cm^2.
Materials and Methods: All the measurements were performed in a Siemens Oncor Impression® 6 MV Linear Accelerator that was equipped with a Multileaf Collimator of 160 leaves whose width was 5 mm at the isocenter. Planar doses were computed by Pinnacle v9.2 Treatment Planning System (TPS) and measured planar doses were carried out in Octavius® Phantom both for films and 2DARRAY. Also, computed doses at isocenter from the TPS were compared to measured doses using a PTW 31003 Semiflex® Chamber for film verification and the central ionization chamber from 2DARRAY.
The comparison between planar doses was made using gamma index (3 mm, 3%, local dose) for Head and Neck and Prostate cancer cases. We used FILM QA PRO® and PTW Verisoft® software for these purposes.
Results: In all prostate cases (N = 32) we obtained a gamma index higher than 95% for 2DARRAY or film verifications when comparing to the TPS planar doses. For head and neck cases (N = 13) we achieved a gamma index higher than 91% for all cases for film dosimetry and even better results for 2DARRAY verification as the results were never less than 95%. For dose at the isocenter the difference between TPS and semiflex® chamber or central chamber from 2DARRAY was never higher than 3% for both sets of cases.
Conclusions: PTW 2DARRAYSeven29® has proved to be a reliable and accurate method for IMRT pre-treatment verifications compared to film dosimetry and has the great advantage of real-time measurements for quality assurance purposes.
No conflict of interest.

1094 POSTER

Impact of inhomogeneous tissue on IMRT QA for MatriXX

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Purpose: By applying self-made inhomogeneous phantom to MatriXX, a group of IMRT plans were delivered, to observe the impact on test results on different measuring condition.
Method: Two foam planks were made to simulate the low density tissue, e.g lung tissue, in the size of (40×40×3)cm, identical to virtual water. Three measurement condition using MatriXX were arranged: A. virtual water only (8 cm top and 5 cm bottom); B. one foam plank was used plus 5 cm virtual water on its top, and 5 cm virtual water on MatriXX bottom; C. two planks were used on the top and at the bottom of MatriXX, with 5 cm and 2 cm virtual water planks wrapped. The sizes in B and C condition were same to A. CT scanning images for three conditions were obtained and transmitted to TPS. QA plans were generated to the scanning images respectively. The original plans were 10 esophageal cancer IMRT plans. The QA plans were calculated in CMS xio-release 4.62, using superposition algorithm, and then delivered to Elekta Synergy. Each plan was measured in different condition, and the gamma passing rate was obtained.
Results: There was no significant difference (P<0.05) among the three measuring condition. The results, i.e gamma passing rate, in B (98.78±1.34)% and C (98.71±1.16)% were as good as in A (98.49±1.10)%.

Conclusion: The results showed that there is no difference in MatriXX measurement, no matter what phantom is used. However, more measurements should be needed to make it confirmed.
No conflict of interest.

1095 POSTER

Multi-dimensional patient-specific plan QA on IMRT and RapidArc techniques

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Background: The aim was to distinguish the differences between IMRT and RapidArc delivery, through comparison of plan QA results in three modalities.
Materials: 20 cases with NPC were enrolled. Based on the simulation CT images and targets, IMRT and RapidArc plans were both generated for every case in Eclipse v8.6. The plans, after approved, were converted into QA plans, using virtual water as phantom. 1. A cylindric ion chamber (PTW 0.125cc) was applied to point dose QA. The selected point was set to iso-center. 2. MatriXX (IBA v1.76) was applied to plane QA. The plane through iso-center was the measurement plane. 3. COMPASS system (IBA v2.0) was applied to volumetric QA. Each QA plan was delivered to Varian Trilogy to be measured. For point measurement, the QA result was the ratio of measurement to planning. For plane and volumetric measurement, the QA results were gamma passing rate with the criteria of 3%&3 mm. The paired *t*-test was used as statistical analysis.
Results: Point QA: the average result was (96.83±0.84)% for IMRT and (97.03±0.46)% for RapidArc, $P = 0.275$.
Plane QA: the gamma passing rate on average was (97.59±0.61) for IMRT and (97.98±0.36)% for RapidArc, $P = 0.055$.
Volumetric QA: the gamma passing rate on average was (96.70±0.81) for IMRT and (97.03±0.83)% for RapidArc, $P = 0.068$.
Conclusion: Although the differences among three QA modalities were not significant, it's found that almost RapidArc plan measurement results were better than IMRT's. The study indicated that RapidArc technique could be as good and safe as IMRT in plan delivery.
No conflict of interest.

1096 POSTER

Dosimetric shield evaluation with tungsten sheet in 4, 6, and 9 MeV electron beams

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Purpose: In electron radiotherapy, shielding material is required for attenuate beam and scatter. A newly introduced shielding material, *Tungsten functional paper* (TFP), has been expected as much useful device which is lead-free, light, flexible and easily processed containing very tiny tungsten powders as much as 80 percent by weight. The purpose of this study is to investigate the dosimetric changes due to TFP shielding for electron beams.
Method and Materials: TFP (thickness 0−15 mm) was placed on water or water equivalent phantom. Percentage depth ionization and transmission were measured by 4, 6, and 9 MeV electron beams with 10×10 and 20×20 cm^2 field size. Off-center ratio was also measured using the film at depth of dmax under the similar condition. Then, beam profiles, transmission with two shielding materials, TFP and Lead, were evaluated.

Table 1. TFP thickness required for 95% and 98% reduction.

Depth	Attenuation	TFP thickness required (mm)					
Energy (MeV)		4		6		9	
Field size (cm^2)		10×10	20×20	10×10	20×20	10×10	20×20
0.0 cm	95%	5.56	5.63	10.57	10.74	15.61*	15.65*
	98%	5.87	6.09	11.86	11.93	16.20*	16.18*
0.5 cm	95%	4.31	4.30	8.88	8.94	15.06*	15.20*
	98%	5.11	5.08	11.14	11.34	15.91*	16.02*
1.5 cm	95%	0.98	0.98	5.67	5.70	11.49	11.99
	98%	1.33	1.34	7.63	7.91	15.12*	15.55*
3.0 cm	95%	–	–	–	–	4.99	5.49
	98%	–	–	0.66	0.77	8.63	11.47

*Estimation value by linear interpolation with transmission curve.

Results: TFP thickness required for 95 % and 98 % reduction is shown Table 1. The reduction of 95% by use of TFP at 0.5 cm depth were 4, 9, and 15 mm with 4, 6, and 9 MeV electron beams, respectively. Beam profile of TFP intended to increase dose at the field edge that might be influenced by thickness. The energy of 4, 6 MeV were not problem in the clinical situation since the transmission under shielding were less than 2%.
Conclusions: This study shows the characteristic of new radiation-shield-material (TFP) was evaluated by using the electron beams. It has several unique features and is highly expected to be useful for radiation protection for the electron beam.
Conflict of interest: *Other substantive relationships: Device (Tungsten functional paper) used in this study was provided by TOPPAN PRINTING CO., LTD, Tokyo, Japan.*

1097 POSTER

Dosimetric comparison of postoperative whole pelvic lymph node intensity-modulated radiotherapy for cervical cancer patients with multiple pelvic lymph node metastases

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Background: To study the dosimetric difference among RapidArc (RA) and intensity-modulated radiotherapy (IMRT) plans applying different energy x-ray for whole pelvic lymph node irradiation.
Material and Methods: Ten cases of cervical cancer who underwent radical surgery and demonstrated multiple pelvic lymph node metastases were treated with radiotherapy. Three plans were generated for each case: 7-field IMRT, one-arc RapidArc (RA1 = 358º)and two-arc RapidArc (RA2 = 716º). For each plan, 6 MV and 15 MV X-ray were applied respectively. The dosimetric differences were compared among different plans.
Results: All plans could meet the clinical requirement. The CI, HI and EVI of IMRT and RA2 were better than RA1 with significantly difference ($p < 0.05$), while the differences between IMRT and RA2 were not significant. There were no significant differences were found in irradiation dose of organs at risk except for small bowel V40 (IMRT < RA2).
Conclusions: Compared to IMRT, there were no significant dosimetric benefits were found except treatment time and monitor unit in radiotherapy for whole pelvic lymph node applying RaidArc. Additionally, the 6MV photons may be the prudent choice.
No conflict of interest.

1098 POSTER

Dosimetric test of collapsed cone convolution superposition algorithm in a heterogeneous media

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Background: The Collapsed Cone Convolution Superposition (CCCS) algorithm is used for dose calculation and intrinsically considers the effects of patient heterogeneities. The purpose of this study is to evaluate the accuracy of Prowess 5.0 (Prowess Inc., Concord, Ca) TPS dose calculations using CCCS algorithm in a heterogeneous phantom.
Material and Methods: Dose calculations of Prowess 5.0 TPS using the CCCS algorithm were compared against measured data. Measurements were performed with ionization chamber (0.057 cm^3) and EBT2 radiochromic films. The films were calibrated in 10 points between 0 and 320 cGy and scanned in Epson Expression 1000 XL scanner. Two different phantoms were used in the measurements and both were imaged using CT scanner for TPS dose calculation at corresponding detector locations. Both phantoms are composed of an 8.6 cm depth cork slab between two 7 cm depth solid water slabs. Each phantom has a rounded shape volume (≈95.5 cm^3) made of wax inside the cork. One wax volume is split at central plane for film placement and the other is made with the ionization chamber build up cap at volume's center. The irradiations were carried out with 6 MV Primus Siemens linear accelerator (Siemens Medical Solutions, Concord, Ca) photon beam with 20x20 cm^2 field size, 90 cm SSD and 200 MU. Three field profiles were acquired with film dosimetry in the crossplane direction: 1) at 7 cm depth (in solid water/cork transition); 2) at the central plane of wax volume; and 3) at 15.6 cm depth (in cork/solid water transition). Further, absolute dosimetry with ionization chamber was performed at two positions: 1) inside the wax volume with the build up cap; and 2) at 16.6 cm depth, inside a solid water ion chamber slot (1 cm deeper than cork slab).
Results: The field profiles did not present dose differences higher than 2% or 2 mm DTA. Inside the wax volume, the dose calculated was 2.6% higher than the measured dose, and in deeper position was 4.5% higher.
Conclusions: The field profiles relative dosimetry presented acceptable agreement with TPS calculation. The absolute measured doses showed

that collapsed convolution superposition algorithm can overestimate dose (up to 4.5%) in a heterogeneous media. Further study is necessary for CCCS algorithm clinical implementation.
No conflict of interest.

1099 POSTER

MicroRNA-regulated pathways of radiotherapy sensitivity and resistance in breast cancer

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Background: Radiotherapy is an important component of primary, adjuvant, and palliative treatment for many types of solid tumour. Because of this, innate or acquired resistance is a major clinical problem. These issues are compounded by the fact that effective biomarkers that can identify this subset of resistant tumours or can otherwise accurately target radiotherapy to those patients who would most benefit from it have yet to be discovered. We previously identified 3 microRNAs (miRs) able to regulate genes associated with key mechanisms of the cellular response to radiotherapy, and which could trigger resistance or sensitivity to clinically-relevant doses of radiation in breast cancer cells *in vitro*. We aimed in the current study to characterise these miRs.
Materials and Methods: Bioinformatics analyses were used to identify putative gene targets of each miR of interest. Target binding was confirmed by luciferase assay, QPCR analyses, and Western blotting. Knockdown of several targets themselves also triggered significant sensitivity or resistance to radiation in breast cancer cells *in vitro*. Four key targets, NEK1, PLK2, SKP2, and RAG1 were further tested as biomarkers predictive of relapse following radiotherapy in two independent early-stage breast cancer patient cohorts.
Results: Microarray gene expression profiling of miR mimic-transfected MCF7 cells together with miR binding sequence prediction algorithms were used to identify putative miR targets. Mimics were confirmed to bind to specific 3′ UTR sequences of several key genes, including those associated with DNA repair, cell cycle control, and reactive oxygen species defence, resulting in their downregulation at both the mRNA and protein level. For radiotherapy-sensitizing mimics this also had functional significance, with impaired DNA repair and increased sensitivity to both radiation and DNA damaging chemotherapy agents. Several miR targets were also effective biomarkers − the expression of miR targets NEK1, PLK2, SKP2, and RAG1 were significantly correlated to relapse-free survival in 435 early-stage breast cancer patients.
Conclusion: The expression of several genes important to the cellular response to radiation are miRNA-regulated, which suggests that the dysregulation of these miRs could lead to resistance to radiotherapy in patients. Furthermore, several of these genes correlate to survival in radiotherapy-treated patients, and could be used to guide treatment in the clinic.
No conflict of interest.

1100 POSTER

Identification of compounds modifying radiation-therapy using a 3D-microtissue technology

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Background: The two key issues in chemo- and radiation therapy is the development of tumor resistance as well as toxic effects on normal tissue. In this sense new strategies are required to increase efficacy of radiation to improve the therapeutic impact and reduce toxicological side effects**.** Material and Methods: The performance of 3D cell culture systems over classical 2D culture systems has been shown to provide a closer representation of tissue-level biology. This has led to the rapid adoption of 3D systems for both drug discovery and toxicology. InSphero has developed a highly reproducible hanging drop technology able to generate monotypic cell spheroids called microtissues in a 96-well format.
Results: The innovative 3D-microtissue plate technology has been adapted for analysis of the cellular response of radioresistant T47D breast cancer and FaDu head and neck cancer cells to combined radio-chemotherapy (RCTx). We have validated the model by comparing the treatment of microtissues with 10 different chemotherapeutic compounds, each tested alone and in combination with an acute 2 Gy radiation exposure. The cancer cells were stably transduced with GFP-lentiviral vector enabling faster high throughput quantification of 3D microtissue growth assessment using an Operetta working Software and detection system 'Harmony 3.0' (PerkinElmer, USA). We studied the ability of RCTx to modify 3D-microtissue growth 3, 6 and 10 days after treatment. Results for five compounds (Actinomycin D, Staurosporine, Docetaxel, Doxorubicin and Vinblastine) showed that the IC50 values were improved by the addition of the single 2 Gy radiation dose, indicating that they are capable of inducing a radiosensitation effect on radioresistant breast cancer cells. Panels of commercial secondary functional assays were adapted to the 3D-microtissue high throughput assay. Cellular viability and cytotoxicity were measured directly in microtissues using the CellTiter-Glo Reagent (Promega, USA). Apoptosis was measured using an ELISA based M30-Apoptosense assay (TECOmedical AG, Switzerland).
Conclusions: These results confirm that the assay operated with the 3D-microtissue model system is able to detect compounds that modulate tumor cell survival after irradiation.
No conflict of interest.

1101 POSTER

Identification of the mechanisms of radiosensitization by human papillomavirus (HPV) in head and neck cancer cell lines

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Background: Several clinical studies have shown that HPV+ head and neck squamous cell carcinomas (HNSCC) present a more favorable outcome and greater response to radiotherapy. Although there are some data supporting the hypothesis that HPV-related tumors have a better survival due to a higher sensitivity to radiation therapy, it is difficult to conclude that the improved clinical outcome of HPV-related HNSCC is only attributable to intrinsic radiosensitivity of the HPV+ cells. As an hypothesis, it is postulated that a complex interaction concurs between intrinsic mechanisms of radio-response and the tumor micro-environment including cells of the immune system stimulated by the presence of HPV. The objectives are to identify the mechanisms of radiosensitization by HPV and to investigate whether irradiated HPV+ cells exhibit an increased immunogenic cell death signal.
Material and Methods: We determined radiosensitivity by clonogenic survival of two HPV+ HNSCC cell lines (UPCI-SCC-154 & UPCI-SCC90) compared to two HPV− (SCC61 & SQD9). Cell cycle distribution and G2/M checkpoint were assessed by flow cytometry. DNA damage repair was evaluated by gamma-H2Ax assay. In addition, apoptosis was investigated in the four cell lines together with immunogenic cell death signal, through membrane exposure of calreticulin.
Results: The surviving fraction at 2 Gy (SF2) for the two HPV+ cell lines was 0.13 and 0.15 for UPCI-SCC-90 and UPCI-SCC-154, respectively while SF2 for SQD9 was 0.49 and 0.16 for SCC-61 a head and neck squamous cell line known to be radiosensitive. Cell cycle distribution indicated a block in G2/M 24 h after irradiation for the HPV+ cell lines not observed in the HPV− cells. In HPV+ cells, gH2Ax kinetics after a single dose of 5 Gy correlated the SF2 data with a slower clearance of gH2Ax for HPV+ cells, compared to HPV− cells. At 24 h after irradiation, less than 5% of cells in all groups were apoptotic, but further time points still need to be analysed. Finally, calreticulin membrane translocation as a measure of immunogenic death signal after irradiation was detected in HPV+ but not in HPV− cell lines, before and 24 h after irradiation.
Conclusions: These results confirm the increased radiosensitivity of HPV+ cells although at this point further investigation is needed to elucidate what are the mechanisms implicated. However, detection of calreticuline translocation as a marker of immunogenic death signal in HPV+ cells opens an interesting hypothesis.
No conflict of interest.

1102 POSTER

Antitumor effect induced by combination of radiation with a novel HSP70 inhibitor pifithrin-mu on human prostate cancer

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Background: Heat shock proteins (HSPs) are constitutively expressed in many cancers, and various types of stress increase their expression. HSPs are thought to make cancer cells resistant to anti-cancer therapy, with HSP70 playing a central role in the resistance. Recently, pifithrin-μ (PFT-μ) has been revealed as a new HSP70 inhibitor. In this study, we investigated the antitumor effects of the combination therapy of radiation with PFT-μ on

human prostate cancer cell lines and attempted to elucidate the underlying mechanisms.
Material and Methods: Three human prostate cancer cell lines (LNCaP, PC-3, and DU145) and a human normal prostate epithelial cell line (PrEC) were used. HSP70 expression in the cancer cells was examined by immunoblot. HSP70 was knocked down with siRNA. Cell viability was evaluated using a WST-8 assay. Clonogenic capacity of cancer cells was determined using a colony formation assay. Cell proliferation was examined by flow cytometry after labeling with carboxyfluorescein succinimidyl ester (CFSE).
Results: Knockdown of HSP70 significantly decreased the viability and the colony-forming capacity of all three prostate cell lines, suggesting a crucial role of HSP70 in the survival of cancer cells. The combination of low-dose radiation (2 Gy) and low-dose PFT-μ (3 μM) significantly decreased the viability and the colony-forming capacity of three prostate cancer cell lines compared with either treatment alone. Importantly, this combination effect was not observed on PrEC cells. In addition, CFSE assay revealed that the combined therapy decreased proliferation of cancer cells, suggesting the induction of growth arrest.
Conclusions: These data indicate that the combination therapy with radiation and PFT-μ can decrease the growth of human prostate cancer cells, and that PFT-μ is a promising reagent to enhance the antitumor effect of radiation.
No conflict of interest.

1103 POSTER

In vitro prediction of radiation sensitivity in patients treated with external beam radiation therapy

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Background: Understanding the basis of clinical radiosensitivity (RS) is considered by many to be a key goal of radiation research. Numerous cellular and molecular assays have been applied to cells from RS cancer patients in an attempt to predict which patients may suffer excessive RS reactions. In this study, a correlation between transformed lymphoblasts and clinical response was investigated using the limiting dilution assay (LDA) in cell lines from clinically RS individuals with seven tumour varieties, compared with controls.
Material and Methods: Lymphoblasts from 29 cancer patients (19 RS patients, 10 controls) who had or had not experienced severe normal tissue reactions, and one ataxia telangiectasia positive control cell line, were exposed to graded doses of gamma-radiation *in vitro* and cell survival assessed via LDA. RS cell lines were created from patients who had RTOG Grade 2 (n = 1), Grade 3 (n = 12) or Grade 4 (n = 3) skin reactions. Cell survival was expressed as the surviving fraction at 2 Gy (SF_2), and data fitted with non-linear regression analysis.
Results: SF_2 ranged from 0.0245–0.3894, with variability in cell survival evident both among and within individuals, with a coefficient of variation of 31% overall. A non-significant trend was seen between acute or consequential late reaction cell lines and LCL radiosensitivity ($p = 0.10$ and $p = 0.08$ respectively). Two RS outliers were detected in the assay corresponding clinically to Grade 3 late breast fibrosis, and Grade 4 osteoradionecrosis of the jaw and odynophagia in a patient treated for head and neck cancer.
Conclusions: The presence of cell survival heterogeneity and a number of patients demonstrating *in vitro* sensitivity but normal clinical response, among other reasons, may limit the usefulness of this assay for predictive purposes. However, two radiosensitive outliers were observed in the present study which may yield insight into the genetic basis of RS, for example by utilizing deep DNA sequencing.
No conflict of interest.

1104 POSTER

Ionizing radiation of esophageal carcinomas leads to alterations of the hyaluronan matrix and stroma mediated cell death of tumor cells in vitro

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Background: Radiotherapy is commonly used in the management of esophageal carcinomas (OSC). Hyaluronan (HA), a major carbohydrate constituent of the extracellular matrix, forms a complex, biologically active matrix with its binding partners (e.g. versican). This network plays an important role in tumor–stroma interactions. However, little is known about the response of the HA-matrix to radiation.
Material and Methods: To investigate changes of the HA-matrix induced by ionizing radiation, mono-cultures of OSC and fibroblasts were irradiated with 10 Gy. The HA matrix was analysed by qRT-PCR, ELSA and immunocytochemistry. Cell cycle was investigated by FACS. Cells were observed by time lapse microscopy. Cell death was measured by visual analysis. The results were confirmed by PARP and Annexin-V analysis. The role of ROS in matrix changes was assessed by the ROS inhibitor N-acetylcysteine (NAC).
Results: Mono-cultures of OSCs and fibroblasts show an altered expression of HA-matrix related genes. The main HA-synthase (HAS)-isoform of OSCs, HAS3, was up-regulated (2.02 ± 0.25 fold of control), whereas the main isoform in fibroblasts, HAS2, was reduced (0.21 ± 0.02 fold of control). Versican mRNA is induced in fibroblasts (1.64 ± 0.08 fold of control), however not changed in OSCs. HA quantification by ELSA showed no differences in irradiated cells, although structural changes evident by the formation of HA-cables were observed in irradiated OSCs. Immunocytochemistry confirmed the increase of versican in irradiated fibroblast. To evaluate functional consequences of the altered HA-matrix in the tumor–stroma interaction, fibroblasts were seeded on OSCs 24 h after irradiation. A significantly increased amount of dead OSCs was observed in co-culture with irradiated fibroblasts compared co-culture with mock-irradiated fibroblasts (36.72 ± 9.68 fold of control). This effect could be abolished by pre-incubation of fibroblasts with NAC. PARP western blots and flow cytometry confirmed the microscopic results.
Conclusions: In conclusion, ionizing radiation leads to stromal cell mediated, ROS dependent, cell death of tumor cells. These effects might be associated with changes of the HA-matrix. In particular, versican has been shown to exhibit pleiotropic effects concerning cell death. Therefore, it might protect stromal cells while driving tumor cells into apoptosis. This effect will be subject to further investigations, thereby possibly leading to new innovative strategies in tumor chemoradiotherapy.
No conflict of interest.

1105 POSTER

Relationship between the quantity of serum reactive oxygen metabolites and skin toxicity grade in the irradiated rat model

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Background: Adverse effects of radiation are one of the major problems for the patients undergoing radiotherapy. It is known that radiation causes damage by producing free radicals or oxidative stress. The aim of this study was to analyze relationship between oxidative stress and reactions to radiation in vivo using rats.
Materials and Methods: 4 MeV Electron beams were irradiated to the skin of the right leg of 6-week-old female Wistar rats. Serum ROMs were quantified with d-ROMs test using blood collecting from caudal vein.
Serum ROMs (reactive oxygen metabolites) were quantified with d-ROMs test instead of directly measuring free radicals, which have extremely short life-time.

1. Rats were divided into 3 groups according to irradiated dose (0 Gy [control], 2 Gy/fraction, 30 Gy/fr.), and then time course of serum ROMs of each group was quantified using blood sample at certain intervals.
2. In another experiment, rats were divided into 4 groups according to irradiated dose (0 Gy [control], 30 Gy/fr., 50 Gy/fr., 70 Gy/fr.). Serum ROMs and skin reactions were examined at certain intervals. Skin reactions to radiation (inflammation, erosion, ulcer, necrosis, etc.) were graded according to the grading system.

Results:

1. In the analysis of time-course of measured serum ROMs, there was a significant difference among the 3 groups (0 Gy, 2 Gy, 30 Gy), and measured serum ROMs were higher in the 2 Gy group than other groups ($p = 0.018$, repeated-measure ANOVA). At 3 days after irradiation, the serum ROMs of 2 Gy-group were significantly higher than those of the other groups (0 Gy vs. 2 Gy: $p = 0.034$, 2 Gy vs. 30 Gy: $p = 0.028$).
2. There were significant differences among 4 groups in the time-course of skin grade in each group ($p < 0.001$), the skin grades were high in the order of 70 Gy-group, 50 Gy-group, 30 Gy-group (and control-group). In the analysis of time-course of measured serum ROMs, there were significant differences among the 4 groups. Measured serum ROMs of 70 Gy-group and 50 Gy-group were significantly higher than that of 30 Gy-group and control-group. The peak of serum ROMs and appearance of skin toxicity were emerged around the same time.

Conclusion: Increasing the amount of serum ROMs by irradiation has been shown. Moreover, it has been shown that an increase in serum ROMs and occurrence time of the skin reactions to radiation were almost concurrent. Measuring serum ROMs may be useful for predicting radiation damage.
No conflict of interest.

1106 POSTER

Inhibition of tumor growth and metastasis in mice by pulsed low-dose (<0.5 Gy) X-ray irradiation

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Background: Main radiotherapy problem of cancer treatment is side-effect as a result of high dose of radiation. All of the modern apparatus for cancer therapy are not enough efficient when low-doses applying. It related with the biological sensitivity and reaction of tumor cells on radiation. Biological effects could be increased by using pulse-modulated radiation. It could allowed to significantly decrease radiation dose with saving antitumor efficacy. The source of low-dose repetitively pulsed X-ray radiation was first developed and created at the Institute of high-current electronics (Russia).
Material and Methods: 'Sinus-150' as a generator of pulse periodic X-ray was applied. A high-voltage pulse had a half-height duration of 4 ns and amplitude of 260 kV. The calculated photon energy spectrum had a maximum at 90 keV, and most of the quantum flux was the 60–200 keV range. Dose per pulse was 0.3 mR, absorbed dose were 0.12; 0.2 and 0.5 Gy for 2-time irradiation (day 6 and 9). Solid-type of Lewis lung carcinoma was prepared by intramuscularly transplantation of 3×10^6 cells into the hind limb of C57BL/6 female mice. Tumor volumes were measured with calipers and a volume calculated (L+W+W/2). The metastases of the lung were counted using a stereoscopic microscope.
Results: Low-dose pulsed X-ray inhibits growth of Lewis lung carcinoma cells at all experimental groups. Irradiation with absorbed dose 0.12 Gy affects 69% of tumor inhibition, 0.2 Gy – 56% and 0.5 Gy up to 46% compare to control group. Inhibition of metastasis growth (by square of colonies) was highest in group 0.5 Gy (72%) and lowest at 0.2 Gy absorbed dose (58%). Applying 0.12 Gy produced 68% decreasing of metastatic colonies square. Same time, index inhibition of metastasis (by number of colonies) was highest both in groups irradiated with 0.12 and 0.5 Gy (84−85%) and only 67% observed in group with absorbed dose 0.2 Gy.
Conclusions: Pulse regime increase antitumor efficacy of low dose X-ray up to 50−70% and antimetastatic action up to 60−80%. Similar effects of non-pulsed X-ray achieved when the absorbed dose exceed 10−20 Gy.
No conflict of interest.

1107 POSTER

X radiation effects on small cell lung cancer and non-small lung cancer − an in vitro study

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Background: Lung Cancer (LC) is one of the most diagnosed cancers, with higher mortality in men and among women is the fourth most commonly diagnosed and the second with highest mortality rate. This cancer is associated with smoking, which is the cause of about 80% in men and 50% in women worldwide. Radiation therapy may be used in all stages of LC, enabling better the disease site control, as well as the reduction of metastatization, however, tumor radioresistance is often a barrier to therapeutic effectiveness. The aim of this study was to assess the effects of ionizing radiation (X-rays) in three LC cell lines, two of non-small cell lung cancer (NSCLC) (H1299 and A549 cells) and one of small cell lung cancer (SCLC) (H69 cells), namely in cell proliferation and viability.
Materials and Methods: To attain the purposed objectives we submitted the 3 LC cells to X irradiation (0.5, 15 and 30 Gy**)** and used spectrophotometry, clonogenic assays and flow cytometry after 48 hours, to analyze the effect on cell proliferation, viability and death, and also to evaluated the effect on cell cycle.
Results: X-rays induces a decrease in cell proliferation and viability in a dose, time and cell line dependent manner, inducing cell death preferentially by apoptosis. These anti-proliferative and cytotoxic effects are in agreement with the observed cell cycle arrest. However, our results show that A549 and H69 cells are more sensitive to cell death induced by radiation, being the H1299 cells more resistant. These results may be related with differences in the p53 expression or stress oxidative response and could contribute to radiotherapy failure in this type of cancer.
Conclusion: Our preliminary results suggest that X-rays leads to a decrease in LC cells viability inducing cell death mainly by initial apoptosis. However, the sensibility and/or resistance to radiation may be dependent on molecular LC characteristics which could influence the response to radiotherapy and consequently treatment success.
No conflict of interest.

1108 POSTER

Prognostic value of the nodal ratio and Ki-67 expression in breast cancer patients treated with postmastectomy radiotherapy

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Background: This study was performed to evaluate the prognostic or predictive factors in breast cancer patients having postmastectomy radiotherapy (PMRT).
Material and Methods: A total of 113 patients received PMRT between 2003 and 2009: 61 patients underwent preoperative systemic therapy, and 52 patients received postoperative systemic therapy. Baseline molecular parameters were evaluated by immunohistochemical analysis, using biopsy specimens (preoperative systemic therapy group) or surgical specimens (postoperative systemic therapy group).
Results: The median follow up time was 72.3 (34.0–109.4) months for surviving patients. The median number of excised lymph nodes was 22 (1−55), and the median nodal ratio (NR) was 0.19 (range, 0−1). Higher NR had association with worse disease-free survival (DFS; relative risk (RR), 3.589; $p = 0.003$), and overall survival (OS; RR, 3.444; $p = 0.019$). Higher baseline Ki-67 was associated with poor locoregional progression-free survival (LRPFS; RR, 2.944; $p = 0.041$), DFS (RR, 3.274; $p = 0.002$), and OS (RR, 3.133; $p = 0.015$). Patients were classified into three subgroups: low risk (NR $\leqslant$0.2 and baseline Ki-67 $\leqslant$20%; n = 34), intermediate risk (NR >0.2 or baseline Ki-67 >20%; n = 63), and high risk (NR >0.2 and baseline Ki-67 >20%; n = 16). At the time of analysis, all the low risk group patients survived. Comparing the high and the low risk group patients, there was a significant difference in LRPFS ($p = 0.040$) and DFS ($p < 0.001$). Between the intermediate and the low risk group, significant difference was observed in DFS ($p = 0.022$), while not in LRPFS ($p = 0.204$).
Conclusions: In breast cancer patients having PMRT, higher NR and baseline Ki-67 were associated with worse outcomes. A prognostic model using these two factors can discern the patients with poor prognosis regardless the setting of systemic therapy, preoperative or postoperative.
No conflict of interest.

1109 POSTER

Spinal cord tolerance dose in fractionated stereotactic body radiation therapy for spinal metastases − can biologic equivalent dose according to linear quadratic model be applied?

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Background: Stereotactic body radiation therapy (SBRT) has been increasingly adopted to treat spinal metastases with its merit of rapid dose fall off near spinal cord. The authors hypothesized that irradiated dose to spinal cord is low (<6 Gy) enough to adopt the linear-quadratic (LQ) model in biological effective dose (BED) calculation with modern SBRT technique. This study is to verify this hypothesis, and report clinical outcome in patients with spinal metastases treated by fractionated SBRT.
Material and Methods: Between January 2010 and March 2012, 44 cases of spinal metastases in 33 patients were treated with Novalis Tx® at Gachon University Gil Medical Center. Spinal cord was contoured starting from 6 mm above the superior of the planning target volume(PTV) to 6 mm below the inferior of the PTV. Spinal cord itself was always excluded from PTV. Prescription doses to PTV ranged from 26−44 Gy in 4−6 fractions. The most common prescription dose was 40 Gy in 5 fractions.
Results: The rapid dose fall off from PTV resulted in much decreased dose to spinal cord. The maximum irradiated dose to spinal cord per fraction varied from 2.8 to 5.5 Gy (average, 4.3 Gy) depending on each PTV shape and fraction size. The maximum dose to spinal cord were 12.1–33.2 Gy (20.5 Gy) which were equivalent to 15.0–62.4 Gy2/2 (2 Gy per fraction with α/β ratio of 2, EQD2/2) (32.9 Gy2/2) according to LQ model. The average maximum dose to spinal cord was 54.8% of prescription dose to PTV. The average dose to the 10% spinal cord volume was 14.3 Gy (18.5 Gy2/2). The mean follow-up period was 9.8 months (0.3–37.4 months). No patient developed radiation-induced myelopathy or other neurologic deficit. During follow-up period, radiological local control rate and pain control rate were 80.1% and 90.9%, respectively. There were 3 compression fractures at 2, 3 and 4 months after treatment, respectively.

Conclusions: The dose to spinal cord was low enough to apply LQ model when spinal cord dose was constrained to 55% of prescription. The clinical outcome until now supports its validity without any radiation-induced myelopathy.
No conflict of interest.

1110 POSTER

Stereotactic body radiotherapy for spinal metastases using CyberKnife

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Background: To evaluate local control and pain and quality of life improvement for spinal metastases, with and without prior irradiation, treated with Stereotactic Body Radiotherapy (SBRT) using CyberKnife.
Material and Methods: Between August 2008 and December 2011, 47 lesions in 30 patients were treated with SBRT for spinal metastases. Twelve lesions (25.5%) were given re-irradiation for recurrence after prior radiotherapy. Patients were treated with a median dose of 27 Gy (range, 18−33 Gy) in a median of three fractions (range, 1−5) by CyberKnife Xsight™ Spine tracking system. The median target volume of 47 spinal metastatic lesions was 28.28 cm^3 (range, 0.9–301.45 cm^3). Radiation was prescribed to the 73−83% isodose line that encompassed at least 90 % of the tumor volume except one re-cyberknife case. SBRT dose was calculated with linear-quadratic model and normalized to a 2-Gy equivalent dose (nBED, α/β=2 Gy for spinal cord, α/β=10 Gy for tumor). Doses to a point within the spinal cord that received the maximum dose (Pmax) were checked. Local failure was defined as progression by imaging and/or clinically or the case that other therapy was given such as surgery or re-irradiation. Pain relief was assessed by Revised Oswestry Disability Index (ODI) Questionnaire before and 3 months after completion of SBRT. The median follow-up period was 6.3 months (range, 1.2–26.4 months).
Results: The local progression-free survival (LPFS) rate at 12 months was 84.7%, and 4 out of 47 (8.5%) tumors have progressed radiologically. Two of 4 treatment failure occurred in re-irradiated tumors, which received 21 Gy in 3 fractions, and their time to local progression was short (3.2 and 3.8 months). The median spinal cord Pmax nBED was 51.1 Gy2/2 (range, 3.4–75.1) in retreatment and 62.6 Gy2/2 (range, 3.2–84.9) in initial treatment. No neuropathy or myelopathy was observed during follow-up periods. No one suffered from spinal compression fracture. All patients experienced pain relief with SBRT. The ODI score dropped significantly from 51.5 to 18.4 on an average.
Conclusions: SBRT using CyberKnife is a safe and effective modality to achieve local control. SBRT offers significant pain relief in spinal metastases and maintenance of quality of life even after previous radiotherapy.
No conflict of interest.

1111 POSTER

Partial breast irradiation margins with two deep-inspiratory breath-hold techniques

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Background: Partial external beam breast irradiation (PBI) is being investigated in a number of ongoing phase III trials (IMPORT LOW, NSABP B-39, RAPID) and it is hoped that this technique will, in selected patients, reduce normal tissue doses whilst maintaining local control rates. Deep-inspiratory breath-hold with the active breathing coordinator™ (ABC_DIBH) significantly reduces the volume of heart irradiated, and voluntary deep-inspiratory breath-hold (v_DIBH) significantly reduces median heart and LAD volumes receiving >50% of the prescription dose. These dosimetric savings are projected to equate to a 10-fold reduction in cardiac deaths. Combining PBI with DIBH would be expected to reduce normal tissue doses yet further, however, data is lacking on suitable PBI margins to account for setup error and organ motion with DIBH. This study aimed to estimate appropriate CTV-PTV margins for using DIBH in combination with PBI.
Material and Methods: The UK HeartSpare Study (Stage IA) compared v_DIBH with ABC_DIBH in terms of positional reproducibility and normal tissue sparing. Patients were randomised to receive one technique for fractions 1−7 and the second technique for fractions 8−15 (40 Gy/15 fractions total). Cone-beam CT (CBCT) images were acquired for 6/15 fractions and matched to planning-CT data. Using clip-based matches, population systematic (Σ) and random errors (σ) were estimated. By applying the margin recipe proposed by van Herk (2.5 Σ + 0.7 σ), appropriate CTV-PTV margins were estimated for both DIBH techniques.
Results: Twenty-three patients were recruited between February and August 2012. Twenty-two patients underwent CBCTs and clip-based matches were possible in 18 (4 patients underwent mastectomy). In all, 126 CBCTs were analysed and uncorrected data was used. Σ for v_DIBH were 2.4 mm (right-left (R-L)), 3.6 (superior-inferior (S-I)), 3.0 mm (anterior-posterior (A-P)) and σ were 2.3 mm (R-L), 2.7 mm (S-I) and 2.7 mm (A-P). Σ for ABC_DIBH were 3.2 mm (R-L), 2.9 (S-I), 2.7 mm (A-P) and σ were 2.3 mm (R-L), 3.4 mm (S-I) and 3.5 mm (A-P). Estimated CTV-PTV margins for v_DIBH were 8 mm (R-L), 11 mm (S-I) and 9 mm (A-P) and for ABC_DIBH were 10 mm (R-L), 10 mm (S-I) and 9 mm (A-P).
Conclusions: Using either DIBH technique, a minimum uniform CTV-PTV margin of 10 mm is suggested for PBI.
No conflict of interest.

1112 POSTER

Accelerated partial breast irradiation (APBI) with tomotherapy HI-ART on 85 patients treated at San Giovanni-Addolorata Hospital Rome: Preliminary report

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Background: Partial Breast Irradiation (PBI) after conservative breast surgery is a novel radiation technique for the tumor bed area where the most frequent local recurrences occur. The smaller irradiated volume allows a higher dose fractionation with shorter overall treatment time (APBI) and reduced total dose to the breast as well as nearby structures. It was recently reported that exposure of the heart to ionizing radiation during whole breast irradiation (WBRT) increases the subsequent rate of ischemic heart disease and the increase is proportional to the mean dose to the heart.
Material and Methods: At the Breast Unit of our Hospital, since April 2011 we have enrolled 85 women in a phase II study on APBI, using a highly conformal external beam approach with Tomotherapy HI ART linac. Inclusion criteria were: age $\geqslant$50 years, unicentric and unifocal tumors smaller than 3 cm diameter, negative surgical margins without an extensive intraductal component (EIC) and lympho-vascular invasion (LVI). Patients received a total dose 38.5 Gy in 3.85 Gy fractions daily per 2 weeks. The clinical target volume (CTV) was the tumor bed and the close area defined by surgical markers. The primary end points of the study are local control and acute and late toxicity. Secondary end points are survival, cosmetic outcome, QoL and patient compliance.
Results: We present a preliminary report in terms of local control, toxicities, cosmetic outcome, QoL and patient compliance. In all cases the treatment was well tolerated and no acute or subacute side effects (according RTOG scale no toxicity > grade 1). Physical examination at 3−6−12 months and bilateral mammogram, US, MRI at 1 year, were performed on all women after radiotherapy. With a median follow-up of 10.5 months (range 3−22), there were no ipsilateral breast tumors and no loco-regional recurrences. The overall average of the mean doses to the whole heart was 0.9 Gy: much lower than that reported in cases of standard WBRT (>4.9 Gy).
Conclusions: The growing evidence obtained from phase I−II studies supports the use of APBI for selected early stage breast cancer. In our experience patients with tumor-related cautionary features will benefit from careful selection and a highly conformal external beam approach with Tomotherapy HI ART linac can significantly decrease the mean dose to the whole heart by at least 1/5 with respect to WBRT. These preliminary results need to be confirmed by longer-term follow-up data.
No conflict of interest.

1113 POSTER

Application of IMRT technique in treatment of malignant gliomas: Assessment of treatment tolerance

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Background: Assessment of tolerance of combined modality therapy of patients with malignant gliomas irradiated using IMRT technique. We compared dose distribution in IMRT and conformal 3D treatment plans.
Materials and Methods: Between 2009 and 2012 in the Oncology Center in Krakow 50 patients with malignant gliomas received combined modality treatment. Mean age was 53 years (range 24−70 years). All patients were in good performance status (WHO 0−1). There were 38 patients with glioblastoma multiforme and 12 with anaplastic astrycytoma.

38 patients underwent complete resection and 12 partial resection. Patient were irradiated using IMRT technique with a total dose of 60 Gy in 30 fractions. All patients concurrently received temozolamide in the dose of 75 mg/m^2. In all patients we performed additional plans using 3D conformal radiotherapy (3D-CRT) techniques and compared with IMRT plans. The 3D-CRT plans were prepared using 3−4 fields and IMRT plans consisted of 7−8 fields. The primary objective was to treat the planning target volume and to minimize the dose to organs at risk (OAR). Volumetric analysis, target coverage and conformity of prescribed doses were used in plan comparison.
Results: Treatment tolerance was vary good in all patients. Only 12 patients needed steroids during treatment. Adjustment of the dose distribution to the target volume was improved and the critical structures were better spared in the IMRT plans than in 3D-CRT plans. For all patients the mean dose and the maximum dose to OAR were significantly reduced in IMRT plans. With respect to target volume, IMRT technique reduced the maximum dose while increasing the minimum dose, resulting in improved conformity. In same patients with tumors located very close to OAR it was impossible to give 60 Gy for target volume with 3D-CRT technique because of not acceptable doses in OAR.
Conclusions: The IMRT technique combined with concurrent temozolamide is well tolerated and offers significant advantages comparing to 3D-CRT. Application of IMRT allows dose reduction at OAR without compromising target coverage.
No conflict of interest.

1114 POSTER

Feasibility of simultaneous integrated boost by helical tomotherapy in whole-pelvis radiation for prostate cancer: From a standpoint of acute toxicity

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Background: The validity of simultaneous integrated boost (SIB) by helical tomotherapy (TOMO) was assessed in terms of acute intestinal and urinary toxicity by comparing with 3-dimensional conformal radiotherapy (3DCRT) in the cases of whole-pelvis radiotherapy (WPRT) for prostate cancer.
Material and Methods: Thirty-eight consecutive patients who underwent curative WPRT were retrospectively reviewed. The pathologic diagnoses for all patients were adenocarcinoma, and median age was 68 years (range, 50−79 years). Twelve patients (31.6%) were treated by TOMO SIB method. A local boost for the prostate circumferential area was added to WPRT sequentially for 3DCRT and concomitantly for TOMO SIB. The median prostate dose was 64.8 Gy (range, 59.4 to 75.6 Gy) for 3DCRT and 66.6 Gy (range, 66.0 to 75.0 Gy) for TOMO SIB. The WPRT dose was 45.0 Gy (range, 41.4 to 45.0) for 3DCRT and 51.0 Gy (range, 50.4 to 54.0 Gy) for TOMO SIB. Acute toxicities were assessed according to RTOG criteria.
Results: The ratio of Grade 2 or higher acute intestinal toxicity was lower in the TOMO SIB group ($p = 0.008$). When intestinal toxicity was analyzed separately for rectum and bowel except rectum (BXR), TOMO SIB showed no significant difference in rectal toxicity ($p = 0.191$) with borderline superiority only in BXR toxicity ($p = 0.047$). The proportion of acute urinary toxicity of Grade 2 or higher was 55.3% (21 patients) with no significant difference in the proportion between the two groups ($p = 0.796$). On dosimetric analysis for the rectum, the mean dose ($p < 0.001$), dose delivered to 80% of the rectum (D80) ($p < 0.001$), V15 Gy ($p = 0.001$), V25 Gy ($p < 0.001$), V40 Gy ($p < 0.001$), and V45 Gy ($p = 0.029$) were higher in 3DCRT. For the bladder, dose delivered to 80% of the bladder (D80) ($p < 0.001$), V25 Gy ($p < 0.001$), V40 Gy ($p < 0.001$), and V45 Gy ($p < 0.001$) were higher in 3DCRT. For BXR, overall dosimetric data did not show significant difference between TOMO SIB and 3DCRT except maximum dose ($p < 0.001$).
Conclusions: Acceptable acute intestinal toxicity results by TOMO SIB should be verified with more detailed anatomic categorization such as rectum and BXR. TOMO SIB could not reduce acute urinary toxicity because of the inevitable high prostatic urethral dose exposure. Current dosimetry system did not reflect acute toxicities directly at the time of full dose WPRT, especially in urinary toxicity assessment. Proper dosimetric guidelines need to be determined in TOMO SIB.
No conflict of interest.

1115 POSTER

Is there a role for IMRT in bilateral breast cancer? Dosimetric comparison of IMRT and standard 3D conformal radiation therapy

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Background: The incidence of bilateral breast cancer is increasing due to improved diagnosis test and methods of screening. In addition, recent trials have shown the benefit of regional nodal irradiation. The aim of our study is to demonstrate if there is dosimetric benefit in women diagnosed with bilateral breast cancer that undergoing bilateral breast and regional nodal irradiation comparing standard 3D conformal radiation therapy 3DCRT) versus IMRT technique after breast conserving surgery.
Material and Methods: Volumes were delineated on 6 patients. The 3DCRT technique involved bilateral tangential fields for breast and two oblique, one anterior and one posterior, to the supraclavicular fossa. IMRT technique involved several multifield coplanar inverse planning. The prescription dose was 50 Gy in 25 fractions. Dose- volume histograms, dose homogeneity and dose to OAR were evaluated.
Results: See Table 1.

	V95 (%)		D99-D1 (%)		Mean dose (Gy)		V20 Gy (%)		V30 Gy (%)	
	IMRT	3D	IMRT	3D	IMRT	3D	IMRT	3D	IMRT	3D
Breast	96	96.6	(92.7–107.1)	(92.5–108.2)						
Supra	96.4	97.8	(91.7–106.4)	(91.1–107.5)						
R-Lung					15.8	18.3	25.7	35.3		
L-Lung					15.7	18.3	25.3	35.8		
R+L							25.5	32.5		
Heart					12.3	9.9			2.3	11.3

IMRT was superior to 3DCRT with improvements in reducing the volume of heart and lung in the high dose region (V30 and V20 respectively) and achieving lower mean lung dose (IMRT: 15.8 Gy versus 3DCRT: 18.3 Gy), although for some patients we would find within the limits of tolerance for lungs with both techniques. This can be explained due to larger gaps between inner parts of both breasts.
However, there were no significant improvements covering the planning target volume. Both techniques are adequate with good coverage in the V95 with no differences in PTV dose homogeneity.
Conclusions: IMRT provided reduction in the high dose heart volume without differences for improvements in coverage. We recommend this technique for cases with breasts showing a big concavity which embraces the heart and there is a high probability of superimposed beams on the skin in the gap between inner parts of both breasts.
No conflict of interest.

1116 POSTER

Impact of 6DOF robotic couch in high volume radiotherapy centre, surveying geometrical, dosimetric, management parameters

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Background: To investigate the impact of Protura 6 degree of freedom (DOF) Robotic Patient Positioning System (CIVCO Medical Solution) in high volume radiotherapy centre, surveying geometrical, dosimetric, management and parameters.
Material and Methods: We enrolled patients with pelvic, brain and head and neck cancer treated by 3D-CRT, RapidArc, IMRT and SRT radiotherapy.
A daily CBCT was acquired before dose delivery. The translational and rotational displacements obtained by 3D automatch were applied on the Protura Robotic Couch to obtain a more accurate alignment. The initial treatment plan was copied to a translated CT (TPt) and a rototranslated CT (TPtr) according by MIM 5.5.2 software according to the collected displacements.
Finally the daily dose volume histogram (DVH) was calculated for both the treatment plans and the dosimetric parameters were compared.
Results: From October 2012 to April 2013, we enrolled 23 patients: 8 affected by prostate cancer treated by RapidArc, 11 by brain cancer treated by RapidArc or 3D-CRT or SRT, 3 by H&N cancer, treated with IMRT.

The mean (±SD) interfraction displacement in vertical, lateral, longitudinal direction and the mean (±SD) interfraction rotations (Pitch, Roll and Yaw) were reported in the table 1.
Regarding prostate displacement, 85% of the translational shifts were <5 mm and 6% of the rotation were >2º. H&N translational shift smaller than 5 mm were 94% while 9% of the rotational shift were bigger than 2º. For brain and SBRT brain displacement, the translational shift <5 mm were 94% and 96% respectively, the rotational displacement >2º were 9% in both the group.
No correlation was observed between the magnitude of translational and rotational shifts.
The mean time for all treatment procedures take just one minute more respect to conventional IGRT without displacement correction by 6DOF robotic couch. The applied protocol is anyway no time consuming and it does not required any extension of staff.
Preliminary linear correlations were observed in a selected subgroup of prostate patients, between shifts and dosimetric parameters differences (PTt vs PTtr): yaw rotation with the V20 femoral heads and pitch rotation with V50 rectum.
Conclusion: Our preliminary results underline the feasibility of IGRT workflow with Protura system in daily clinical practice and in standard patient care. The data show the relevance of the translational and rotational errors and their dosimetric effect analysis is ongoing.
No conflict of interest.

Table 1. mean (±SD) interfraction translational and rotational patient setup error

Location	Translational error (mm)			Rotational error (º)		
	x axis (Lat)	y axis (Lng)	z axis (Vrt)	Pitch	Roll	Yaw
Prostate (n = 223)	0.5±3.8	−1.8±4.4	−1.8±4.1	−0.4±1.1	−0.2±1.1	−0.1±0.7
Brain (n = 164)	1.2±2.6	0.5±3.4	−1.2±1.8	−0.2±1.2	0.7±1.2	0.9±1.0
H&N (n = 24)	0.8±2.8	0.5±3.1	0.7±2.8	−0.3±0.7	0.95±1.2	0.1±0.5
SBRT brain (n = 17)	0.7±3.7	−1.2±3.4	−1.2±2.3	−0.5±1.0	−0.1±1.2	0.9±1.3

1117 POSTER

The role of stereotactic body radiation therapy for hepatocellular carcinoma refractory or unsuitable for other therapeutic modalities

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Background: The aim of this study was to evaluate safety and efficacy of stereotactic body radiotherapy (SBRT) for the naive or salvage treatment of inoperable hepatocellular carcinoma (HCC) were unsuitable for other therapies.
Methods: The authors reviewed the medical records of 30 patients that were treated by SBRT in our institution when they had HCC without another standard treatment option or complete response of loco-regional therapy between August 2010 and November 2013. All patients SBRT dosages (24−60 Gy from two to five fractions) were administered according to tumor volume. Survival, response, and toxicities were evaluated. Response evaluation was performed according to modified Response Evaluation Criteria for Solid Tumors.
Results: Twenty-five patients had Child-Pugh class A disease, 5 patients had class B disease. Eleven patients had macrovascular invasion (7 portal vein thrombosis, 2 hepatic vein thrombosis, 2 both venous thrombosis), 2 patients had bile duct invasion. The median greatest tumor dimenstion was 32.5 mm (range, 10–170 mm). The median survival was 9.5 months (range 4−28 months) and the median progression-free survival was 6 months (range 1−19 months). Twenty-five patients (83.3%) achieved complete response within 6 months after complete SBRT, 2 patients (6.7%) had a partial response, 3 patients had stable disease, and 1 patients had progression disease. Infield local recurrence was observed in 3 patients, and outfield failure was 13 patients. Three patients (10%) experienced grade 3 gastrointestinal toxicity, 1 patients (3.3%) experienced grade 4 gastric ulcer perforation, and 4 patients (13.3%) experienced pneumonitis.
Conclusions: This study suggests that SBRT can be effective and safe modality that achieves promising rates of local control in inoperable HCC, even with vascular invasion. A further well controlled, large scaled study to reduce gastrointestinal and pulmonary toxicity is recommended.
No conflict of interest.

1118 POSTER

A comparison study utilizing portable bladder scanner versus cone beam computed tomography (CBCT) to measure bladder volumes in post-prostatectomy patients having radiotherapy

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Background: In post-prostatectomy radiotherapy to the prostatic bed, consistent bladder volume is essential to minimize the amount of small bowel within the radiotherapy fields and to maintain the position of the treatment target volume. We assessed the differences between bladder volume readings from a portable bladder scanner (BS-V) and those obtained from planning CT (CT-V) or cone-beam CTs (CBCT-V). Inter-fraction bladder volume variation was also determined.
Material and Methods: BS-Vs were recorded in the treatment position pre- and post-planning CT or CBCT. The percentage difference between the readings using the two imaging modalities, standard deviations, and 95% confidence intervals were determined. Data was analyzed for the whole patient cohort and separately for the older BladderScan™ BVI3000 and newer BVI9400 model. Inter-fraction bladder volume variation was evaluated by determining the percentage differences between the CT-V with CBCT-V. Treatment duration incorporating the BS and CBCTs were determined.
Results: Fourteen patients were enrolled into this study, producing 133 datasets for analysis. BS-Vs were taken using the BVI9400 in four patients (43 datasets). The mean BS-V and CT-V or CBCT-V was 253.2 mls and 199 cm^3, respectively. The mean percentage difference between the two modalities was 19.7% (SD 42.2; 95% CI 12.4 to 26.9). BVI9400 model (n = 43) produced more consistent readings with a mean percentage difference of −6.2% (SD 27.8; 95% CI −14.7 to −2.4%). The mean percentage difference between CT-V and CBCT-V was 31.3% (range −48%- 199.4%). Treatment duration from time of first BS reading to CBCT was on average 12 minutes (range 6−27).
Conclusions: The BS produces bladder volume readings of an average of 19.7% difference from those CT-V or CBCT-V and can potentially be used to screen for large inter-fraction bladder volume variations in radiotherapy to prostatic bed. The observed inter-fraction bladder volume variation suggests the need to improve bladder consistency. Incorporating the BS into practice is feasible.
No conflict of interest.

1119 POSTER

Verification of mechanical accuracy of new irradiation technique with simultaneous gantry and ring rotation

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Background: Vero4DRT (MHI-TM2000) is a unique image-guided radiotherapy system consisting of an O-ring gantry that is designed to rotate ±185º around the patient (gantry rotation) and ±60º around its vertical axis (ring rotation). This system can realize a new irradiation technique called Dynamic WaveArc (DWA) which employs continuous and simultaneous gantry and ring motion during dose delivery. The purpose of this study is to verify the mechanical accuracy of DWA irradiation.
Material and Methods: (1) Verification of irradiation accuracy during ring rotation. Beam outputs during ring rotation (rotation range were −30º − +10º and −10º − +30º for clockwise (CW) and counter clockwise (CCW) directions) were measured using a farmer type ionization chamber and cylindrical phantom, and compared to the output at static irradiation. At the same time, the mechanical accuracy was assessed by analyzing linac log files. The ring position error (E_R) and accumulated MU error (E_{MU}) at each time were evaluated as the differences between planned and actual values recorded in the log files.
(2) Mechanical verification of DWA irradiation by log file analysis. Some test pattern irradiations with different ring rotational range (±5º, 10º, 15º, 30º), direction (CW, CCW), and speed (1.0, 2.0, 3.0 deg/s) were examined. In all test plan, gantry were rotated from 270º to 90º (CW direction). The E_R, E_{MU}, and gantry position error (E_G) at each time were evaluated by the log files.
Results: (1) Beam output variation with ring rotation was less than 0.2% on the basis of the output value with static irradiation. E_R and E_{MU} were less than 0.03º, 1.1 MU, respectively.
(2) E_R, E_{MU}, and E_G were less than 0.11º,3.4 MU, and 0.13º, respectively. Although each mechanical motion were stopped momentarily (for about 0.5

sec) in the turning point of gantry and ring speed, the beam irradiation was continued with low dose rate (nearly 100 MU/min) in the actual treatment machine. Therefore, maximum E_{MU} were occurred in the suspended time. These differences were compensated in about 2 seconds after that time. Except these time, E_{MU} were less than 1.5 MU.
Conclusions: As an initial experiment, we have demonstrated that Vero4DRT has sufficient mechanical accuracy and beam output constancy during gantry and ring rotation. A more quantitative evaluation of irradiation accuracy, treatment planning and dose distribution are needed to apply this new irradiation technique in clinical settings.
Conflict of interest: *Advisory board: T. Mizowaki and M. Hiraoka have consultancy agreement with Mitsubishi Heavy Industries Ltd., Japan. Other substantive relationships: M. Yamada and S. Kaneko have substantive relationship with Mitsubishi Heavy Industries Ltd., Japan.*

1120 POSTER

Development and evaluation of a system based on 3D printer to create IMRT compensator blocks

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Background: In this study a system based on 3D printer was developed and evaluated to manufacture IMRT compensator blocks from a fluency map. This alternative method doesn't use milling machines.
Material and Methods: A fluency map of a prostate case planned with Jaws-Only IMRT (Prowess Panther®, v.5.01) was selected from our clinical database. An algorithm was developed to convert an image file into a STL file (used by 3D printers). The gray levels of the intensity map were converted into a STL file representing a mold thicknesses. The mold was printed by a 3D printer (Z Corp®, model 310). It was made with a thermal resistant powder. Then it was filled with *cerrobend* alloy. After solidification time, the mold was removed and the final IMRT block was achieved. The algorithm considered previously data acquired about linear attenuation coefficient and beam hardening factor of the *cerrobend* alloy. In order to evaluate the block, dosimetric tests were performed in 3 planes of a phantom (depths: 2.5, 6.5 and 15.5 cm) using a matrix with 729 ionization chambers (PTW®, 2D Array). Phantom/detector CTs were used to generate reference dose distributions of the selected beam (intensity map) predicted by a Jaws-Only IMRT algorithm. The gamma-index function (3%, 3 mm) was used for dose distribution evaluation. The Monitor Units (MU) were defined carrying out measurements of absolute dose using a thimble ionization chamber in a homogeneous dose region. It was used the MU that provided a dose closer than that predicted by TPS. Further, absolute doses were measured in 7 depths for 2 regions of the IMRT block. The block thicknesses of these regions were 0 and 1.5 cm.
Results: The mold printing and the manufacturing of the IMRT block took 4 h. The MU used was 10% less than that reported by the same Jaws-Only IMRT plan. The MU used was 60 (dose deviation of 0.66%). The measurements using a matrix of detectors provided 81, 99 and 91% of the assessed points approved for the depths of 2.5, 6.5 and 15.5 cm respectively. The absolute doses measurements presented dose deviations up to 1.8% for all depths and both regions.
Conclusions: The 3D printers can be effectively used to manufacture IMRT compensator blocks. The advantages to this approach are: it can be fully conducted inside a radiotherapy facility; 3D printers are easier to operate. The results suggest lower cost and production time. Further investigations are in progress to permit the clinical use.
No conflict of interest.

1121 POSTER

Dosimetric relevance in prostate cancer of 6 degree of freedom patient correction with Protura Robotic Couch System

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Background: To investigate the magnitude and the dosimetric relevance of translational and rotational errors on IGRT prostate RapidArc using Protura 6 degree of freedom (DOF) Robotic Patient Positioning System (CIVCO Medical Solution).
Material and Methods: We enrolled patients with cT3aN0M0 low risk for nodal involvement prostate cancer, treated with RapidArc simultaneous integrated boost. PTV2 was obtained adding margins of 0.7 cm to seminal vesicle base (CTV2), while PTV1 adding to prostate (CTV1) a margin of 0.7 cm in all directions and 1.2 cm as lower margin. A daily CBCT was acquired before dose delivery. The translational and rotational displacements obtained by 3D automatch were applied on the Protura Robotic Couch to obtain a more accurate alignment. The initial treatment plan was copied to a translated CT (TPt) and a rototranslated CT (TPtr) according by MIM 5.5.2 software according to the collected displacements. Finally the daily dose volume histogram (DVH) was calculated for both the treatment plans and the dosimetric parameters were compared.
Results: From October 2012 to April 2013, we enrolled 8 patients with a median age of 76 yrs (range 72−77). We performed 223 CBCT studies, 223 TPt and 223 TPtr. The mean (±SD) interfraction displacement in vertical, lateral and longitudinal direction was-1.8±4.1 mm, 0.5±3.8 mm and −1.8±4.4 mm respectively, with 85% of the shifts <5 mm. The mean (±SD) interfraction rotations were: Pitch= −0.4±1.1º, Roll = −0.2±1.1º and Yaw = −0.1±0.7º, with 6% of the rotations >2º. No correlation was observed between the magnitude of translational and rotational shifts. Dosimetric evaluation is ongoing and nowadays it was carried out on 4/8 patients We observed two linear correlations between yaw rotation and the V20 femoral heads and pitch rotation with V50 rectum. Regarding prostate target coverage, V95% and V105%, no significant difference between the TPt and TPtr was observed.
Conclusion: Our preliminary data show the relevance of rotational shift in prostate patients. The preliminary dosimetric data underlines that the used PTV margins are such as to compensate all translational and rotational shifts detected before treatment. Dosimetric effects evaluation of PTV reduction margins, useful to promote dose escalation studies, is ongoing.
No conflict of interest.

1122 POSTER

Stereotactic Body Radiotherapy (SBRT): Are we improving? Trends from a single Brazilian institution

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Background: The possibility of delivering radiation in a single high dose or with short radiation courses of high doses/fraction is very attractive. Though, the use of SBRT for curative or palliative purposes is becoming very popular besides the fact that the technology needed for such treatment is not yet worldwide available. The objective of this study was to make a profile of the indications of SBRT in the institution.
Materials and Methods: Data of patients' registers from May/2007 (first treated patient) to February/2013 were retrospectively collected. We extracted data on patients' characteristics (demographics), treatment sites, data processing, fractionation, dose and technique. Two independent researchers performed data collection.
Results: 74 patients, 47 (63.5%) men, with histologically proven primary or metastatic tumors (clinical/radiographic or by biopsy) were treated. The median age was 73 years (31−96 years). Ten (13.5%) patients were treated from 2007 to 2009 (period 1), and 64 (86.5%) from 2010 to 2013 (period 2). The most usual treated site was lung, comprising 51/74 (70%) lesions (39 primary and 12 metastatic tumors). In period 1, all 10 treated patients had primary lung tumors. In period 2, there was still a predominance of lung tumors 41/64 (64.1%). In addition, 17 (26.5%) bone tumors (4 primary and 13 metastatic), 5 (7.9%) liver metastases and 1 (1.5%) primary prostate cancer was also treated. One to five fractions from 7 Gy to 24 Gy with total doses ranging from 12 to 60 Gy were delivered. Single doses were mostly used for bone tumors, and lung and hepatic lesions were treated with 3 or 5 fractions. Prescription ranged from 78 to 85% isodose. The equivalent dose to 2 Gy fractions (EQD2) was calculated for evaluation of the different fractionation schemes. Three-dimensional (3D) conformal technique was the most widely used (81%), followed by volumetric arc therapy (VMAT) (15%) and intensity modulated radiotherapy (IMRT) (4%). In period 1, only 3D techniques was used, and in period 2, 78.2% of patients were treated with 3D, 15.6% with DA, and 6.2% with IMRT. In all cases, prescription and plan analysis was based on already published protocols (RTOG and others) on the respective disease site, and 74% of the plans respected absolutely all the required dosimetric criteria of the protocols; the others were approved with minor deviations.
Conclusion: In this private institution, there has been an increase in the use of SBRT along the years. A progressive indication for different tumor sites, as well as an evolution of the treatment technique was observed. All treatments were based in already published and well-established protocols.
No conflict of interest.

1123 POSTER

Is what you move what you get? A phantom study of surrounding tissue importance in delineation of moving targets

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Purpose: To evaluate the relevance of surrounding tissues for contouring of moving targets in tissue specific phantoms.
Material and Methods: The xy-table (SunNuclear®) was combined with a self-developed equipment. This equipment enabled programable motion in 3 dimensions of a 3.4l PMMA box. A water filled table tennis ball simulated the tumor. The ball was placed centrally in PMMA box, surrounded by three different materials: corkboards to simulate lung tissue (lung phantom − LunPh), animal fat to simulate fatty soft tissue (fatty tissue phantom − FatPh) and water with contrast medium with hounsfield units (HU) adapted to simulate liver tissue (liver phantom − LivPh). Slow planning 3D-CT (Somatom Emotion, Siemens Medical Solutions®) were aquired with and without phantom movements (period 3s). Linear motions in y direction (cranio caudal) with amplitudes of 5 and 10 mm, respectively and complex motions with simultaneous amplitudes in x, y and z directions (2.5, 10, 2.5 mm, period 3 s) were performed. Additionally, patients' tumour trajectory were reconstructed using the center of mass motion of GTVs delineated in the 10 phases of 4D-CT scans. These movements were simulated with each phantom. The ball volume was contoured using the Eclipse 10 planning system (Varian Medical systems®) in optimal window settings The contoured ball volumes were compared with the mathematically calculated ball volumes.
Results: The relative differences between contoured and calculated volumes are presented in the table. The volume of the ball without movement was overestimated in LunPh and FatPh and underestimated in the LivPh. As compared to the real volume, the volume of the moving target was underestimated in all phantoms. Further, significant differences were found between the three phantoms.

Table: Relative difference between contoured and calculated ball volume

Motion amplitude	Relative difference [%]		
	LunPh	FatPh	LivPh
0	111.9	112.4	96.4
y 5 mm	94.4	97.4	69.6
y 10 mm	91.2	90.8	70.3
x 2.5 mm, y 10 mm, z 2.5 mm	89.7	91.5	82.7
Patients (average ± standard deviation)	93.7±7.0	91.9±2.8	71.5±5.4

Conclusion: Our results showed relevant differences between real target volumes and contoured target volumes if the target is surrounded by different tissues. This could have an impact on the gross tumor volume and internal target volume delineation, and needs to be critically considered when delineating target volumes at different anatomical sites.
No conflict of interest.

1124 POSTER

Quantitative study of 18F-fluorodeoxyglucose and 18F-fluorothymidine PET characteristics in esophageal squamous cell carcinoma staging

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Objective: PET has become the key investigative tool with its expanding role in esophageal carcinoma diagnosis, staging and assessing or predicting response to therapy. Until recently, early detection and surgery are the hope of cure for patient with esophageal carcinoma. In addition, precise pretherapeutic staging is crucial in choosing best available therapy for esophageal carcinoma patient. The aim of this study was to quantitatively evaluate the value of diagnostic information provided by both ^{18}F-FDG and ^{18}F-FLT PET and quantitatively investigated whether ^{18}F-FLT PET had a better performance compared with ^{18}F-FDG PET in esophageal squamous cell carcinoma (ESCC) staging and delineation.
Materials and Methods: 26 patients with newly diagnosed ESCC and underwent pretreatment ^{18}F-FDG and ^{18}F-FLT PET were included in this study. The indices such as the standardized uptake value (SUV), gross tumor length and extracted texture parameters between ^{18}F-FDG and ^{18}F-FLT PET were compared, respectively. Moreover, the indices' relationship between ^{18}F-FDG and ^{18}F-FLT PET mentioned above, were analyzed using Spearman's correlation coefficient and Paired T-test. Subsequently all patients received esophagectomy and the extracted PET indices' capability in ESCC pathological staging were assessed by Kruskal-Wallis test and Mann-Whitney test. In addition, tumor delineation length on ^{18}F-FDG (SUV threshold 2.5) and ^{18}F-FLT (SUV threshold 1.4) PET were validated by pathologic gross tumor length.
Results: ^{18}F-FDG highly correlated with ^{18}F-FLT possessing a high correlation coefficient value r approximate 0.8 and $p < 0.001$ in SUVmax or SUVmean. ^{18}F-FDG uptake was significantly higher than ^{18}F-FLT with respect to average SUVmax(^{18}F-FDG: 11.48, ^{18}F-FLT: 6.07) or average SUVmean (^{18}F-FDG: 6.09, ^{18}F-FLT: 3.80), with Paired T-test result $p < 0.001$. In terms of texture parameters' relationship Entropy and Correlation (two derived texture parameters) showed statistically significant difference. Both of ^{18}F-FDG and ^{18}F-FLT PET SUV, some of texture parameters,gross tumor length and shape feature showed statistically significant difference with respect to their feasibility in ESCC staging. The mean±standard deviation pathologic longitudinal tumor length was 5.52±2.56 cm and delineation length for ^{18}F-FDG and ^{18}F-FLT were 5.60±2.32 cm and 5.49±2.43 cm, respectively.
Conclusion: The ^{18}F-FDG and ^{18}F-FLT PET scans have their own advantages in ESCC staging and tumors were well identified as the nonphysiologic distribution of radiotracers intensity typically higher than normal tissues on either PET scans. Delineation on the two types of PET with proper threshold can both provide accuracy estimation of pathologic tumor length. Those different indices extracted from PET scans can be potentially employed to differentiate AJCC and TNM in ESCC stage.
No conflict of interest.

1125 POSTER

Comparative study of the position and/or volume of diaphragm dome, lung and heart between quiet end-inspiration and end-expiration three dimensional CT assisted with active breathing control and corresponding phases in four dimensional CT

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Background: To compare the position and/or volume of diaphragm dome, lung and heart between quiet end-inspiration and end-expiration three dimensional CT (3DCT) assisted with active breathing control (ABC) and the corresponding phases in four dimensional CT (4DCT).
Material and Methods: Eighteen patients with peripheral lung cancer underwent 4DCT simulation scan during free breathing and 3D-CT simulation scans in end-inspiratory hold (CT_{EIH}) and end-expiratory hold (CT_{EEH}) in succession. The 4DCT images from each respiratory cycle were sorted into 10 phases: the 0% phase was defined as end-inspiratory phase (CT_0), while the 50% phase was defined as end-expiratory phase (CT_{50}). The left and right lungs, heart and both diaphragm domes were delineated separately on CT_0, CT_{50}, CT_{EIH} and CT_{EEH} images.
Results: In the cranio-caudal direction, between CT_{EIH} and CT_{EEH}, CT_0 and CT_{50}, the mean displacement differences of both diaphragm domes were not larger than 1.5 mm and were not statistically significant (P = 0.228, 0.106). Between CT_{EIH} and CT_0, CT_{EEH} and CT_{50}, the centroid position differences of two lungs and heart were found all statistically significant (P = 0.001–0.047) in the cranio-caudal direction, and not statistically significant (P = 0.128–0.798) in the radial directions. The volumes of two lungs were both larger in CT_{EIH} and CT_{EEH} than in CT_0 and CT_{50}, and the differences between them were found both statistically significant (P = 0.000–0.041); while the volume of heart was larger in CT_0 and CT_{50} than in CT_{EIH} and CT_{EEH}, but the differences between them were found both not statistically significant (P = 0.054, 0.085).
Conclusions: Compared with quiet end-inspiration and end-expiration 3DCT assisted with ABC, in the corresponding limited phases of 4DCT, the centroid positions of lungs and heart had obvious hysteresis in the cranio-caudal direction, and the volumes of lungs were obviously larger in the former than in the latter, while the volumes of heart were smaller in the former than in the latter. From the point of view to protect lung and heart, when other conditions were same, gated radiotherapy in quiet end inspiration was better basing on ABC than basing on 4DCT.
No conflict of interest.

1126 POSTER

Impact of anatomic changes and treatment parameters on simulated dose to lung tumors in a patient cohort with sequential 4D-CTs

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Background: The physical and biological properties of scanned carbon ion beam therapy potentially permit more conformal irradiation than photons. Range sensitivity and interplay renders treatment of moving tumors complex. Purpose of this study is to investigate adaptive treatment of lung cancer in a sequential 4DCT planning study.
Materials and Methods: For 7 NSCLC lung tumor patients from MDACC (The University of Texas MD Anderson Cancer Center), a total of 55 weekly 4DCT datasets were available. Reference phases of each subsequent CT were registered rigidly (based on bony anatomy or the complete CT) to mimic patient setup. Motion phases of each 4DCT were registered non-rigidly. Gating plans were simulated using the GSI treatment planning system TRiP4D, including 4D-dose reconstructions. For each calculation, the target point was set as the center of the CTV in reference phase. The impact on dose coverage (V95) of variations in focus size and length of the gating window was analyzed. Three beam foci (6, 10 and 15 mm) and three gating windows (11.9%, 30% and 50% of the amplitude) were investigated. To assess the need of margins, these initial simulations were performed without a CTV-PTV extension.
Results: The largest effects on dose coverage were caused by anatomic variations such as tumor shrinkage but also different patient positioning with deformed soft tissue. For three patients, such variations reduced V95 below 75% for all studied parameter combinations.
A larger beam focus and a shorter gating window increased the homogeneity of the dose, but not sufficiently to compensate the anatomic changes. The worst configuration of longest gating window and smaller focus yielded a mean V95 value of 79.7% (from 51.3% to 96.3%) while the best configuration of shortest gating window and largest focus yielded V95 = 91.2% (71.0% to 99.7%).
Conclusions: Dose coverage deteriorated due to anatomic changes as well as patient setup. Gating window and beam focus size could partially recover 4D-dose coverage, but adaptive treatment schemes appear necessary. CTV-PTV margins will most likely cover patient setup uncertainties and will be included as a next step.
No conflict of interest.

1127 POSTER

External beam radiotherapy target volumes for cervical cancer: A multi-institutional study assessing contouring variability on magnetic resonance imaging (MRI) and computer tomography (CT)

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Background: Accurate delineation of target volumes for external beam radiotherapy is a crucial step in radiation treatment, but can be associated with considerable uncertainty and variability. The aim of this study was to compare target volume delineation on MRI vs CT and to compare Simultaneous Truth and Performance Level Estimation (STAPLE) generated contours with expert clinician contours.
Material and Methods: Nine expert clinicians from five tertiary centres across Australia participated. Each clinician independently contoured target volumes on a CT and a T2 weighted 3T MRI dataset for a cervical cancer patient. Gross tumour volume (GTV), uterus, cervix, vagina and parametrium were each delineated using RTOG consensus guidelines and the individual volumes were combined into a clinical target volume 'CTV'. To evaluate inter-observer agreement the kappa co-efficient was calculated for each structure, and the dice similarity co-efficient (DSC) was used to compare individual clinician contours for each structure to both a clinician determined consensus contour and the STAPLE contour.
Results: The GTV_{staple} volume for MRI was 2.5 times smaller than the CT volume (17.1 cm^3 vs. 43.1 cm^3) and there was less inter-observer variation when contouring the GTV on MRI compared to CT, with a kappa coefficient (corrected for chance) of 0.70 for MRI and 0.52 for CT. The MRI contours for the uterus and CTV demonstrated substantial agreement between clinicians with kappa coefficients 0.64 and 0.68 respectively. The remaining contours completed on MRI showed moderate agreement with kappa coefficient of 0.41 for cervix, 0.43 for vagina and 0.56 for parametrium. The cervix contours on CT only showed slight agreement with a kappa coefficient of 0.31. The remaining structures on CT (uterus, vagina, parametrium and GTV) demonstrated moderate or substantial agreement. The MRI GTV_{staple} contour demonstrated a high concordance with the clinician determined consensus contour with a DSC of 0.77. The MRI $uterus_{staple}$, $parametrium_{staple}$ and CTV_{staple} contours all exhibited a good concordance with the clinician determined consensus contour with DSCs of 0.74, 0.69 and 0.80 respectively.
Conclusions: GTV delineation on MRI resulted in a smaller GTV and reduced inter-observer variability compared to CT. STAPLE contours on MRI demonstrated a high level of agreement with expert clinician consensus contours for GTV, uterus, parametrium and CTV.
No conflict of interest.

1128 POSTER

Dosimetric comparison of four different irradiation techniques to treat mediastinum in Hodgkin Disease (HD) and lung cancer (LC) patients (pt): Three dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT) and helical tomotherapy (HT)

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Aims: To compare PTV coverage and OAR dose distribution in the treatment of mediastinum in HD and LC pt, treated with 30 Gy and 50 Gy using 3DCRT, IMRT, VMAT, HT.
Methods and Materials: 10 HD and 9 LC pt were treated with 3D-CRT. 2 experimental plans were calculated for each technique and patient: 1 optimized for PTV coverage, 1 for lung dose reduction. IMRT static fields(f) plans were evaluated with a 5 and 8f combination. In LC pt, for HT plans optimized for the reduction of lung doses, 2 plans were calculated (collimation width 1 cm /2.5 cm); 9 and 10 plans were calculated for each pt. Optimal PTV coverage required D95 and D98 >95% of prescribed dose; lungs constraints were V20 <20% and V5<50%. PTV and OAR doses were directly compared. The best experimental plan was compared with that used to treat the pt. Differences were considered significant if $p < 0.01$ (T-student).
Results: Results are presented in the tables. LC: a statistical direct correlation was shown between 'PTV length/lung length' ratio (PLLLR) and lungs V5 for 3D-CRT, IMRT with 8f and VMAT plans and an inverse correlation between PLLLR and PTV D95 for HT plans.
Conclusion: For HD the dose distributions obtained with HT seem to be better than with the other techniques, with a high target coverage and a reduction of high doses to lungs and spinal cord. For LC IMRT with 8f is the best technique to obtain the goals of the optimization. VMAT can be used when the PLLLR is low. HT doesn't allow to maintain an acceptable PTV coverage if the ratio is high. Clinical correlates needed to evaluate impact on practice of the findings.
No conflict of interest.

Table 1 (abstract 1128). Dose optimization in HD

		5f vs 8f IMRT		8f IMRT vs VMAT		VMAT vs TOMO		3D-RT vs TOMO	
		target	lung	target	lung	target	lung	target	lung
PTV	D(95%), Gy	ns	ns	$p < 0.005$	ns	ns	ns	$p < 0.005$	$p < 0.01$
	D(98%), Gy	$p < 0.001$	ns	$p < 0.01$	ns	ns	ns	$p < 0.005$	ns
Lung	V(5 Gy), %	$p < 0.01$	ns	ns	ns	ns	ns	$p < 0.005$	$p < 0.01$
	V(20 Gy), %	ns	ns	ns	ns	$p < 0.005$	$p < 0.005$	$p < 0.005$	$p < 0.005$
	D_{avg}, Gy	$p < 0.005$	$p < 0.005$	ns	ns	$p < 0.005$	$p < 0.005$	ns	ns
CI		ns	ns	ns	ns	ns	ns	$p < 0.005$	$p < 0.005$

Table 2 (abstract 1128). Lung reduction dose optimization in LC

		5f vs 8f IMRT			8f IMRT vs VMAT			8f IMRT vs HT			3D-CRT vs HT		
		5IMRT	8IMRT	p	8IMRT	VMAT	p	8 IMRT	HT	p	3D-CRT	HT	p
PTV	D(95%)	47.2 Gy	48.1 Gy	ns	48.1 Gy	46.8 Gy	0.005	48.1 Gy	45.7 Gy	ns	46.5 Gy	45.7 Gy	ns
	D(98%)	45.4 Gy	46.7 Gy	ns	46.7 Gy	44.9 Gy	0.005	46.7 Gy	43.5 Gy	0.005	45 Gy	43.5 Gy	ns
Lungs	V(5 Gy)	48.5%	46.3%	ns	46.3%	44.2%	ns	46.3%	50%	0.01	53.3%	50%	ns
	V(20 Gy)	18.3%	17.9%	ns	17.9%	14.9%	0.005	17.9%	16.2%	0.01	17%	16.2%	ns
	D_{avg}	10.5 Gy	10.5 Gy	ns	10.5 Gy	9.1 Gy	0.005	10.5 Gy	9.6 Gy	0.005	10.7 Gy	9.6 Gy	ns
CI		1.7	1.9	ns	1.9	1.6	0.005	1.9	1.3	0.005	1.8	1.3	0.005

1129 POSTER

Study of usefulness of megavoltage computed tomography for electron beam treatment planning for conjunctival MALT − lymphoma

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Background: The Kilo-voltage Computed Tomography (KVCT) has been used for electron beam treatment planning for conjunctival MALT − lymphoma; however, its lens shielding generates metal artifact, leading to inaccurate treatment planning. This study assessed the usefulness of treatment planning using the Mega-voltage Computed Tomography (MVCT) images without metal artifact.
Material and Methods: The Image Value-to-Density Table (IVDT) of KVCT and the IVDT of MVCT was calculated by using the Cheese Phantom® and then the density values calculated from the above process was input in the Pinnacle®. As establishing the treatment planning and measuring the projection result with the EBT3 Film® using the Elekta Infinity™, the $10\times10\,cm^2$ electron cone with 6-MeV and 9-MeV electron beam was used at 300 MU and the Source-Skin Distance (SSD) was set to 100 cm.
First, the treatment planning of KVCT was matched to that of MVCT using the IVDT to measure the consistency.
Second, the error of treatment planning of KVCT caused by metal artifact (generated by lens shielding) was compared with that of MVCT caused under the same conditions.
Third, the treatment planning with the above settings was executed for the MVCT image (with lens shielding) matched using the IVDT and the electron beam was projected to the EBT3 Film® (with lens shielding) with the same conditions. The acquired MVCT result and EBT3 Film® result were analyzed using Axial PDD, D_{max} beam profile, and R_{50} beam profile.
Results: First, for the γ − index between the KVCT and the MVCT matched using IVDT, the γ value has not exceeded 1 at 3%/3 mm and 2%/2 mm.
Second, the radiation difference between the KVCT and the MVCT with the lens shielding was calculated as about 74%.
And third, after analyzing the level of radiation projected to the MVCT image for treatment planning and to the EBT3 film, the γ value has not exceeded 1 at 3%/3 mm for 6-MeV and 9-MeV. However, for 6-MeV at 2%/2 mm, 6.34% of axial PDD and beam profiles of D_{max} and R_{50} were 3.48% and 4.21%, respectively, and for 9-MeV at 2%/2 mm, 10.68% of axial PDD and beam profiles of D_{max} and R_{50} were 3.85% and 6.23%, respectively.
Conclusion: This study assessed the error rate of treatment planning, caused by metal artifact, between the KVCT and the MVCT.
As shown in the study, metal artifact was generated at the MVCT, too. However, as comparing to the result of EBT3 Film®, the error rate was lower than 3%, within the clinically-allowable range.
The result showed that the MVCT could get images which allowed establishment of an accurate treatment planning without being affected by metal artifact. It will be a new solution to improve the weak point of KVCT, inaccurate electron beam treatment planning for conjunctival MALT − lymphoma.
No conflict of interest.

1130 POSTER

Evaluation of dose distribution using positioning CT in IMRT for prostate cancer

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Background: In room cone beam CT (CBCT) is a popular modality for reducing setup errors nowadays, however, CT numbers of CBCT is not reliable enough for the dose calculation by treatment planning system (TPS). We analyzed dose distribution using conventional diagnostic CT image that was obtained for checking the patient position just before the treatment.
Material and Methods: The dose distributions for 8 patients with prostate cancer were evaluated. IMRT was done by step and shoot technique with 7 fields. The CTV included prostate and proximal seminal vesicle, and the PTV margin was 5 to 7 mm in the posterior direction, and 10 mm in other directions. The prescribed dose was 72 Gy at D50 of the PTV. We daily used Linac graphy to check setup errors and also used CT image that was acquired in the separate CT room weekly. Patients were transported to the treatment room in the fixation device after CT scanning and underwent radiotherapy. After the CT image dataset for verifying the isocenter was transferred to TPS (Xio), the target volumes and organs at risk (OARs) were contoured by the same physician in the same manner as done on planning CT image. The IMRT plan was imported as a QA plan, and dose calculation and evaluation of dose for contours were performed.
Results: The dose evaluation could be done with total of 41 CT datasets, 1 to 8 (median of 6) times for each patient. For the CTV, the mean EUD was 2.00 Gy, ranged from 1.97 to 2.03 Gy and D98 was more than 1.92 Gy except for one CT. For the PTV, the mean EUD was 1.93 Gy (range, 1.31–2.01 Gy) and D98 was more than 1.9 Gy only in two CT, which implied the presence of low dose area in the PTV. Regarding OARs, the dose constraint was not satisfied only in one CT for the rectum because of large rectal volume, and in four for the bladder by reason of small bladder volume.
Conclusions: It was verified that the dose for the CTV was sufficient mostly without exceeding dose constraint for the OARs and the PTV margin used in this study was considered to be appropriate.
No conflict of interest.

1131 POSTER

First experience with rotational IMRT with a Siemens accelerator ARTISTE®

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Introduction: In our departement, since February 2012 a Siemens accelerator ARTISTE ® is in clinical use. The dose rate with flattened beam is 300MU/min for 6MV photons respectively 500MU/min for 15MV photons. Simultaneaously with the start of patient treatment at this accelerator also IMRT with the step&shoot method was established in our department. Although Siemens quit the business in radiation therapy, we got the opportunity to test the already developed method of rotational IMRT (mARC®) at our accelerator. In this investigation, both methods of IMRT will be compared according treatment time, monitor units and plan quality.
Material and Method: In this new variation of rotational IMRT, the dose is delivered during a continuous rotation of the gantry in bursts over short gantry angels with static leaf positions. Between these dose bursts, the MLC leaves are moving rapidly in order to form the next field segment.
For IMRT treatment planning a direct aperture optimization algorithm DAO (Panther® DAO, Prowess Inc.) is used. The planning of the rotational IMRT is done with the proarc option of the Panther treatment planning system.
In a retrospective study, this new technique will be compared with the step&shoot IMRT used for treatment. For both methods the same dose prescription to the target volumes and the same dose limits for organs at risk is used. The IMRT techniques are compared regarding the nessescary monitor units (MU), the treatment time, target coverage (TC), conformity index (CI) and conformity number (CN).

	MU/Gy	Treatment time [s]	TC	CI	CN
Prostate					
Step&Shoot	212.6±10.3	283.0±22.3	0.91±0.03	0.84±0.07	0.88±0.33
mARC	222.0±20.9	217.3±18.4	0.94±0.03	0.92±0.70	0.99±0.34
difference [%]	+ 4.4	−23.0%	+ 3.6	+ 9.6	+ 12.7
p	0.22 (n.s.)	0.0000013	0.11 (n.s.)	0.09 (n.s.)	0.58 (n.s.)
Head & Neck					
Step&Shoot	185.5±15.5	386.8±33.8	0.921± 0.03	0.884±0.02	0.814±0.03
mARC	169.6±10.6	306.4±24.5	0.957±0.11	0.887± 0.02	0.849±0.02
difference [%]	−8.5	−20.8	+3.8	+0.3	+4.2
p	0.103 (n.s.)	0.0032	0.036	0.85 (n.s.)	0.061 (n.s.)

Results: The first results for patientes treated for prostate cancer indicate a slight increase (+4.4%) in monitor units (212.6±10 MU/Gy for Step&Shoot

IMRT compared to 222±21 MU for the mARC-technique) while the treatment time is reduced significantly by 23% (283±22sec (Step&Shoot) vs 217±18sec (mARC)).
For head&neck cases, with the mARC-technique a reduction of monitor units and treatment time could be observed. The monitor units could be reduced by 8.5% from 185.5±16 MU/Gy (Step&Shoot) to 169.6±11 MU/Gy (mARC). The mean treatment time of 306±25sec with the mARC method has been reduced by 20% compared to a mean treatment time if 387±34sec in case of step&shoot IMRT.
In all cases, the plan quality according to TC, CI and CN could be improved slightly with the mARC techniqe.
Conclusion: In comparison to Step&Shoot IMRT, the mARC technique shows comparable or improved dose distributions with a significant reduction in treatment time even for an accelerator with flattening filter. A further reduction of treatment time might be expected in case of flattening filter free beams with a higher dose rate.
No conflict of interest.

Poster Session (Sun, 29 Sep)
Imaging

1150 POSTER

Monitoring of pulmonary tumors in computed tomography: Thresholds for volume-based response assessments and target lesions selection

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Background: The change in lung tumor volume is an emerging imaging biomarker that is expected to be more sensitive to disease evolution than Longest Axial Diameter (LAD). Several aspects of volume-based response assessment are still under investigation. One aspect to be clarified is the magnitude of significant volume changes that allows classifying response as Progressive Disease (PD), Partial Response (PR) and Stable Disease (SD). A second aspect is the selection of target lesions usually restricted to 'Measurable' lesions (ML). So far, no precise definition of volume measurability is available despite its probable impact on the response performance. This study proposes a solution for volume-based response assessments that provides, thresholds for volume-based response of ML and a method for automatic identification of ML.
Material and Method: Our study relies on data published by the Quantitative Imaging Biomarker Alliance (QIBA) which reports an inter reader (IR) Limits of Agreement (LoA) of repeated ML assessments of +/−30%. Considering a standard deviation of measurement as 15%, we used Geary Hinkley (GH) transformation to model response thresholds with a 5% Type I error. We used Training (Tr) and Testing (Te) datasets of respectively 99 and 100 pulmonary lesions. Tr and Te data were segmented twice by two imaging scientists (IS) and two expert radiologists (ER). 79 image-based lesion features, such as statistics of intensities and morphology, were computed from segmentations. We labelled all data as 'Non Measurable Lesions' (NML) when repeated measurements exceeded the LoA. We used labels and computed features to train a Support Vector Machine (SVM) classification system. Sensibility (Se) and Specificity (Sp) at detecting ML have been computed.
Results: With 95% confidence, our model gives response thresholds for volume as: 35% reduction reports for PR, 55% increase for PD and SD otherwise. Our Tr and Te datasets disclose 27.3% and 27% of NML respectively. Performance in classifying ML was Se=91.3%; Sp=48.2%.
Conclusions: We provide response thresholds and validate an approach to detect ML. In documenting these two aspects we make the volume a usable biomarker applicable to lung tumors in CT imaging. However, these aspects of the biomarker cover only metrological considerations, and should be validated by clinical investigations.
No conflict of interest.

1151 POSTER

Characteristics of lung cancer diagnosed with low dose chest CT

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Background: Role of chest CT in early diagnosis of lung cancer is controversial between benefits revealed by recent NLST study showing mortality reduction in high risk gruop and harms of overdiagnosis and radiation hazards. The clinical characteristics of lung cancer detected on CT screening is not well known in general population. This study aimed to find clinical characteristics of lung cancers with screening chest.
Material and Methods: This study included 15,615 Korean adults who received low dose chest CT(LDCT) screening in voluntary health checkup program in Healthcare system gangnam center from October 2003 to June 2010. Patients of lung cancer diagnosed on CT screening were reviewed retrospectively about clinical parameters such as sex, smoking et al and final pathology and stage of lung cancers.
Results: 35 lung cancer patients occured. Lung cancer detection rates were 0.22%(crude annual incidence rate 61.0/100,000/year). Male and female ratio was 6:4. 18 of 35 lung cancers occurred in high-risk groups(>20 pack-year smoking) and 17 in low risk groups(ex-smokers and non-smokers). 76% of lung cancers showed less than 3 cm tumor size(<1 cm − 30%, <2 cm −22%, <3 cm − 24%).
The comparison of clinical characteristics with Korean national cancer registry showed that features of lung cancers detected in CT screening showed less advanced stage(stage I 60.6% vs 17.5%), more frequent histology of adenocarcinoma(68.6% vs 36.1%) and relatively higher rates in non-smokers and females than general population.
Of 35 patients with lung cancer, VATS segmentectomy or VATS lobectomy was performed in 10 patients and lobectomy in 16. 4 patients underwent chemotherapy and 5 patients was managed with supportive therapy because of advanced stage or old age. 2 patients died despite of treatment and other patients survived during followup. Adenocarcinoma including BAC histology was more prevalent and most of patients could be treated in early stage.
Conclusion: Lung cancers detected in CT screening had somewhat different clinical characteristics such as less advanced stage and higher frequency of adenocarcinoma from general population. LDCT screening may be useful in diagnosis of lung cancer in early, operable stage.
No conflict of interest.

1152 POSTER

Comparison of moving target delineation using slow 3D-CT, CBCT and MVCT: A phantom study

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Background: To assess whether different motion patterns have an impact on delineation of a moving target in a lung phantom using planning CTs (slow 3D-CT) and IGRT-CTs (Conebeam-CT [CBCT], Megavoltage-CT [MVCT]).
Material and Methods: A commercial xy-table (SunNuclear®) was combined with a self-made installation wich enables programable motion of a box in 3 dimensions. The box was filled with corkboards and a water-filled table tennis ball to simulate a tumour inside the lung. Using this phantom, slow 3D-CT (Somatom Emotion, Siemens Medical Solutions®), CBCT (Clinac DHX, Varian Medical Systems®) and MVCT image series (Tomotherapy, Accuray Inc.®) were acquired during phantom movement. Different motion patterns were performed: linear motion in x or y direction with amplitudes of 5 and 10 mm, each with periods of 3 and 5 s. Additionally, a linear motion with amplitudes in x, y and z directions (2.5, 10, 2.5 mm, periode 5 s) and a patient tumour trajectory was applied. The latter was constructed using the center of mass motion of GTVs delineated in a 4D-CT scan.
The ball volume was contoured in all image series (Eclipse 10, Varian Medical systems®) using a lung window setting of 200 HU to −1000 HU. The contoured ball volumes were compared with the mathematically calculated ball volumes.

Table: Relative difference between contoured and calculated ball volume

Motion amplitude	slow 3D-CT		CBCT		MVCT	
	period 3 s	period 5 s	period 3 s	period 5 s	period 3 s	period 5 s
0	11.9	11.9	2.4	2.4	21.5	21.5
x 5 mm	−0.5	−8.5	−8.1	−18.0	−30.2	−14.5
x 10 mm	−6.0	−18.4	−10.9	−19.1	−63.5	−43.9
y 5 mm	−5.6	−7.4	−4.6	−8.3	−8.0	−13.4
y 10 mm	−9.2	−18.8	−7.5	−11.4	−10.9	−25.2

Results: The relative differences between contoured and calculated volumes are presented in the table. The static ball volume was overestimated in all imaging methods. Ball motion resulted in underestimation of the contoured volumes. The volume decreases as the motion amplitude increases. In the slow 3D-CT and CBCT smaller differences were determined for motion period of 3 s than for 5 s. For CBCT and MVCT

ball motion in y direction resulted in smaller deviations than motion in x direction. The largest underestimation of volumes was found for MVCT. Complex motion patterns resulted also in underestimated volumes (−4% to −29%).
Conclusion: Due to movement, contoured volumes were underestimated for all imaging methods. Depending on the applied technique, motion amplitude, direction and period have different impact on target delineation which has to be considered in clinical assessments.
No conflict of interest.

1153 POSTER

Evaluation of a cloud-based local read paradigm for imaging evaluations in oncology clinical trials

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Background: Imaging evaluation in oncology heavily depends on human readers performances. In clinical trials, regulatory authorities have been recommending an Independent Central Review (ICR) with several readers to mitigate potential biases resulting from variance between investigator sites. Based on recent publications promoting site based evaluation as imaging endpoint, they currently investigate an alternative to ICR. The goal of this study is to evaluate a cloud-based paradigm implementing software solutions and services that standardize the imaging evaluations among international investigator sites.
Material and Methods: 10 patients, who received chemotherapy for lung cancer and for which chest CT scans were available at 3 different time points, were retrospectively selected. CT scans were evaluated according to the RECIST 1.1 criteria by two oncologists (Saga University) and one radiologist (Nice University Hospital) independently, through web software solutions (MEDIAN Technologies). Such solutions were hosted by the data center (Canon IT Solutions, Japan) and used by readers and data managers (CANON and MEDIAN Technologies) for de-identification, quality control and centralization of the images and their evaluations. The study compared evaluations between readers and analyzed the reasons for discordances.
Results: Readers with different medical training and education, working at distant locations were able to reliably perform radiological evaluations from the same cloud system. The cloud quality control service detected2 non-conformances in applying RECIST 1.1 and had the readers changed their evaluations, resolving discrepancies. Between the oncologists and the radiologist, a discordance rate of 35 % (14/40 evaluations) was observed when considering RECIST overall response (CR, PR, SD, PD) at all time points.
The main reason for discordance in RECIST overall response was a difference in the selection of the target lesions (50%, 7/14). Those discordances represented 78% (7/9) in the group where target selection was different.
Conclusions: The study shows the feasibility of imaging evaluation based on cloud services for clinical studies involving multiple international sites. Centralization of data made possible the on-going monitoring of evaluations through specialized services reducing variability among sites. Analysis of discordances between readers identified areas of improvement for cloud-based services such as consensus process for target selection at baseline evaluation to reduce discrepancies.
Conflict of interest: *Corporate-sponsored research: MEDIAN Technologies, France. Canon Inc, Japan*

1154 POSTER

Hepatic blood flow using CT perfusion as a prognostic imaging biomarker for esophageal squamous cell carcinoma

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Background: According to the previous reports, preoperative evaluation of hepatic blood flow by diagnostic imaging such as ultrasound and scintigraphy could identify patients of malignancy with high risk of recurrence. CT perfusion (CTP) is a noninvasive, functional imaging which can quantify a perfusion of the target organ, by an analysis of the time-density curve of the injected contrast material. The purpose of this research is to evaluate the change of hepatic blood flow measured by preoperative CTP and identify the high-risk group of postoperative recurrence in patients with esophageal squamous cell carcinoma.
Material and Methods: Forty-five consecutive patients with esophageal squamous cell carcinoma treated with surgical resection at Chiba University Hospital from Jun 2010 to December 2012 were enrolled in this study. Radical subesophagectomy with field lymphadenectomy was performed. Prior to surgery, hepatic CTP images were obtained using a 320-row area detector CT with a 0.5-mm slice thickness. Data was analyzed by perfusion software (Body Perfusion; Toshiba, Tokyo, Japan), based on the dual input maximum slope method. Perfusion parameters, arterial blood flow (AF: ml/min/100g tissue), portal blood flow (PF: ml/min/100g tissue) and %AF (AF/AF+PF x100), were measured by placing region of interest in the abdominal aorta, in the portal vein, in the right hepatic lobe and spleen excluding vessels. We compared the perfusion parameters with pathological Stage (TNM classification of UICC) and postoperative course.
Results: The following factors, which might have influence to a hemodynamics, had no significant correlation with the hepatic perfusion parameters; age, sex, systolic blood pressure, body surface area, hematocrit, serum asparate aminotransferase (AST) and estimated glomerular filtration rate (eGFR). In the comparison of the mean values of the parameters for each stage, there was no significant difference. The postoperative recurrence has observed in 8. The types of recurrence were as follows: hematogenous metastases 9, lymph node 6 and peritoneum 2 (duplication was included). %AF of recurrent cases was significantly higher than that of without recurrence (24.8 vs. 15.9, $P = 0.0027$). The predictive value of recurrence have a sensitivity of 87.5% and a specificity of 88.9%, by setting a cut-off %AF value (%AF=20) from Receiver Operating Characteristic analysis. If divided into two groups, high %AF group ($\geqslant$20) and low %AF (<20), the relapse free survival rate of low %AF group was significantly better than that of high group ($P<0.0001$). Multivariate analysis using the Cox proportional hazards model showed that preoperative high %AF was an independent risk factor of recurrence (Hazard ratio: 26.1, P value: 0.0029).
Conclusions: Hepatic CTP is a non-invasive modality and a valid functioning tool to predict postoperative recurrence of esophageal squamous cell carcinoma, furthermore its potentiality, as an imaging biomarker, has been suggested.
No conflict of interest.

1155 POSTER

A novel approach for cancer risk reduction associated serial CT scanning in pediatric hydrocephalus

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Background: Pediatric patients with acute hydrocephalus are frequently subjected to serial CT studies to confirm ventricular shunt patency. It is not uncommon for patients to receive up to 12 CT scans/year resulting in substantially increased lifetime cancer risk. This feasibility study investigates the ability to accurately measure ventricle size as CT dose is reduced far below the child-size CT protocols routinely employed in pediatric imaging. By narrowing the diagnostic goal to a determination of ventricle size, rather than exclusion of all possible pathology within the scan region, the radiation dose can be greatly reduced.
Materials and Methods: Initial studies were performed using phantom materials with CT Hounsfield units matched for brain and CSF. These images were acquired at various kVp, mAs, slice thickness using axial and helical acquisitions. The data was processed using a variety of reconstruction kernels and several post-processing and volume rendering algorithms to modulate image smoothing.
In addition, three fresh cadaver heads were imaged using a wide range of CT protocol parameters, varying kVp, mAs, axial versus helical, and reconstruction kernels to maximize the dataset for analysis. Raw and reconstructed data was saved for post-processing using 3D workstations as well as image processing toolkits provided in commercial image analysis software.
Results: Ventricular dimensions were estimated using both 3D volume rendered and 2D image analysis algorithms. Concordance of measurements between the maximum dose and reduced dose datasets was analysed and confirmed as was the lack of significant interobserver variability between three experienced neuroradiologists.
The range of CTDI from the maximum dose protocol to the minimum dose protocol was greater than two orders of magnitude. In spite of this extreme dose reduction, ventricular dimensions could still be accurately measured despite a 100X dose reduction.
Conclusions: Radiation exposure from serial CT scans results in an increased risk of malignancy later in life and is particularly significant in young patients. CT scanning required to exclude acute obstructive hydrocephalus related to shunt malfunction may result in radiation exposure levels known to significantly increase cancer risk in pediatric patients. A method to reduce dose by more than 2 orders of magnitude associated with

serial CT scanning in suspected shunt malfunction has been developed that can reliably exclude acute hydrocephalus in a vulnerable pediatric population. This strategy to maximally reduce dose while maintaining accurate identification of key image parameters to reliably resolve a specific clinical question can reduce cancer risk while ensuring appropriate patient management.
No conflict of interest.

1156 POSTER

Predictive value of optimal morphologic response to first-line chemotherapy in patients with colorectal liver metastases

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Background: It was reported that morphologic response to preoperative chemotherapy was an independent prognostic factor in patients who underwent hepatic resection of colorectal liver metastases (CLM). The aim of this study was to evaluate the predictive value of morphologic response to first-line chemotherapy in patients with CLM.
Methods: We assessed 41 patients with CLM who received fluorouracil-based chemotherapy with or without bevacizumab as first-line chemotherapy at two institutions between April 2006 and June 2012. All patients underwent enhanced computed tomography (CT) at the start of chemotherapy and then every 2−3 months. Three blinded radiologists evaluated CT images and classified as optimal, incomplete or none response according to the morphologic criteria (Chun YS, et al. JAMA 302: 2338−44, 2009). Response to systemic chemotherapy was also evaluated according to RECIST. Progression-free survival (PFS) was calculated with the Kaplan–Meier method and statistical differences with survival curves were determined by the log-rank test. Predictive factors associated with PFS were identified in multivariate analysis.
Results: Patients characteristics were as follows: median age=67 years (range 52−80); Male: female=29:12; PS 0:1:2:3=24:13:3:1. Thirty two patients had synchronous liver metastases and 9 had metachronous liver metastases. Five patients had solitary liver lesions and 36 had multiple liver lesions. Twenty three patients (54%) received chemotherapy with bevacizumab, while 18 patients (46%) received chemotherapy without bevacizumab. Optimal morphologic response was observed in 11 patients (48%) treated with bevacizumab and, in 5 patients (28%) treated without bevacizumab. Eight patients (20%) underwent hepatic resection after chemotherapy. The median follow-up period was 31.3 months. The median PFS was 12.7 months for patients with optical morphologic response and 8.1 months in those with incomplete/none morphologic response ($p = 0.0026$). On multivariate analysis, PS and morphologic response were significant independent predictors of PFS. Morphologic response was superior to RECIST for prediction of PFS.
Conclusions: Optimal morphologic response was significantly associated with PFS in patients with CLM who were treated with fluorouracil-based chemotherapy as first-line chemotherapy. Chemotherapy with bevacizumab tends to have a higher optimal morphologic response than chemotherapy without bevacizumab.
No conflict of interest.

1157 POSTER

The value of chest CT for prediction of breast tumor size: Comparison with pathology measurement

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Background: To date, no data are available on the use of chest CT for prediction of breast tumor size in patients with breast cancer, although the CT examinations are increasing in practice. The purpose of this study is to evaluate the value of chest CT for prediction of breast tumor size using the pathology measurement as the reference standard.
Materials and Methods: We retrospectively analyzed the tumor size on the preoperative chest CT for 295 patients with surgically proven unifocal, invasive carcinoma. The maximal diameter of tumor on chest CT and pathologic result were compared by linear regression and Spearman's rho correlation coefficient. Concordance between CT and pathology was defined as a difference $\leqslant 0.5$ mm. Sub-groups analysis was also performed by tumor size (<2 cm and $\geqslant 2$ cm), and histologic grades.
Results: CT and pathology tumor size showed positive correlation (Pathology tumor size = 1.092 × CT tumor size − 1.013, Spearman's rho correlation coefficient = 0.84, P <0.001). Most of the tumors (n = 232, 78.6%) showed concordance in the size on chest CT and pathology, and 42 of tumors (14.2%) showed underestimation (average underestimation of CT = 12 mm) and 21 of tumors (7.1%) showed overestimation on CT (average overestimation of CT = 10 mm) compared with that of pathology. No significant difference was found in the sub-group analysis by tumor size and the histological subtypes.
Conclusion: CT tumor size positively correlates with pathology size in the breast cancer patients. Most of the tumors show difference less than 5 mm in the size on chest CT and pathology. The tumor size and histological subtype is no significant indicator for prediction of tumor size on CT.
No conflict of interest.

1158 POSTER

Geographical analysis of hypoxic subvolumes in locally advanced head and neck tumours during primary chemoradiotherapy in serial 18-F-MISO-PET imaging

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Background: Hypoxic subvolumes (HV) in head and neck tumours are associated with worse prognosis and outcome, attributed to increased chemo- and radioresistance. Tumour hypoxia can be visualized using PET imaging. 18-Fluoro-Misonidazole (F-MISO) was the first tracer clinically validated and established. The incorporation of biological information into radiotherapy planning can personalize radiotherapy (e.g. by dose painting).
Material and Methods: In a pilot project, 16 patients with locally advanced head and neck tumours underwent 3 consecutive F-MISO-PET scans (weeks 0, 2, 5) before and during primary chemoradiotherapy (70 Gy, Cisplatin) in addition to FDG-PET, CT and MRI (week 0). Tumour localisations included oral cavity (n = 1), oropharnynx (n = 7), hypopharynx (n = 5) and larynx (n = 3). Normalised standardized-uptake-values (SUV) were generated for all patients (index SUVmax Tumour/SUVmax Muscle) on the F-MISO-PET scans. The size, localisation and overlap of the HV between the F-MISO-PET scans were analysed. Volume delineation was done using a semi-automatic algorithm: A sphere containing normal tissue contralateral to the tumour site was defined for all patients and scans. A 1.5-fold increase over the spheres' mean SUV yielded the threshold for the HV for each scan and patient. Analyses were carried out with BrainLAB iplan.
Results: For an index of 1.5, quantitative evaluation showed tumour hypoxia in week 0 in 16/16, in week 2 in 5/14 and in week 5 in 0/11 patients. The mean tumour volume − as defined on FDG-PET and validated with CT and MRI − was 28 cm^3, the mean HV initially 28 % with a decrease to 15 % after 2 weeks. HV completely resolved in the majority of patients. Mean HV overlap between the first and second scans was 55 % of the HV on the first scan, indicating a relatively high proportion of initial hypoxia persisting at the same localisation in later scans. Similarly, the majority of the later HV have already been hypoxic before (mean overlap 72 % of the HV on the second scan). Descriptive analyses showed both stationary and dynamic components in those patients with persisting hypoxia (decreased or increased).
Conclusions: Tumour hypoxia decreased or regressed in a majority of patients; however, HV showed a geographically relatively stable conformation in those patients with persistent hypoxia. This might make an inclusion into radiation treatment planning possible.
No conflict of interest.

1159 POSTER

Visualization of solid tumors and metastasis using an uPAR specific NIR fluorescent-labeled antibody

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Real-time near-infrared (NIR) fluorescent imaging is a novel technique used to intraoperatively visualize tumor cells. For this purpose NIR light-emitting fluorophores are conjugated to tumor protein-specific tracers. One potential target for tracing tumors is the urokinase plasminogen activator receptor (uPAR). uPAR plays an important role in the development of cancer, tumor invasion, angiogenesis and metastasis. Over-expression of uPAR is found on the majority of human carcinomas, in cancer as well as stromal cells.

This study investigates the potential of an uPAR-specific NIR fluorescent antibody for the *in vivo* identification of tumor cells.
The NIR fluorophore MSAP-ZW800−1 was conjugated to a humanized monoclonal uPAR specific antibody and an isotype IgG control. The conjugation and binding capacity of both compounds were validated *in vitro* using photospectrometry and plate-assay analyses on tumor cells. Athymic mice were subcutaneously injected with human colon adenocarcinoma HT-29 cells or orthotopicly in the tongue with OSC-19 cells, a metastasizing human squamous cell carcinoma. After establishment of the tumors, 1 nmol of either uPAR-specific or control IgG were injected intravenously (IV). At sequential time points up-to 120 h after injection images were obtained with the PEARL Impulse small animal imager and the intraoperative FLARE™ imaging system. A dose-range study was performed with doses of 150 μg (1 nmol), 100 μg, or 50 μg per mouse. *Ex vivo* fluorescence imaging and histology was performed to demonstrate distribution of the compounds and tumor specificity.
In vivo, the tumors were clearly fluorescently delineated, with the highest tumor-to-background ratios (TBR) at 72 hours after injection of 3.6±0.4 in the HT-29 model and 2.3±0.1 in the OSC-19 model respectively (n = 3). The control compound showed a mean TBR of 1.8±0.2 in the HT-29 model and 1.1±0.2 in the OSC-19 model, whereas injection of the fluorophore alone showed a mean TBR of 0.8 ±0.1 in both animal models. Unexpected fluorescent spots were found in the cervical region of the OSC-19 tumor-specific compound group, which histologically turned out to be cervical lymph node metastases. Two-way repeated measurements ANOVA analysis showed significant differences between the tumor-specific compound and control groups in the HT-29 model at all time points later than 24 hours ($p < 0.01$) and for the OSC-19 model at every time point from the start ($p < 0.01$). *Ex vivo* evaluation showed a tumor-specific signal in both the OSC-19 primary tumors and lymph node metastases. No significant differences were found among the dose groups, indicating the potential of this anti-uPAR compound to be used in the lower micro-dose range.
In conclusion, this study describes a new tumor-specific fluorescent probe, targeting uPAR, which provides visualization of solid tumors including their metastases in real time using a NIR fluorescence imaging system.
Conflict of interest: *Ownership: Kuppen stockholder of Antibodies for Research Applications BV; Mazar stockholder and consultant of Tactic Pharma.*

1160 POSTER

Non-invasive monitoring of pharmacodynamics and -kinetics of a death receptor 5 antibody: Induction of apoptosis depends on treatment schedule

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Background: Using fluorescence- and bioluminescence-imaging, the pharmacodynamics and tumor saturation kinetics of a Death Receptor 5 antibody (anti-DR5) was examined to optimize treatment schedules of a combination therapy with Doxorubicin (DOX).
Material and Methods: Split-luciferase based bioluminescence imaging allowed us to monitoring apoptosis non-invasively in living mice. A human glioblastoma cell line stably transfected with the split-luciferase apoptosis reporter was applied to screen various chemotherapeutics and anti-DR5 on their ability to induce apoptosis in cells *in vitro* as well as *in vivo*. Fluorescence labeled anti-DR5 was injected i.v. and tumor saturation kinetics was monitored.
Results: We found that DOX treatment *in vitro* led to significant apoptosis induction within 48 hours and to a 2.3-fold increased anti-DR5 binding to the cell surface in contrast to Cisplatin and 5-FU treatment. Induction of apoptosis by treatment with anti-DR5 was dose- and time-dependent (both *in vitro* and *in vivo*). Simultaneous visualization of fluorescence labeled anti-DR5 in tumor tissue and apoptosis revealed maximal apoptosis induction immediately after the compound had reached tumor site. Regarding combination therapy of anti-DR5 and DOX, we found that the sequential application of DOX before anti-DR5 resulted in synergistically enhanced apoptosis reporter activity. In striking contrast, anti-DR5 given before DOX did not lead to increased apoptosis induction.
Conclusions: We suggest that DOX-induced recruitment of DR5 to the cell surface impacts the enhanced apoptotic effect which can be longitudinally monitored by apoptosis imaging. This study demonstrates that the combination of apoptosis and antibody accumulation imaging is an excellent method for optimizing dosing and treatment schedules in preclinical cancer models.
Conflict of interest: *Ownership: Roche Diagnostics GmbH*

1161 POSTER

The hybrid tracer ICG-99mTc-nanocolloid aids surgical visualization of the sentinel node in different basins

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Background: Conventionally a combination of radiocolloid and blue dye is used for sentinel node (SN) biopsy. The radiocolloid allows preoperative lymphoscintigraphy and SPECT/CT for SN mapping, and intraoperatively its gamma rays can be traced to guide the surgeon to the SN. An intraoperative injection with blue dye prior to the start of the procedure is then used to enable optical lymphatic ducts and SN identification. Recently we introduced the hybrid, radioactive and fluorescent, tracer indocyanine green (ICG)-99mTc-nanocolloid. With this tracer, one single injection enables preoperative SN mapping and intraoperative radio- and fluorescence guidance to the SN. In this study we compared SN identification via the fluorescence component of the hybrid tracer to SN identification using blue dye in different drainage basins.
Materials and Methods: One-hundred-ninety-six patients were included in the study: 77 patients with melanoma and 119 patients with squamous cell carcinoma of the penis or vulva. The hybrid tracer was injected surrounding the lesion/scar 3−27 hours prior to surgery. The SNs were then preoperatively identified using lymphoscintigraphy and SPECT/CT imaging. Prior to the start of the operation vital blue dye was injected. The SNs were intraoperatively traced using a gamma ray detection probe and a portable gamma camera. In addition, SNs were visualized via fluorescence imaging and/or blue dye detection.
Results: Intraoperatively, a total 342 basins was explored from which a total of 609 SNs were excised. In the 43 neck-basins a total of 68 SNs were excised with 33% of these SNs being blue and 97% being fluorescent. In the 247 inguinal basins (461 SNs), 54% of the SNs was blue whilst 92% was fluorescent. Eigthy-one percent of the SNs located in the 44 axillary basins was blue while 92% was fluorescent. Three SNs were located in other basins namely the elbow (n = 1) and supraclavicular (n = 2); here 20% of the SNs was stained blue vs. 100% being fluorescent. Aberrant drainage to the periscapular region was found in 4 patients, to 4 basins with a total of 4 SNs. Drainage to one prepubic SN was found in a patient with penile carcinoma. Of these abberant draining 5 SNs only 1 SN was blue whereas they were all fluorescent.
Discussion: For all nodal basins studied significantly ($p < 0.001$) more fluorescent SNs (average 93%) than blue stained SNs (average 54%) were visualized and removed. This was especially true for the neck. The fluorescence feature of the hybrid tracer might, therefore, provide a valuable alternative for optical SN identification in the operating room.
No conflict of interest.

1162 POSTER

89Zr-cetuximab imaging in advanced colorectal cancer patients: A feasibility study

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Systemic treatment for advanced, wild type K-RAS colorectal cancer (wtK-RAS CRC) includes Epidermal Growth Factor Receptor (EGFR)-inhibition with anti-EGFR antibodies like cetuximab. Only 40% of patients with wtK-RAS CRC do benefit from this treatment, while the others are intrinsically resistant. Potential causes of resistance include aberrations in the EGFR-signaling cascade and/or differential pharmacokinetics of anti-EGFR-antibodies in patients. We hypothesize that high EGFR-expression in normal tissues, such as in normal liver, may lead to insufficient availability of anti-EGFR-antibodies to effectively target tumor lesions and thereby may be responsible for resistance.
To study our hypothesis, we first investigated whether accumulation of cetuximab can be detected in tumor lesions of patients with wtK-RAS CRC by PET-imaging with radiolabeled cetuximab (^{89}Zr-cetuximab).
Six patients with histopathologically confirmed advanced wtK-RAS CRC who were candidates for monotherapy with cetuximab, were included in this feasibility study upon their consent. Based on a 40% clinical benefit

rate of cetuximab we hypothesized that 40% of patients would show ^{89}Zr-cetuximab tumor uptake. This hypothesis would be correctly accepted if uptake would be present in $\geqslant$1 and $\leqslant$7 of 10 patients (power >90%, type I error <5%). ^{89}Zr-cetuximab PET-imaging was performed at the start of treatment with cetuximab. ^{89}Zr-labelled cetuximab (10 mg, 37MBq) was injected within 2 hours after the first dose of cold cetuximab (500 mg/m^2) on day 1. PET scans were performed on days 1, 2, 3, 4 and 7. While high liver uptake of ^{89}Zr-cetuximab was found in all patients, specific uptake of ^{89}Zr-cetuximab was detected in non-hepatic metastases of 3 patients during subsequent scans (standard uptake values between 3 and 8.5 on day 7). In the other 3 patients, no specific ^{89}Zr-cetuximab uptake was detected in non-hepatic metastases. Detailed imaging results will be shown at the meeting. The patients did not experience any toxicity related to ^{89}Zr-cetuximab; only known adverse events to cetuximab were observed, none exceeding grade 2. We conclude that PET imaging with ^{89}Zr-cetuximab for determination of tumor uptake in non-hepatic lesions is feasible. Based on these results, we initiated a clinical trial in which we will investigate the correlation between tumor uptake and tumor response by ^{89}Zr-cetuximab PET-imaging of non-hepatic lesions. Our goal is to guide treatment decisions for the individual patient with wtK-RAS CRC using a non-invasive, patient-friendly imaging strategy.

No conflict of interest.

1163 POSTER

Segmentation of subsequent FMISO-PET before and during radiochemotherapy: Experts versus swarm intelligence

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Background: Researchers in the field of imaging diagnostics for oncology increasingly incorporate new PET tracers such as [18F]fluoromisonidazole (FMISO) for hypoxia localisation in clinical trials to determine its prognostic potential. However, reproducibility of FMISO-PET measurements is part of controversy. To determine the stability of contours derived from subsequent FMISO PET imaging, we compared manually-outlined target object definitions and automatically-created contours.
Material and Methods: As part of a prognostic trial on head and neck cancer, 35 patients were imaged using FMISO-PET before and after the first week of combined radiochemotherapy. Three experts outlined FMISO-positive objects related to the primary tumor in the PET data sets. The analogously applied automatic routine is based on swarm intelligence. The algorithm utilizes virtual ants that move in the PET image stack and accumulate inside potential target objects.
Comparison of manually- and automatically-created contours was performed using the Jaccard-Index for determination of the degree of contour overlap. The comparison included expert-versus-expert analysis on both single FMISO-PET scans to estimate inter-observer-similarity, inter-scan-comparison to determine intra-observer- and intra-algorithm-similarity and algorithm-versus-expert comparison to estimate the reliability of automatic contours.
Results: In 25 of the 35 data sets, all experts consistently outlined objects which were further analysed. The Jaccard-Index was JI_{EvE}=45% and JI_{iE}=36% for inter- and intra-observer-similarity, respectively. Automatically-generated contours matched to the manually-created contours with JI_{AvE}=45%, which was a similar measurement as inter-observer-similarity. However, automatic contours matched by JI_{iA}=53% between both scans.
Conclusions: Automatically delineated contours matched to manually-created contours to a degree as the latter matched to each other. However, the similarity of contours between both scans was significantly increased using automatic delineation. The fact that intra-observer-similarity between the scans was decreased may partly be explained by changes of the tumour microenvironment during the first week of therapy between both PET scans.

No conflict of interest.

1164 POSTER

Diffusion-weighted imaging in the follow-up of patients after primary surgical and non-surgical treatment for rectal cancer

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Background: Accurate detection of recurrent disease after primary rectal cancer treatment is crucial to allow for curative salvage surgery. Standard imaging is known to experience difficulties in differentiating between post-treatment effects (inflammation and fibrotic scar tissue) and recurrent disease. Diffusion-weighted MRI (DWI) is a technique that analyses differences in tissue cellular density to differentiate between hypercellular (tumour) and low or normocellular tissues (fibrosis and inflammation). Aim of this study was to evaluate the value of DWI in the follow-up of patients after primary surgical or non-surgical treatment for rectal cancer.
Material and Methods: The study group (n = 117) consisted of 36 patients who had previously undergone rectal cancer treatment, consisting of either standard surgical resection with or without neoadjuvant (chemo-)radiotherapy (n = 36), a local transanal excision (n = 40, of which 15 after chemoradiotherapy) or a non-operative 'wait-and-see'-policy (n = 41). During clinical follow-up (FU) patients underwent on or more FU-MRIs (1.5T) including DWI (highest b-value b1000), as part of routine FU or because of a suspected local recurrence after surgery. Two readers in consensus evaluated each MRI and scored the b1000 DWI-images as 'no high signal', 'high signal suspected of recurrence' or 'not adequately assessable due to artefacts'.
Results: Patients underwent a mean number of 3 FU-scans (range 1−11) with a mean FU-time of 44 months (4–144). 27/117 patients developed a local recurrence, of which 23 (85%) were accurately detected on DWI. The other 90 patients (without recurrence) together underwent a total of 261 FU scans, of which 194 (74%) remained consistently true negative (no high signal) on DWI. 57 DWI-scans (19%) could not adequately be assessed due to artefacts. 14 DWI-scans were false positive (mainly at the first FU-scan after surgery/local excision), of which 50% again normalised during further FU.
Conclusion: DWI is a useful tool in the follow-up of patients after primary rectal cancer treatment. False positives may occur immediately after surgery, but the DWI signal normalises again during follow-up.

No conflict of interest.

1165 POSTER

Superparamagnetic iron oxide nanoparticles (SPIONs) modified with epidermal growth factor (EGF) or heat shock protein Hsp70 for targeting the brain tumor

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Background: Superparamagnetic iron oxide nanoparticles (SPIONs) due to their high magnetic moment have the ability to function as theranostic agents. They could be used both as contrast agents for MRI, and as delivery vehicles for anti-cancer agents and thermotherapy. In series of *in vitro* and *in vivo* experiments we analyzed brain tumor targeting with magnetic nanoparticles conjugated with epidermal growth factor (EGF) or heat shock protein Hsp70.
Material and Methods: Human recombinant Hsp70, EGF were produced by genetic engineering. SPIONs modified by EGF, Hsp70 were characterized by spectrophotometry, ELISA assays, atomic-force microscopy and NMR. Proton magnetic relaxation times T_2 were measured with the help of the NMR-spectrometer (CXP-300, Bruker) in magnetic field of 7.1 T. The *in vitro* binding and uptake of SPIONs, Hsp70-SPIONs and EGF-SPIONs conjugates were assessed on the C6 glioma cells culture by confocal and electron microscopy. The *in vivo* traffic was analyzed in the model of intracranial C6 glioma. MR images (gradient echo (FLASH), T_1- and T_2-weighted, multi-sc and multi-echo (MSME T_2-map) of rat glioma were obtained by Bruker Avance II NMR spectrometer 11 T.
Results: SPIONs measured relaxivity corresponded to properties of negative contrast agents with a hypointensive change of resonance signal

in MR imaging. According to *in vitro* studies SPIONs were incorporated into C6 cells mostly by endocytosis pathway. Intriguingly, the conjugation of protein Hsp70 or EGF to the SPIONs increased the internalization of nanoparticles as was demonstrated by confocal microscopy (by the receptor-mediated endocytosis: EGFR for EGF-SPIONs, CD40 for Hsp70-SPIONs). *In vivo* studies confirmed the tumor targeting ability of modified SPIONs. I.v. injected nanoparticles accumulated inside C6 glioma tumor with a significant decrease of signal on T2-weighted images. Confocal microscopy images confirmed the Hsp70-SPIONs or EGF-SPIONs accumulation within the tumor cells cytoplasm.
Conclusions: Modified SPIONs application represents a promising approach for the targeted therapy and imaging of malignant tumors. SPIONs conjugated with heat shock protein Hsp70 or EGF increased the uptake of nanoparticles by glioma cells and, what is more important, − provided the selectivity of tumor targeting in *in vivo* conditions. The proposed technology based on magnetic nanoparticles exhibits the high diagnostic potential and could be further transferred to the thermotherapy of brain tumors.
No conflict of interest.

1166 POSTER

Diffusion-weighted magnetic resonance imaging at 3.0-T versus fluorine 18 fluorodeoxyglucose positron emission tomography/computed tomography for detection of pulmonary malignant tumors

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Background: Emerging evidences suggest that diffusion-weighted magnetic resonance imaging (DW MRI) at 1.5-T could be useful for tumor detection, together with N and M staging in patients with lung cancer, especially non-small cell lung cancer (NSCLC), in place of fluorine 18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) most recently. This investigation prospectively examined whether DW MRI at 3.0-T might be as useful as FDG PET/CT for detection of pulmonary malignant tumors.
Material and Methods: This study was approved by the institutional review board, and written informed consent was obtained from all patients. DW MRI and FDG PET/CT were performed before therapy in 113 patients with pulmonary nodules, including lung cancer, lung metastases, and benign lesions, diagnosed by pathological examination. Mean apparent diffusion coefficient (ADC), maximal standardized uptake value (SUV_{max}), and five-point visual scoring were assessed. Immunohistochemical staining for Ki-67 was performed in 36 patients with lung cancer, and Ki-67 score was evaluated. Receiver operating characteristic (ROC) curve analysis was used to determine feasible threshold values. Diagnostic capabilities for detection of pulmonary malignant tumors were compared with the McNemar test on a per-patient basis, and correlation between malignant degree of lung cancer and ADC or SUV_{max} was analyzed by Spearman rank test.
Results: As for diagnostic capability, area under ROC curve (A_z) for ADC (0.91) were significantly higher than that for SUV_{max} (0.78, P <0.05), and A_z value for DW MRI (0.94) were not significantly different from that for FDG PET/CT (0.92, P >0.05). For quantitative assessment, specificity and accuracy of ADC (91.7%, 92.9%) proved to be significantly higher than those of SUV_{max} (66.7%, 77.9%, P <0.05), although sensitivity of ADC (93.5%) was not significantly different from that of SUV_{max} (83.1%, P >0.05). When feasible threshold values were used to assess qualitatively, sensitivity, specificity, and accuracy of DW MRI (96.1%, 83.3%, 92.0%) were also not significantly different from that of FDG PET/CT (88.3%, 83.3%, 86.7%, P >0.05). Significant correlation was found between Ki-67 score and ADC (Spearman coefficient r = −0.66, P <0.05), as well as ADC and SUV_{max} (r = −0.37, P <0.05). On the contrary, Spearman coefficient was −0.11 between Ki-67 score and SUV_{max} (P >0.05).
Conclusions: Quantitative and qualitative assessments for detection of pulmonary malignant tumors obtained with DW MRI at 3.0-T are as useful as, even superior to, those obtained with FDG PET/CT. Furthermore, another significant outcome of this study was that ADC in DW MRI at 3.0-T can also play a role in prediction for malignant degree of lung cancer in particular, but SUV_{max} did not in FDG PET/CT.
No conflict of interest.

1167 POSTER

Associations between BRCA mutation status, pathologic findings, and MR imaging features in patients with breast cancer who have high risk factors for mutation

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Background: We investigated the relationship between BRCA mutation, pathologic findings, and magnetic resonance imaging (MRI) findings in patients with breast cancer who had risk factors for the mutation.
Materials and Methods: Genetic testing for BRCA mutation was performed in 275 breast cancer patients with at least one risk factor for the mutation. Using the Breast Imaging Reporting and Data System MR lexicon, morphologic and kinetic features on MRI were reviewed for 230 tumors in 209 of these patients. The relationship between BRCA mutation, pathologic findings, and MRI findings was examined by chi-square or Fisher's exact tests. Disease recurrence was also estimated.
Results: BRCA mutation was detected in 48 (23.0%) patients; BRCA1, 21 (10.0%); BRCA2, 25 (12.0%). Two (1.0%) patients had mutations in both genes. Tumors in patients with BRCA1 mutations more frequently showed a high nuclear grade (p = 0.0041) and triple-negative (TN) phenotype (p <0.0001). On MRI, the tumors were seen as mass types in 182 (79.1%) of 230 lesions and non-mass types in 48 (20.9%) cases. Among the MRI features, rim enhancement was significantly associated with molecular subtypes based on immunohistochemistry (p <0.0001) and nuclear grade (p = 0.0387) in multiple logistic regression. Rim enhancement on MRI, along with advanced pathologic T stage, was associated with increased disease recurrence (p = 0.0023) in multivariate analysis. However, the proportion of mass types and non-mass types and the distribution of morphologic shape, margin, internal enhancement, or kinetic features on MRI were not different according to BRCA mutation status.
Conclusion: In patients with high-risk breast cancer, BRCA1 mutation was associated with aggressive pathologic characteristics and TN phenotype. However, direct association between BRCA mutations and MRI features was not observed. Rim enhancement was frequently seen on MRI in high grade tumors and in TN phenotype, and a significant predictor of increased early recurrence of disease.
No conflict of interest.

1168 POSTER

Preoperative assessment of gastrointestinal stromal tumors using diffusion-weighted magnetic resonance imaging

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Background: In Gastrointestinalstromal tumors (GIST), surgical indication is an important problem, and the malignant evaluation is indispensable. In recently modified Flecher risk classification and UICC-TNM are made, and it was shown for the risk evaluation that mitosis count and the tumor size are index. The establishment of clinical diagnostics count is a problem.
Method and Materials: Fifty-three patients who underwent surgical resection were enrolled (esophagus 1, stomach 39, small bowel 7, Cecum 1 and rectum 5; mean size 4.3 cm, range 1.4−21 cm). Prior to surgery, Diffusion-weighted Magnetic Resonance imaging was performed by SENSE-STIR-EPI TR/TE 10000/75 ms, 4 mm, b=0, 1000 sec/mm2. Apparent diffusion coefficient Minimum value (ADCmin) of the tumor was measured Histological diagnosis was made by immunohistological staining of c-kit and CD34. Risk groups were estimated by assessing tumor size and mitosis per 50 HPFs based on modified Flecher risk classification and UICC-TNM. We evaluated the relationship between ADCmin and risk groups, Stage.
Results: There was a correlation of ADCmin between tumor size (R = −0.43, P = 0.001). There was a correlation of ADCmin between mitosis (R = −0.41, P = 0.003). ADCmin of very low-risk group was 1.39 +/− 0.26, low-risk 1.23 +/− 0.29, intermediate-risk 1.29 +/− 0.18 and high-risk 0.80 +/− 0.23. ADCmin of high-risk group was higher than that of other groups with a statistical difference (P = 0.001). The cut-off ADCmin level of 0.8 revealed 76.9% sensitivity and 97.5% specificity and 90.9% positive predictive value and 92.9% negative predictive value and 92.5% accuracy in predicting high-risk group. ADCmin of Stage I group was 1.28 +/− 0.29, Stage II 1.20 +/− 0.18 and Stage III/IV 0.75 +/− 0.23. ADCmin of Stage

III/IV group was higher than that of other groups with a statistical difference (P = 0.001).
Conclusion: Diffusion-weighted MRI may enable to discriminate high-risk group from other groups with high accuracy and to discriminate high-risk group from others with high specificity. It may become one of the valid clinical modalities for evaluating risk group of GIST.
No conflict of interest.

1169 POSTER

Diagnostic performance of the combination of multi detector-row computed tomography and fluorodeoxyglucose-positron emission tomography and diffusion-weighted magnetic resonance imaging for preoperative esophageal squamous cancer lymph node

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Background: Lymph node diagnosis is important in determining the course of treatment of esophageal cancer. Lymph node metastasis of esophageal cancer currently is done by multi detector-row computed tomography (MDCT) mainly, it is made in the size and morphological evaluation to identify the lymph nodes. MDCT is superior in resolution, but is poor in qualitative diagnosis. fluorodeoxyglucose-positron emission tomography (FDG-PET) and diffusion-weighted magnetic resonance imaging (DWI) is superior to qualitative diagnosis, utility as a diagnostic aid in the lymph nodes of esophageal cancer is not being considered.
We use MDCT and DWI and FDG-PET to the lymph nodes preoperative diagnosis. We examined the usefulness of DWI and FDG-PET in the diagnosis.
Material and Methods: 47 cases of esophageal squamous cell carcinoma resection with no preoperative treatment. 2813 lymph nodes were dissected, it was identified in the CT 252(9.0%). The meta diagnosed with a case in which diameter more than 10 mm and ratio of the major axis and single size 0.7 or more are met. Further, diagnosis of metastasis even if it meets rim enchancement. Line of SUV value was set to 3.0 and Line of ADC value was set to 1.5 than the data in the normal tissue and abnormal tissue of esophageal cancer. Line of ADC was possible to distinguish 100% non-metastatic lymph nodes allow the diffusion suppression and metastatic lymph nodes that allow the diffusion suppression in DWI.
Result: Sensitivity 19.1% positive predictive value 69.2% correct diagnosis rate 83.3% in the CT diagnosis. Sensitivity decreases to 12.8% by the addition of PET to CT diagnosis, PPV was increased to 100%, overall accuracy rate was increased to 83.7%. By adding a DWI in CT diagnosis sensitivity is next to 48.9%, PPV is next 100%, overall accuracy rate became 90.2%. DWI was increased the sensitivity significantly.
Conclusions: Combination of the PET is not lead to increase overall accuracy rate, but it is suitable to maintain a high PPV.
Combination of DWI increased sensitivity and overall accuracy, and improve the diagnostic performance of the lymph nodes.
No conflict of interest.

1170 POSTER

Diffusion weighted magnetic resonance imaging for assessing the early response to chemoradiotherapy for advanced esophageal squamous cell carcinoma

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Background: Predicting the outcome at an early stage of chemoradiotherapy (CRT) for advanced esophageal squamous cell carcinoma (eSCC) can prevent the exposure of the patient to ineffective and unnecessary toxicity. Identifying the patients of which treatment is effective could increase the probability of surgical resection and finally improve the prognosis of locally advanced eSCC. The aim of this study was to investigate the utility of the apparent diffusion coefficient (ADC) value in Diffusion Weighted Magnetic Resonance Imaging (DWMRI) for prediction and early detection of treatment response in advanced eSCC.
Materials and Methods: Twenty-seven consecutive patients with primary cT4 eSCC who underwent CRT were retrospectively evaluated. Patients received accelerated radiotherapy. Chemotherapy was performed with 5FU and CDDP. CRT response was assessed at the end of a 40 Gy the clinical response of the primary tumor was discriminated as follows: CR; disappearance of tumor, PR; at least a 30% decrease, PD; at least a 20% increase, SD; not CR, PR nor PD. CR and PR were estimated as responders. Responder patients underwent operation. Meanwhile, non-responder patients underwent definitive CRT until the 60 Gy. DWMRI was performed before CRT, after 20 Gy and after 40 Gy. We measured tumor ADCs (x 10^{-3} mm^2/s) and compared with the therapeutic effect between responders and non-responders.
Results: The ADC value of 20 Gy was significantly higher in responders in comparison to non-responders (1.13 vs. 0.93; P = 0.005). Cut-off ADC value was set at 1.00 by Receiver Operating Characteristic analysis. The ADC predicted the responders with a sensitivity, positive predictive value(PPV), and accuracy of 79%, 73%, and 74%, respectively. The increase rate of the ADC at the period of 20 Gy (ADC20) was also significantly higher in the responders in comparison to the non-responders (35.4% vs. 1.5% P = 0.0007). An ADC cut-off value for ADC20 of 15% predicted the responders with a sensitivity, PPV, and accuracy of 71%, 100%, and 85%, respectively. At the time of 20 Gy, eleven patients were less than cut-off level both of ADC and ADC (Group A). Ten patients of Group A were non-responders. Sixteen patients were more than cut-off level either ADC or ADC (Group B). Thirteen patients of Group B were responders.
Conclusion: DWMRI is a non-invasive functional modality for eSCC. It may predict early response after CRT and also available to estimate outcome after the treatment.
No conflict of interest.

1171 POSTER

Detection of liver tumors by indocyanine green fluorescence: Results and perspectives

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Introduction: The gold standard to treat liver metastases from colorectal cancer is a parenchymal resection that achieves a R0 result at final pathology. This is a major determinant for a prolonged disease free survival. However the current imaging techniques can face a limit of resolution. Possibly one could find an intraoperative staging worse that expected from the preoperative workup. Recently Indocyanine green fluorescence has been proposed to improve the intraoperative staging of liver tumors in synergy with IOUS.
Material and Methods: 30 patients with colorectal metastases were enrolled. Each had a i.v. bolus of ICG (0.5 mg pro kg of body weight) 24 hrs before surgery. ICG fluorescence, which accumulates around neoplastic lesions as a result of defected biliary clearance, was detected intraoperatively with a specifically near-infrared camera system (PDE-PhotoDynamicEye). We recorded the total number of lesions detected by PDE-ICG, intraoperative ultrasound (IOUS) and preoperative computed tomography (CT).
Results: The combined use of PDE-ICG and IOUS revealed 30% more nodules than IOUS alone and 40% more than preoperative CT. While the detection was quite similar for nodules >3 mm, PDE-IOUS was significantly superior for nodules <3 mm.
Conclusions: The chase for radical liver surgery requires imaging techniques that effectively detect all the tumor deposits. PDE-IOUS detection could foster our ability to find and remove undiscovered liver nodules. Probably we should recognize that current imaging still has limits. New technologies will probably modify our approach to liver resections.
No conflict of interest.

1172 POSTER

Evaluation of malignancy for esophageal cancer by dynamic FDG-PET

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Background: One of the basic characteristics of cancer includes heterogeneity. The heterogeneity of the tumor tissue is thought to have influence to the sensitivity such as an anticancer agent or the radiation and is thought one of the treatment-resistant causes. In late years a cancer stem cell hypothesis is advocated, and the biological malignancy evaluation of cancer by the molecular biologic technique attracts attention. It is the present conditions that there are few reports about the heterogeneity of the tumor tissue. We analyze heterogeneity in the glucose metabolism of the esophageal cancer by applying a fractal dimensional analysis using Dynamic FDG-PET (dPET). The fractal dimension is a parameter of heterogeneity and it is used for brain blood flow evaluations by the SPECT, for example.
Methods and Materials: Our evaluation study included 30 patients of esophageal cancer. dPET studies were performed after intravenous injection of 370 MBq ^{18}F-FDGfor 60 min. All patients were examined with

a 23-frame protocol (10 frames of 1 min, 5 frames of 2 min, and 8 frames of 5 min). The evaluation of the dynamic PET was performed using the software package PMod (PMod Ltd.,Zurich, Switzerland). Fractal dimension (FD) was calculated for the time-activity-data in each individual voxel of a VOI (volume of interest, consists of several regions of interest (ROI) over the target area). We compared SUVmax with FD and examined a change of FD in before and after preoperative adjuvant therapy, and an association of clinical progress.
Results: FD has a stronger correlation in a clinical progression than SUVmax; by the comparison between a clinical depth of tumor invasion (cT) and FD, $r^2 = 0.603$ whereas $r^2 = 0.5733$ SUVmax, and by the comparison between a clinical stage of tumor (cStage) and FD, $r^2 = 0.5929$ whereas $r^2 = 0.5694$ SUVmax. When we compared a rate of decline of FD before and after treatment in preoperation, in the case with the rate of decline of FD more than 10 the effect was grade 2 or 3 in postoperative pathology, in the rate of decline of FD is less than 10 the grade was 1. It was confirmed pathologically that the rate of decline of FD reflected an effect of the treatment more exactly than that of SUV in preoperation.
Conclusions: FD is a useful parameter for indicating heterogeneity of tumor, and clinically it is thought that FD is feasible for a preoperative curative effect judgment. It becomes the new parameter for the SUV.
No conflict of interest.

1173 POSTER

Optical coherence tomography (OCT) in pigmented lesions

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Background: Cutaneous malignant melanomas are diagnosed worldwide in about 200,000 patients per year. To reduce mortality, early diagnosis is important. Optical coherence tomography (OCT) measures backscattered light like ultrasound measures backscattered sound waves. The backscattered light versus the depth is described by the attenuation coefficient (μ_{oct}). We hypothesize that OCT images of benign nevi will differ qualitatively and quantitatively from malignant melanomas, enabling the dermatologist real time, non-invasive measurement of suspicious lesions.
Material and Methods: Forty lesions from thirty-three consecutive patients were imaged with OCT. Directly after data acquisition, excision was performed. Images were studied with attention to morphological details. Epidermal layer thickness was measured and values of μ_{oct} were extracted from 200 OCT images of pigmented lesions.
Result: Morphologically, absence of the lower border of the lesion was characteristic for melanoma ($p = 0.02$). Also, the attenuation coefficient (μ_{oct}) was different between benign and malignant lesions ($p = 0.02$). There were no differences in epidermal layer thickness of benign lesions and malignant melanoma.
Conclusion: This study shows that quantitative analysis of OCT images in pigmented skin lesions gives valuable additional information about lesions characteristics. When using the attenuation coefficient, it becomes possible to distinguish between benign lesions and malignant melanoma.
No conflict of interest.

1174 POSTER

Optical coherence tomography (OCT) in neoplasia of the penis

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Introduction: Optical coherence tomography (OCT) measures backscattered light like ultrasound measures backscattered sound waves. With OCT, non-invasive micro-scale resolution volumetric *in vivo* image datasets of (pre)malignant lesions of the penis are obtained, closely resembling histopathology. Moreover, the OCT-signal can be quantified, using the attenuation coefficient (μ_{oct}). This quantitative parameter, μ_{oct}, may vary along different histological types of tissue. We hypothesize that qualitative and quantitative measurements of penile skin with OCT can differentiate between benign and (pre)malignant tissue.
Material and Methods: OCT-imaging was performed at the outpatient clinic of the NKI-AvL. All OCT- images were conducted in vivo and were analyzed afterwards. Directly after imaging, a punch biopsy was performed. One investigator, blinded for pathology, performed the qualitative analysis as well as the quantitative analysis. Qualitative analysis consisted of epidermal layer thickness measurements and determination of visible lower border of the lesions, quantitative analysis comprised of determination of the μ_{oct} of the suspicious lesions. All results were grouped according to histopathology reports.
Results: OCT images of 18 penile lesions of 18 patients were analyzed. Qualitative analysis showed a statistically significant difference ($p = 0.047$) between benign and (pre)malignant lesions with regard to the visibility of the lower border of the lesions. Also, epidermal layer thickness was significantly different between benign and (pre)malignant tissue ($p = 0.001$). Quantitative analysis showed an attenuation coefficient (μ_{oct}) of benign and (pre)malignant lesions of 2.47 mm^{-1} (SE 0.52 mm^{-1}) and 5.23 mm^{-1} (SE 0.32 mm^{-1}) respectively ($p < 0.001$).
Conclusion: OCT imaging and quantitative analysis of suspicious penile lesions has the ability to differentiate benign penile lesions from (pre)malignant penile lesions.
No conflict of interest.

1175 POSTER

Optical coherence tomography in vulvar squamous cell carcinoma

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Objective: Vulvar squamous cell carcinoma (VSCC) is the fourth most common gynaecological type of cancer with an incidence of approximately 2−3 per 100,000 women. VSCC arises from, and occasionally next to, premalignant lesions called vulvar intraepithelial neoplasia (VIN). VIN and VSCC are diagnosed through painful and invasive punch biopsy.
Optical coherence tomography (OCT) is a non invasive optical imaging technique that measures backscattered light like ultrasound measures backscattered sound waves. OCT has the potential to reduce the number of biopsies by performing an optical tissue diagnosis. We hypothesize that: a) specific qualitative features in the OCT images will differ between normal vulvar skin, VIN and VSCC, b) thickness of the epidermal layer of the skin, measured in the OCT-images, is different for normal, VIN and VSCC tissue, c) quantitative measurements of the OCT image, such as the attenuation coefficient (μ_{oct}), can differentiate between VIN, VSCC and normal vulvar tissue.
Material and Methods: Eighteen consecutive patients diagnosed with VSCC were included. Tumour and surrounding tissues were imaged with OCT. Directly after data acquisition, biopsies for histopathological correlation were taken. Thereafter, wide local excision or (partial) vulvectomy was performed. In the OCT-images specific features were sought, that could differentiate between the different tissue types In addition, epidermal layer thickness was measured and values of μ_{oct} were extracted from the OCT data. For both methods, statistical analysis was performed using mixed effects regression analysis.
Results: Qualitative analysis of OCT images showed an evident epidermal layer and a clear basement membrane layer in normal vulvar skin, while these layers could not be observed in VIN and VSCC ($p < 0.0001$).
OCT images showed a significant difference in epidermal layer thickness between normal vulvar tissue and VIN or VSCC ($p < 0.0001$) where no difference was found between VIN and VSCC. When looking at μ_{OCT}, a statistically significant difference between normal skin and VIN ($p = 0.001$) was found as well as between normal vulvar skin and VSCC ($p < 0.0001$). There was no difference between the μ_{OCT} of VIN and VSCC ($p = 0.68$).
Conclusion: This study demonstrates that OCT may be a helpful technique for non invasive tissue diagnosis of vulver malignancies.
No conflict of interest.

1176 POSTER

Pitfalls with the independent audit method of PFS endpoint trials with central imaging

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ODAC (Oncologic Drug Advisory Committee) discussed the pros and cons of implementing subpopulation audit methods of sites' assessments in oncology trials with PFS endpoints. Instead of a complete Blinded Independent Central Review (BICR) of the entire study population only a few selected cases should undergo BICR.
The discussion is about two potential methods introduced by Dodd et al., 2008, 2011 and Amit et al., 2011. In these papers the authors attempt to reduce the risk of informative censoring, optimize trial conduct and reduce associated cost.
Both authors describe novel and interesting methods to be used. Based on logistical and even more so statistical complexities inherent in both these methods in their current form neither will achieve any of the proposed goals of reducing cost, complexity, time and data censoring challenges.
This paper challenges the proposed processes and provides detailed explanations to introduced obstacles logistically, timewise, statistically, operationally. Either method increases the complexity of conducting Oncology trials. The study duration can not be shorter but rather longer in most study designs. The statistical impact of any such discrepancy between Local Evaluations (LE) and BICR are not foreseeable and not at all defined. Operationally, any sponsor and imaging CRO together need to invent new and abandon well established and industry-accepted processes. This will increase the risk, complexity and as such any chance for errors.
Based on experience and daily practice this paper gives examples why the proposed audit methods of PFS endpoints with central imaging are not feasible for Oncology trials and rather put patients, sponsors and study data at risk.
No conflict of interest.

1177 POSTER

3D SPECT/CT-based navigation to the sentinel node in the groin

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Background: To further improve the accuracy with which a sentinel node can be detected, the Declipse® SPECT-system (SurgicEye, Munich, Germany) was introduced. This navigation system can incorporate preoperatively acquired SPECT/CT information. By projecting this dataset onto the patient, it enables intraoperative mixed-reality-based navigation to the area of interest (e.g. the sentinel node). This study evaluated the accuracy of the navigation during open- and laparoscopic sentinel node biopsy in urological malignancies.
Materials and Methods: Following tracer injection in penile carcinoma (n = 10) patients, who were scheduled for sentinel node biopsy, preoperative SPECT/CT was performed with a reference target fixed on the patient. For the penile carcinoma patients the reference target was placed on the pubic bone. The location of the reference target was then marked with indelible ink. Prior ot the start of the operation a sterile ReT was repositioned on the patient. A second reference target was positioned on the gamma probe as such allowing the surgeon to navigate the tip of the gamma probe to the sentinel node. Navigation was provided in mixed-reality, in 3D, based on the preoperatively acquired SPECT/CT imaging. The accuracy of the navigation approach was determined in relation to the location pointed out by the conventional gamma probe (coronal plane). The depth measured on the axial CT slices (distance skin surface − sentinel node; sagittal plane) was compared to the depth measured with the navigation system.
Results: In the 10 penile cancer patients, compared to the results obtained with the conventional approach, the average error of navigation was 5.0 mm and 5.3 mm in the coronal and sagital plane, respectively. During exploration, the inaccuracy of navigation could be overcome by both gamma tracing and fluorescence imaging of the sentinel node.
Conclusion: 3D SPECT/CT mixed-reality-based navigation allowed the identification of the sentinel node and has the potential to more accurately guide the surgeon to the area of interest.
No conflict of interest.

1178 POSTER

Quantification of baseline [18]F-FDG PET images predicts treatment response and progression free survival in Hodgkin's lymphoma

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Background: Efforts to tailor treatments to individual prognosis are important in Hodgkin's Lymphoma (HL) which has a relatively good prognosis but a high chance of developing late treatment effects. Interim PET has shown prognostic value in HL but baseline PET has not yet been extensively studied. In solid tumours the heterogeneity of ^{18}F-FDG uptake as measured by image heterogeneity analysis has been associated with treatment response and survival.
We investigated whether similar predictive and prognostic value exists in the baseline pre-treatment ^{18}F-FDG images.
Material and Methods: 55 consecutive patients with stage II−IV disease were retrospectively analysed (median FU 34 months), defining the nodal mass with the highest SUV on the baseline scan. Interval and end-of-chemotherapy responses were classified according the Deauville Score (Responders = Deauville 1, 2 & 3; Non-responders = Deauville 4 & 5); Overall treatment response was assessed using the Deauville Score combined with clinical evaluation. In-house software was used to measure Standard Uptake Value (SUV) parameters alongside 1st and 2nd order heterogeneity features.
Results: SUVmean, max and peak from the baseline ^{18}F-FDG PET image predicted the end of chemotherapy and overall treatment response ($p \leqslant 0.01$), as well as progression free survival (SUVmax $p = 0.016$, SUVpeak $p = 0.028$). 1st order parameters from region of interest (ROI) analysis similarly predicted end of chemotherapy Deauville response and overall treatment response ($p \leqslant 0.05$).
The 2nd order heterogeneity parameters measured on the baseline PET image using grey-level co-occurrence matrices (GLCM) and grey-level run length (GLRL) analyses predicted the Deauville response of the early interval PET ($p = 0.01$–0.05).
Conclusions: Baseline ^{18}F-FDG PET SUV and other 1st order parameters predict end of chemotherapy Deauville response, overall treatment response and PFS. GLCM and GLRL 2nd order heterogeneity measures of the baseline PET image predicts early response to chemotherapy.
No conflict of interest.

1179 POSTER

Preoperative assessment of gastrointestinal stromal tumors using positron emission tomography

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Background: In Gastrointestinalstromal tumors (GIST), surgical indication is an important problem, and the malignant evaluation is indispensable. In recently modified Flecher risk classification and UICC-TNM are made, and it was shown for the risk evaluation that mitosis count and the tumor size are index. The establishment of clinical diagnostics count is a problem.
Method and Materials: Eighty-seven patients who underwent surgical resection were enrolled (esophagus 5, stomach 66, small bowel 8, Cecum 2 and rectum 6; mean size 5.0 cm, range 2.0−30 cm). Prior to surgery, PET imaging was performed after injection of 370MBq of F18-DG tracer. Standardized uptake value (SUV) of the tumor was measured for evaluation. Histological diagnosis was made by immunohistological staining of c-kit and CD34. Risk groups were estimated by assessing tumor size and mitosis per 50 HPFs based on modified Flecher risk classification and UICC-TNM. We evaluated the relationship between SUV and risk groups, Stage.
Results: There was a correlation of SUV between tumor size (R=0.41, P = 0.0007). There was a correlation of SUV between mitosis (R=0.52, P = 0.0000002). SUV of very low-risk group was 4.0 +/− 2.1, low-risk 3.6 +/− 1.6, intermediate-risk 3.5 +/− 2.0 and high-risk 8.9 +/− 5.4. SUV level of high-risk group was higher than that of other groups with a statistical difference (P = 0.000001). The cut-off SUV level of 5.5 revealed 76.0% sensitivity and 87.5% specificity and 73.1% positive predictive value and 90.2% negative predictive value and 85.1% accuracy in predicting high-risk group. SUV of Stage I group was 3.5 +/− 1.6, Stage II 4.3 +/− 2.3 and

Stage III/IV 10.1 +/− 5.0. SUV level of Stage III/IV group was higher than that of other groups with a statistical difference (P = 0.000001).
Conclusion: FDG PET may enable to discriminate high-risk group from other groups with high accuracy and to discriminate high-risk group from others with high specificity. It may become one of the valid clinical modalities for evaluating risk group of GIST.
No conflict of interest.

1180 POSTER

Utility of PET scan for early diagnosis of bleomycin induced pneumonitis in Hodgkin's Lymphoma

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Background: Bleomycin induced pneumonitis (BIP) is an inflammatory process occurring with use of Bleomycin. This is an idiosyncratic response which is debilitating, potentially irreversible and at times ending in fatality (up to 27%). Currently, signs & symptoms, pulmonary function tests (PFT), carbon monoxide diffusion capacity (DLCO) and high resolution computed tomography (HRCT) are used to diagnose BIP. Unfortunately these reveal only manifest BIP. Positron emission tomography (PET), has shown promise to detect early inflammatory changes, a key feature of early BIP. We prospectively explored the abilty of PET scan to detect early BIP and compared it with standard existing modalities such as DLCO and HRCT in our patients with Hodgkin's Lymphoma (HL).
Methods: This was a prospective observational single centre study wherein, newly diagnosed HL treated with the ABVD regimen from November 2011 to July 2012 was included. After baseline staging evaluation, ABVD was instituted. All were monitored every two cycles for any form of BIP, assessed clinically, by PFT, DLCO and PET scan with HRCT chest. If none occurred they were followed up until completion of treatment. Data was analyzed using SPSS v 16.0.
Results: 75 patients were enrolled in the study and 59 were evaluable for final analysis. 49% had advanced stage, 12% were smokers and 8% had history of tuberculosis. 25 (40%) had features suggestive of BIP based on any one or combination of tests. 11/25 showed PET positivity but 14/25 were negative on PET while showing clinical or PFT findings indicative of BIP. 7/25 and 9/25 were positive only on PET and DLCO respectively but were asymptomatic for BIP. 5/25 were clinically symptomatic for BIP and correlated with DLCO but were negative on PET. Only 2/25 was both positive by PET and PFT combined but remained asymptomatic. 2/25 patients had all three parameters indicative of BIP. 34 patients remained negative.
Conclusions: Our study showed PET scan to be sensitive in detecting early BIP but did not directly correlate with standard testing and clinical suspicion. It however provides a platform for exploring its utility for detecting early BIP.
No conflict of interest.

Table 1. Bleomycin induced pneumonitis in 25 patients

	Number	Percentage
CLINICAL +PFT	5	8.5
PFT	9	15.3
PET	7	11.9
PET+PFT	2	3.4
CLINICAL+PFT+PET	2	3.4

1181 POSTER

Role of the maximal standardized uptake value on fluorine 18 fluorodeoxyglucose positron emission tomography /computed tomography for predicting malignancy grade of operable breast cancer

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Background: [18F]-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) is potentially useful not only in examining and assessing metastasis but also in predicting prognosis of recurrent breast cancer and measuring treatment effects.
Material and Methods: Stage I−III breast cancer patients who underwent preoperative FDG-PET/CT and who were able to undergo radical surgery at the Hiroshima University Department of Breast Surgery and the Shikoku Cancer Center between January 2006 and December 2011, were included in this study (median follow up period:26.5 months). The maximal standardized uptake value (SUVmax) were assessed for predicting disease free survival (DFS). For the evaluation of relationship between SUVmax values and prognostic factors such as hormone receptors, human epidermal growth factor receptor 2 (HER2), nuclear grade, lymph node metastasis and tumor size, statistical analyses were performed using Student t test and log-rank test, and p values of less than 0.05 were considered to indicate statistically significant differences.
Results: Clinical Stage included were I (n = 194, 56.4%), II (n = 134, 39.0%) and III (n = 16, 4.7%). Tumors with estrogen receptor (ER) positive were 292 (84.9%) and negative were 52 (15.1%). All patients were divided into two groups according to cut-off SUVmax established on the basis of receiver operating characteristic (ROC) analysis ($\leqslant$3.0 vs >3.0, AUC=0.713). There was a significant difference in DFS between two groups (p = 0.001) and, hormone receptor, HER2, nuclear grade, lymph node metastasis were found strong relation to SUVmax values. SUVmax and ER status were predictive factors with multivariable analysis using cox proportional hazard regression model (p = 0.033 and p = 0.004, respectively). Furthermore patients were categorized in 3 subtypes including luminal (ER+, HER2−, n = 260), HER2 (ER− or ER+, HER2+, n = 47), and triple-negative type (ER−, HER2−, n = 37), and average SUVmax in each subtype were 3.24$\pm$2.64 in luminal, 5.01$\pm$3.60 in HER2, 4.99$\pm$4.57 in triple-negative type.
Conclusions: Our results suggest that SUVmax on preoperative FDG PET/CT have a predictive value for high-grade malignancy and prognosis in clinical Stage I−III breast cancer and it might be necessary to determine the cut-off points for each subtype for use in determining the course of treatment.
No conflict of interest.

Subtype	n (total 344)	SUVmax (average$\pm$SD)	Recurrence (total 17)
Luminal	260	3.24$\pm$2.64	6
HER2	47	5.01$\pm$3.60	5
Triple-negative	37	4.99$\pm$4.57	6

1182 POSTER

Nuclear medicine in the study of multidrug resistance in hepatocellular carcinoma: Studies with 18F-FDG and 99mTC-MIBI

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Background: Hepatocellular carcinoma (HCC) is known to be resistant to chemotherapy, which is due in part to overexpression of multidrug resistance proteins (MDR). A method to evaluate the function of these proteins involves the measure of radiolabeled substrate ^{99m}Tc-MIBI uptake. Studies have demonstrated that ^{18}F-FDG uptake is associated with MDR proteins expression in HCC. Other studies have demonstrated that ^{18}F-FDG uptake by HCC is associated with p53 expression since tumors with lower expression or mutated expression of this protein has a higher uptake of this tracer. This study aims evaluate the uptake and retention of ^{18}F-FDG and ^{99m}Tc-MIBI in three human HCC cell lines and to correlate them with the expression of three MDR proteins and with p53 expression.
Methods: Cell lines used were HepG2 (wp53), HuH7 (mp53) and Hep3B2.1−7 (p53null). Uptake and retention studies with ^{18}F-FDG or ^{99m}Tc-MIBI were performed. Cells grown were evaluated in low glucose medium (5mM) and in high glucose medium (25mM) in order to verify the influence of the glucose on ^{18}F-FDG and ^{99m}Tc-MIBI uptake and retention. Pgp, MRP1 and LRP proteins were determined by flow cytometry. To evaluate MDR modulation, retention studies were performed in the presence of verapamil (Pgp inhibitor) prior to incubation with ^{18}F-FDG or ^{99m}Tc-MIBI.

Results: For all cell lines used, ^{18}F-FDG and ^{99m}Tc-MIBI uptake and retention were higher when cells grown on low glucose medium. For both media formulations Hep3B2.1−7 cell line has higher uptake and retention of ^{18}F-FDG and ^{99m}Tc-MIBI. HepG2 cell line has a lower uptake and retention and a higher expression of MRP1. Through modulation studies with cells incubation with verapamil, a considerable increase of ^{18}F-FDG and ^{99m}Tc-MIBI retention in all cell lines were obtained.
Conclusions: It is concluded that medium glucose concentration influences the uptake and retention of both radiopharmaceuticals. There is an inverse relationship between MRP1 expressions and uptake and retention of ^{99m}Tc-MIBI and ^{18}F-FDG. Through modulation studies it was found that Pgp has an active role on MDR in HCC. Uptake and retention profiles for the two radiopharmaceuticals are similar, showing that the ^{18}F-FDG can be used to study the MDR proteins function in HCC cells, being an alternative to ^{99m}Tc-MIBI. We also conclude that p53 expression influences ^{18}F-FDG uptake once Hep3B2.1−7 and HuH7 cell lines have higher uptake than HepG2.
No conflict of interest.

1183 POSTER

The effect of respiratory motion of diaphragm on positron emission tomography/computed tomography for patients with clinical stage IA lung adenocarcinoma

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Objectives: F-18-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) is reported to be a surrogate marker of tumor malignancy grade in lung adenocarcinoma. However, respiratory motion of diaphragm resulted in reducing the measured maximal standardized uptake value (max SUV) on PET/CT of tumors, especially localized in the lower zone of lung. The purpose of this study is to compare the diagnostic significance of max SUV to predict tumor malignancy and prognosis between upper zone (UZ, containing segment 1, 2, 3 and 6) and lower zone (LZ, containing segment 4, 5, 7, 8, 9 and 10) in patients with early stage lung adenocarcinoma.
Methods: 608 consecutive patients with clinical stage IA lung adenocarcinoma who had undergone preoperative PET/CT were enrolled in this study. Tumor location (UZ, n = 383; LZ, n = 225) and surgical results were retrospectively analyzed for all patients.
Results: Although there were no significant differences between UZ and LZ patients in terms of sex, age, whole tumor size, solid component size, lymphatic invasion (ly), vascular invasion (v), pleural invasion (pl) and lymph nodes metastasis (n), max SUV in UZ is significantly higher than that in LZ (2.4±2.4 VS 2.0±1.8, respectively, p = 0.013). All receiver operating characteristics area under the curve of max SUV for predicting ly, v, pl, n, and high-grade malignancy (ly, v, pl or n) were larger for UZ tumor than those for LZ tumor. Moreover cut-off values of maxSUV for predicting pathological malignancy (ly, v, pl, and n) in UZ and LZ were 2.4 vs 1.9, 2.5 vs 1.9, 2.3 vs 1.9, and 2.8 vs 1.6, respectively. The predictability of all outcomes on the basis of maxSUV in UZ seemed to be better than that in LZ and cut-off values in UZ tended to be higher than that in LZ.
Conclusion: MaxSUV of tumors in LZ may be affected by the respiratory motion of diaphragm and apparently become lower than those which reflects a real malignant potential of tumors. Deep-inspiration breath-hold PET/CT could resolve this problem in order to precisely evaluate the malignant grade of tumors and to select appropriate surgical procedures.
No conflict of interest.

1184 POSTER

Characterization and analysis of tumorous 18F FDG-avidity in deaths due to differentiated thyroid cancer

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One of the major roles of ^{18}F Fluorodeoxyglucose (FDG) PET in managing differentiated thyroid cancer (DTC) is to detect the non-iodine avid or dedifferentiated tumors and therefore, the FDG avidity is regarded as a poor prognostic indicator. In this study we attempt to characterize and analyze the FDG PET findings in patients dying due to advanced DTC.
Material and Methods: Our institutional cancer registry has maintained a record of all patients with malignancies seen at our hospital since 1983. The registry was searched for cases with diagnosis of thyroid cancers and also to determine if the death cause is thyroid cancer-related. A total of 290 such patients were known to be expired during the follow-up and 67.9% (197/290) were ascribed to die from thyroid cancer after exclusion of non-cancer related deaths (N = 60) or dying due to other known (N = 21) or unknown (N = 12) malignancies. We further review the cases ever assessed by FDG PET within 2 years before their death and categorized the patterns and FDG avidity of tumors on PET. The lesional FDG avidity of each case was measured from the most dominant ones and presented as maximal standardized uptake value (SUVmax).
Result: Totally 38 cases of FDG PET were analyzed and 26 of them showed extensive FDG-avid metastatic lesions including: lung (N = 17), bone (N = 9), liver (N = 3), brains (N = 2), neck and mediastinal lymph nodes (N = 11) and other soft tissues (N = 6). There were 8 cases with only loco-regional tumor with FDG uptake at neck region. The SUVmax of bony lesions were significantly higher than the others whereas the pulmonary and cervical lesional FDG-avidity could vary greatly, 1.1 to 8.4 (lung), 1.3 to 7.2. However, there were four cases showing none of obvious FDG-avid lesion demonstrated on the PET.
Conclusion: As FDG PET begins to gain its role in assessing advanced DTC and our observation of FDG-avid metastasis pattern as well as tumor FDG uptake of different tumor sites in these DTC patients with imminent death might raise more clinical interests in related investigation.
No conflict of interest.

1185 POSTER

Predictive outcome assessment of extravasation injuries by use of indocyanine green video angiography

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Background: Extravasation of cytotoxic drugs constitutes a serious complication of cancer treatment. So far, a reliable method for early and predictive assessment of tissue damage is still missing. In this study, we evaluated superficial blood flow as assessed by indocyanine green (ICG) angiography in the affected extravasation area as a possible prognostic parameter. Aim of the study was to discriminate between sufficiency of conservative treatment versus the need for later surgical intervention.
Material and Methods: 29 patients were evaluated by ICG angiography after extravasation of vesicant or highly irritant cytotoxic drugs administered by peripheral i.v. infusion. To this aim, 0.2 mg/kg ICG (Pulsion Medical Systems, Germany), tricarbocyanine dye that binds quantitatively to plasma proteins, were injected i.v. to the contralateral extremity. Perfusion index and maximum pixel intensity of the defined regions of interest were individually calculated after recording by dynamic laser-fluorescence-videography (IC-VIEW®).
Results: The perfusion index at the site of extravasation differed significantly between patients (n = 22) with reversible tissue damage and thus healing under conservative management versus those (n = 7) who needed surgical intervention due to the development of necrosis (p = 0.0001). In patients benefiting from conservative management, the perfusion index was significantly higher in the central extravasation area denoting hyperaemia, when compared with the peripheral area (p = 0.0001).
Conclusions: In this cohort of 29 patients, ICG angiography as indicator of superficial local perfusion within the extravasation area of i.v. cytotoxic drugs was of prognostic value for tissue damage. ICG angiography could thus be used for the early identification of patients at risk discriminating between the appropriateness of conservative or surgical measures in the management of extravasation of cytotoxic drugs.
No conflict of interest.

1186 POSTER

Early esophageal squamous cell cancer by high-barium esophagography using flat panel X-ray detector in comparison with histological findings

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Background: In Japan Esophageal squamous cell cancer (eSCC) has been increasing and 5-year survival rate has prolonged in recent years due to standard operation, subtotal esophagectomy with thoraco-abdominal radical lymphadenectomy. Also endoscopic submucosal dissection (ESD) for superficial cancer has become not rare treatment. Because curative operation for eSCC is one of the high invasive surgical treatments of gastro-intestinal diseases, the therapeutic indications for surgery or ESD should be assessed precisely. The aim of this study is to evaluate the depth of tumor

invasion of superficial esophageal cancer by high-barium esophagography (HBE) using flat panel X-ray detector(FPD) and to compare X-ray findings with histological results.
Methods and Materials: 146 lesions of 132 consecutive patients of superficial eSCC in 2007–2012 who underwent esophagectomy or ESD were included. Histological tumor depth was classified into three groups; A (pT1a-EP/pT1a-LPM): carcinoma in situ/invades lamina propria, B (pT1a-MM/pSM1): invades muscularis mucosae/upper 1/3 in submucosa, C (pSM2/pSM3): invades middle 1/3 submucosa or extended to under 1/3. Group A: N = 68, Group B: N = 42, Group C: N = 36. HBE was performed with double-contrast method with 200–230w/v% of bariumsulfate using FPD by three experienced gastroenterologists. X-ray findings were evaluated by morphological findings as follows: longitudinal fold, aggregated nodularity, degree of the depression, roughness, double line in the lateral image, deformation and compliance of wall.
In early period (2007–2010, N = 101 lesions) we compared these X-ray findings with histological results postoperatively, and established new X-ray criteria according to these findings. The accuracy rate was re-evaluated according to the new criteria. In latter period (2011–2012, N = 48 lesions) we examined the criteria prospectively.
Results: The detectability of superficial cancer was 97.0%. **In early period** we scored on each X-ray findings from 0 to 6 point, and by the total number of points, we divided to three clinical groups; 0−5 points was group 'a' (cT1a-EP/cT1a-LPM), 6−12 points was 'b' (cT1a-MM/cSM1), and 13−21 was 'c' (cSM2/cSM3). We establishednew criteria retrospectively, and its accuracy rate was 81.2%. Then in latter period, we tried the new criteria prospectively, the accuracy rate was 79.2%.
Conclusions: HBE with FPD may enable to assess the depth of superficial eSCC in detail. These morphological findings are valid features to discriminate between T1a and T1b of superficial eSCC lesions. This study is clinically available for appropriate selection of the treatment, surgery for T1a cancer or endoscopic resection for T1b cancer.
No conflict of interest.

1187 POSTER

Prognostic factors of ductal carcinoma in situ in association with mammographic characteristics

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Background: The aim of this study is to examine the correlation between mammographic characteristics of Ductal Carcinoma In Situ (DCIS) and tumor Grade, Estrogen(ER)/Progesterone Receptors(PR) expression and amplification of the oncogene HER2/neu respectively.
Material and Methods: During 2012, 145 women with microcalcifications in their mammogram, classified as BIRADS$\geqslant$4, underwent Vacuum Assisted Breast Biopsy(VABB) with the use of radiofrequency device(Breast Lesion Excision System).
Histology identified 92 Ductal Carcinomas In Situ, which were classified as high, intermediate or low nuclear grade, as positive(+) or negative(−) for immunohistochemical (IHC) expression of ER and PR receptors and as low(1+), intermediate(2+) or high(3+) HER2/neu protein expression, respectively.
We studied the biopsy results and we evaluated the former prognostic histological parameters in association with the mammogrpahic pattern of microcalcifications.
Results: From 92 DCIS, 35 were evaluated as high, 31 as intermediate and 26 as low nuclear grade respectively. The expression of ER and PR was positive in 77% of DCIS, and HER2 overexpression was observed in 72% of the tissue samples. Casting/linear calcifications were present in 54% of high grade DCIS, in 25% of intermediate grade and in 21% of low grade respectively. Casting/linear and granular/irregular calcifications were also present in 92% of DCIS with intermediate and high HER2 expression. No correlation was established between morphologic characteristics of calcifications and ER/PR receptors status.
Conclusions: Mammographic manifestation of casting/linear and/or granular/irregular calcifications in a biopsy confirmed DCIS, might be associated with poor prognosis, since it seems to correlate with high tumor Grade and intermediate and high HER2 expression.
No conflict of interest.

1188 POSTER

Microinvasive ductal carcinoma in situ: mammographic features and pathologic findings

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Background: The aim of our study was to evaluate the mammographic and pathologic findings of microinvasive Ductal Carcinoma In Situ.
Material and Methods: Our study sample consists of 15 patients who underwent Vacuum Assisted Breast Biopsy(VABB) with the use of radiofrequency device(Breast Lesion Excision System) for excision of suspicious non palpable mammographic lesions, presenting as microcalcifications. These 15 patients were diagnosed with microinvasive Ductal Carcinoma In Situ. We retrospectively evaluated the BIRADS classification, the tumor size and nuclear grade as well as the biological pattern of the tumors.
Results: The mammographic lesions, as interpreted in our Breast Unit, by two separate radiologists, were classified as BIRADS 4b in 8 cases and BIRADS 4c in 7. The mean tumor size was 7.95 mm(range 4−15 mm). Based on the pathologic report, 4 carcinomas were non-high grade while 11 were high grade. Furthermore, 10 out of 15 tumors were ER(+), 9 out of 15 were PR(+) and 10 were Her2(+).
Conclusions: The presence of suspicious for malignancy microcalcifications (classified as BIRADS 4b and 4c) might be indicative of microinvasive Ductal Carcinoma In Situ. Such tumors often present with an aggressive phenotype, as indicated from their high nuclear grade and the increased rate of Her2 positiveness.
No conflict of interest.

1189 POSTER

About techniques to choose the right anti-cancer agents and determine the proper dosage

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Background: Various anti-cancer drugs have been developed. Suitable agent and dose for each patient should differ. I announce that we have developed a way to achieve that goal.
Material and Methods: *New-Matsumoto method*:
1. Using the MH method, living blood cells are taken from a patient, and divided into two layers, upper and lower (i.e., ULRBC(U) and LLRBC(L): hereinafter referred to as 'U' and 'L'). Then, each layer of blood cells is put into 3 ml of RPMI-1640 solution and cultured at 37degrees in a 5%-CO_2 incubator.
2. Assuming that the entire amount of daily dosage of drug administered to the patient (α) is absorbed in 5L of blood, the absorbed amount of drug in 3 ml of blood (X) is calculated as follows: X:3=α:5000, i.e. X=3$\times\alpha$/5000.
3. The calculated amount of drug (X) is added to 3 ml of saline, solution and fully mingled together.
4. The solution, which the drug is dissolved, is sterilized by filtering twice in a clean bench.
5. The sterilized solution is put into U and L, and cultured at 37degrees in a 5%-CO_2 incubator.
6. They are monitored with an inverted scanning microscope, and recorded on photos and VTRs.
7. U and L which the drug-dissolved solution is not added to are used as the control groups.

Judgment method: The most appropriate medicine is that alteration and deformation of blood cells is less, also life span of the cell is increased, compared with the control without the addition of drug.
Results:
1. The conventional dose is overdose in most cases. 1/3 is a proper equivalent in many medications.
2. Inappropriate drug will be easily clear.

Conclusions: This method is very beneficial to the patient and should be used widely from now on.
No conflict of interest.

1190 POSTER

Implementation of hybrid PET/MRI for target volume delineation in stereotactic body radiotherapy of liver tumors

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Background: Stereotactic treatment of liver metastases is a treatment option for patients not eligible for surgical resection. PET/MRI could be a helpful tool to improve target volume delineation. The aim of this report is to assess whether hybrid (^{18}F)FDG PET/MRI is feasible for stereotactic treatment planning and whether the implementation of this new imaging modality into the daily routine wokflow is effective.
Material and Methods: Patients diagnosed with liver metastases or recurrent primary tumor of the liver, who were not eligible for surgical resection, were referred to stereotactic body radiation by a multidisciplinary tumor board. Prior to the start of stereotactic treatment all patients were imaged in the same session on a hybrid 3-Tesla MRI with an integrated PET scanner as well as a on a conventional PET/CT-scanner. For stereotactic treatment planning, patients were positioned using a vacuum couch and scanned with a conventional slow CT as well as a respiratory gated 4-D CT. Images were then transferred to a commercial treatment planning system and a rigid co-registration was performed. Gross target volume (GTV) was delineated in PET-CT(GTV_{PETCT}), slow planning CT (GTV_{CT}), SUV corrected PET(GTV_{PET}) and T2-weighted MRT (GTV_{MRT}). Liver Volume was delineated in PET-CT($Liver_{PETCT}$), slow planning CT ($Liver_{CT}$), respiratory gated CT at maximum expiration(GTV_{4-D}) and MRI (GTV_{MRI}).
Results: There was a good reproducibility concerning liver volume delineated on PET/CT compared to PET/MRI, with the volume delineated on MRT being slightly smaller ($Liver_{MRT}$/$LiverPET_{CT}$ = 93.0% $\pm$ 5.5%). The best correlation was seen between liver volume delineated on PET/CT and respiratory gated 4-D CT ($Liver_{4-D}$/$Liver_{PETCT}$ = 97.8% $\pm$ 3.6%). The average GTV_{CT} was 84.2 ml, GTV_{PETCT} 82.6 ml, GTV_{PET} 108.8 ml and GTV_{MRT}.75.8 ml. Volumes delineated in PET were in average 32.8% larger than volumes delineated on contrast enhanced CT.
Conclusions: Combining MRI and FDG-PET imaging using a hybrid PET/MRI scanner lead to increased patient comfort by acquiring both modalities at a single appointment. First experiences demonstrated a good reproducibility of target volume delineation. Further studies will be performed to test whether the precision of target volume delineation might be increased by using PET/MRI images.
No conflict of interest.

1191 POSTER

Simultaneous cone beam CT scans captured during prostate radiotherapy; image quality and the effect of arc delivery time

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Background: Cone beam CT (CBCT) images can be acquired during delivery of VMAT rotational radiotherapy. We assessed the quality of simultaneous CBCTs captured during prostate radiotherapy and studied the effects of arc delivery time on image quality.
Methods: Fifty patients with localised prostate cancer were treated with radical VMAT radiotherapy. Treatment was delivered using a single 8 or 10 MV arc on an Elekta linear accelerator fitted with a Synergy CBCT system. Standard and simultaneous CBCT's were captured on fractions 1, 6, 11 and 16. The simultaneous CBCT data was reconstructed and image quality was improved using in-house software. The quality of the CBCT images was assessed using a previously validated scoring tool. The scoring clinician was blinded to whether the scan was a standard or simultaneous CBCT.
Results: 392 CBCT scans were performed on 49 patients who completed radical radiotherapy. 74 simultaneous CBCT scans were performed with a mean arc delivery time of 120 seconds during which 688 CBCT frames were acquired (slow simultaneous CBCT). Following a software upgrade the subsequent 122 simultaneous CBCTs were obtained with a mean arc delivery time of 83 seconds during which 502 CBCT frames were acquired (fast simultaneous CBCT).
All standard CBCTs and 101 (52%) simultaneous CBCTs were deemed to be clinically useful. Further results are given in table 1.
The image quality from fast simultaneous CBCT was significantly worse than image quality from slow simultaneous CBCT (chi squared test, $p < 0.001$).
Conclusion: Simultaneous CBCT scanning can produce images which are clinically useful. Prostate CBCTs are affected by bowel gas and patient habitus. Simultaneous CBCTs are also affected by scatter from the MV beam. Reducing the arc delivery time and the number of CBCT frames acquired by approximately one-third reduces the quality of simultaneous CBCTs.
Further development and refinement of simultaneous CBCT scanning is warranted. Future reductions in arc delivery times may have to be limited if the use of simultaneous CBCT scanning becomes standard practice.
No conflict of interest.

Table 1. The quality of cone beam CT scans (CBCTs) according to method of acquisition and arc delivery time.

	Standard CBCT	Slow simultaneous CBCT	Fast simultaneous CBCT
Low quality CBCT (Not clinically useful)	0	12 (16%)	83 (58%)
Intermediate quality CBCT (Clinically useful)	86 (44%)	62 (84%)	39 (32%)
Good quality CBCT (Clinically useful)	110 (56%)	0	0

1192 POSTER

Visualization of the left anterior descending coronary artery on computed tomographic images used for breast radiotherapy planning

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Background: The purpose of this study was to assess the visualization of the left anterior descending coronary artery (LAD) on CT images that were used for breast radiation treatment planning.
Material and Methods: Twenty-five breast cancer patients (including 11 left breast tumors) had radiation treatment. The delineation of the LAD artery was achieved by one radiologist and one radiation oncologist independently on 2 sets of images for each patient: one set was a pre-operative CT scan using intravenous contrast media (IV) to determine the primary gross tumor volume (GTV) and the second set was a post-operative CT scan used for treatment planning. A Student's paired t-test was used to compare the number of CT slices in which the LAD was visible for each patient in the 2 series by each observer. Interpolations and extrapolations of the LAD volume were performed for the left-sided cases using a published heart atlas. Doses to the interpolated LAD structure and the heart were reported for the group of left-sided cancer patients.
Results: There was a non-significant difference between the results with and without IV ($p = 0.34$ for the radiologist; $p = 0.90$ for the radiation oncologist). The visible LAD corresponded to a 30% portion (range 12−47%) of the interpolated structure. The maximum dose to the left artery as measured by D2% varied widely, from 2.7 Gy to 41.7 Gy, in the group of patients with left breast tumors. The largest values (>25 Gy) corresponded to those patients in whom the LAD distal extremity lay inside the breast fields.
Conclusions: With the current planning CT protocol, only one-third of the LAD could objectively be visualized. Contrast-enhanced imaging used for GTV delineation before the breast surgery did not improve the visualization of the artery. The large range of doses to the LAD artery reported in the literature may be partially due to imaging artifacts and consequently to variations in the delineation. This study has revealed the lack of consistency that may be encountered when contouring heart vessels, thereby questioning the reliability of dose reporting.
No conflict of interest.

1193 POSTER

Validation of biomarkers to predict PFS with DCE-US in 539 patients treated with different anti-angiogenic drugs: analysis of sub-groups

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Background: The prospective multicentre French National Program for the Evaluation of DCE-US has studied the technique in different tumor types and anti-angiogenic treatments.

The aim was identify perfusion parameters to predict tumor response to different anti-angiogenic treatments.
Methods: DCE-US was performed at baseline and at 4 time-points (Day 7, 15, 30, 60). At each examination, we quantified 7 DCE-US parameters. We also estimated the variation between baseline and each post-baseline time-point. The main endpoint was freedom from progression assessed according to RECIST. We first selected the best parameters: for each parameter and each time point, we studied the trend between the parameter value and freedom from progression. After, the best cut-points were searched through a grid search. The best single cut-point was that with the lowest P-value for progression free survival. We performed analyses according to the treatment and type of tumor, looking for the groups of patients that contribute the most to the heterogeneity.
Results: A total of 1968 DCE-US were performed in 539 patients. The median follow-up was 1.65 year. The mean transit time (MTT) was the only significant parameter at day 7 (P = 0.002). The best cut-point to predict tumor progression was 12 seconds (P = 0.02), a MTT >12s being of good prognosis. Variations from baseline were significant at day 30 for several parameters. The area under the curve (AUC) was the parameter with the lowest P-value (P = 0.00004); Patient with a decrease of more than 40 % had a better prognosis. The groups defined accordingly were different for both FFP (P = 0.009) and OS (0.03).
The analyses according to treatment suggested heterogeneity. We performed a separate analysis for RCC treated with Sunitinib: the best cutoff for AUC at 30 days was 0.1, corresponding to a decrease of 90%. A total of 122 patients treated with Bevacizumab were analysed: 61 Metastatic colon cancer and 61 breast cancer. The median follow-up was 1.65 year. The MTT was the only significant parameter at day 7 (P = 0.002). PFS was significantly different according to MTT < or >12S for 122 patients (<0.05), breast cancers (P<0.05) and Colon cancers (P<0.001).
Conclusion: DCE-US is the first functional imaging technique that validated predictors of tumor progression in a large multicentric cohort. This study confirms the potential of DCE-US as imaging biomarker to monitor different anti-angiogenic treatments in different type of tumors.
No conflict of interest.

Poster Session (Sun, 29 Sep)
Oncotechnology

1200 POSTER

Isolation of stem cells and production of extracellular matrix powder from fat tissue for tissue engineering: in vivo and in vitro tests

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Objectives: Due to easy accessibility and large amounts, adipose tissue could provide ideal source of stem cells. The aim of this study is to isolate stem cells and produce natural matrix from human fat tissue and then examine the growth potential of stem cells on that natural scaffold with in vivo and in vitro tests.
Material and Methods: Adipose tissue is obtained on sterile conditions from waste materials of liposuction in plastic surgery clinic of Tehran. Stem cells are isolated, examined by flow-cytometry, cultured on DMEM plate with or without acellular matrix powder (natural scaffold). In order to provide appropriate scaffold, we use physical, chemical and enzymatic digestion of abdominopelvic fat. To proof decellurisation and structure of the scaffold, hematoxylin and eosin and immunochemistry staining is used. We compare the proliferation, adhesion and differentiation potential of cultured stem cells as well as transplantation of that as graft on the subcutaneous tissue on the back of immunosupressed rats.
Results: The mesenchymal nature of the stem cells was confirmed by expression of CD90, CD105, CD166, and lack of expression of haematopoietic markers of CD34, CD31, and CD45. IHC markers showed heavy staining for collagen IV and no staining for vimentin, laminin, or S100. Assessment of stained stem cells by electron-microscopy and live cell counting examination showed increased proliferation and adhesion of adipose stem cells after adding scaffold to medium for one week (in vitro test). After six weeks of animal phase of study, increased graft size, surface vascularisation, more differentiation of stem cells, neovascularisation, and penetration of host cells to the graft and less necrosis or fibrosis were seen with microscopic examination of stained scaffold contained grafts in comparison to stem cells alone (in vitro test).
Conclusion: Our study shows that our produced human decelluralised fat scaffold provided a suitable environment to increase proliferation, differentiation, adhesion and migration of stem cells. This product should be checked in clinical setting for tissue repair.
No conflict of interest.

1201 POSTER

KRAS, BRAF and TP53 deep-sequencing for colorectal carcinoma patient diagnostics

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Background: In colorectal carcinoma, *KRAS* and *BRAF* mutations have emerged as predictors of resistance to anti-EGFR antibody treatment and worse patient outcome, respectively. In this study, we aimed to establish a high-throughput deep-sequencing workflow based on 454 pyrosequencing technology to cope with the increasing demand for sequence information at medical institutions.
Material and Methods: A cohort of 81 patients with known *KRAS* mutation status detected by Sanger sequencing was chosen for deep-sequencing. The workflow allowed us to analyze seven amplicons (1 *BRAF*, 2 *KRAS*, 4 *TP53* exons) of nine patients in parallel in one deep-sequencing run.
Results: Target amplification and variant calling demonstrated reproducible results with input DNA derived from FFPE tissue ranging from 0.4 to 50 ng using different targets and multiplex identifiers (MIDs). Equimolar pooling of each amplicon in a deep-sequencing run was necessary to counterbalance differences in patient's tissue quality. Five *BRAF* and 49 *TP53* mutations with functional consequences were detected. The lowest mutation frequency detected in a patients tumor population was 5% in *TP53* exon 5. This low frequency mutation was successfully verified in a 2nd PCR and deep-sequencing run.
Conclusion: Our workflow allows to process 315 targets a week and provides the quality, flexibility, and speed needed to be integrated as standard procedure for mutational analysis in diagnostics.
No conflict of interest.

1202 POSTER

An interactive web portal for patient empowerment in cancer survivorship

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Background: Interactive web portals are an effective tool to enhance patient empowerment, but they are still uncommon in oncology. In the Netherlands Cancer Institute we are developing such a portal for breast and lung cancer survivors. The aim of this abstract is to report on the developmental phase of this project.
Material and Methods: We determined the portal requirements based on a literature review and on focus group discussions. We used 3 electronic databases to identify relevant literature on interactive, web-based interventions for various chronic diseases, and used available guidelines for cancer survivorship care to evaluate the relevance of these interventions for the oncology setting. We held focus groups with cancer survivors and health care professionals to better identify the desired features of a web portal from the perspective of these stakeholders.
Results: The literature review indicated that although the content, duration and frequency of interventions varied considerably, features commonly used included education, self-monitoring, feedback, self-management training, individualized exercise, and communication with either health care providers or patients. These elements were evaluated as appropriate to fulfil recommendations for survivorship care. The analysis of the focus group transcripts indicated that breast and lung cancer survivors were primarily interested in those features of a web-base portal that could fulfil their information needs: a survivorship care plan, access to their medical record, and an overview of their medical appointments. Health care professionals considered telemonitoring, patient-reported outcomes plus related feedback and a rehabilitation program as the most useful elements of such a portal. Cancer survivors and health care providers agreed on the potential value of a survivorship care plan and on the possible risks of a patient forum, but were less in agreement with regard to access to medical records and e-consultation (survivors were positive).
Conclusions: Based on our literature study and focus group discussions we were able to formulate requirements for an interactive web portal to empower breast and lung cancer survivors: information provision by means of a survivorship care plan and interactivity by providing feedback on patient- reported outcomes (on, for example, quality of life and physical

activity behaviour). These features will be transformed into prototypes of the web-based portal and will be evaluated. We will present screenshots, algorithms for automated feedback, and additional patient and professional views on late draft versions of the portal. The final version of the web portal will be implemented and evaluated.
No conflict of interest.

1203 POSTER

ARRACT − a real-time randomisation application for clinical trials

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Introduction: In investigator-initiated trials there is a need for affordable and adequate tools to randomise patients.
Relational database technology and internet-based connectivity offer resources to facilitate development of efficient randomisation procedures.
At Department of Oncology, Herlev University Hospital, we have developed a web application – ARRACT. The system covers the following aspect of the randomisation process:
- **Various Algorithms:** Range based n-factors stratified balanced randomisation and permuted block randomisation.
- **Patient Randomisation:** Enables randomisation of patients.
- **Monitoring and Management of data:** Enables on-going data management and monitoring in step by step visual logging.
- **Administration:** Allows overall system oversight, configuration, and reporting by administrators.
- **Test Environment:** Allows simulations on existing treatments with fixed factors and levels and performs generic multiple n-trials simulations.
- **Integration:** Use of web services to integrate with clinical remote data entry system (OpenClinica) − Under development.

Materials and Methods: Commercial and Open Source randomisation systems were investigated as well as relevant literature to establish the minimum requirements in respect of the systems functionality and security.
A data model for the system was designed and a database was created in Microsoft SQL server 2005. The web application was programed in Visual Studio 2010.
As part of the implementation plan we tested:
- IQ – Installation Qualification
- OQ – Operational Qualification
- PQ – Performance Qualification
- Site Standard Operational Procedure (SSOP)

Results: We have conducted several simulation with the system especially the Stratified Balanced Allocation Method: A test study was setup and simulated 1000 times with satisfactory results in respect of imbalance.
At least two clinical trials are awaiting the final implementation.
Discussion: Many investigators are still forced to use inadequate methods such as 'envelope method' for randomisation in their trials.
An option might be to turn to the Open Source programs available. Currently, however, we have not found any Open Source programs suitable for our needs.
To succeed in developing and implementing systems one needs: adequate resources, funding, an implementation plan and a skilled staff.
The final aim is to use ARRACT for all investigator-initiated randomised studies.
No conflict of interest.

1204 POSTER

National online portal for registration of chemotherapy side effects

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Background: The department of oncology at Roskilde Hospital has a large outpatient ward for patients treated for CRC, Breast cancer, lung cancer and ovarian cancer. At the clinical research unit we wanted to capture data regarding the side effects of chemotherapy. Currently we register the side effects of chemotherapy by contacting the patients and register data in a pre-printed paper template. This can be biased as no current instructions currently are available on how to interview the patient.
The best sources of information about how patients experience their side effects are the patients themselves, so it seemed as an obvious choice to get patients to register themselves It has been shown that easy access to relevant information regarding disease improves patient empowerment. Studies also indicate that the better the patients handle the adverse reactions to chemotherapy, the more they are able to complete a course of treatment as planned.
Aim: The first aim was to create an online portal that could provide patients with better access to relevant guidance and accurate information about side effects in real time. By providing the patients with relevant information in due time they will increase their empowerment to act and comply with the treatment.
The second aim was the development of a database based on all the registrations done by the patients for further research and developmental projects.
Methods: We created an online portal for patients to record their side effects. This portal is part of a national project for patient based registration of data and observations linked to their chronic diseases. Roskilde is pilot site for cancer treatments.
Each side effect reported is graded according to CTCAE standards, and users get practical advice on how to act precisely to what they are experiencing. In addition, patients will be able to get a visual overview of the development of their own side effects, and compare with other patients receiving similar treatments.
Result: Patients have increased their abilities to manage their cancer treatment and compliance and are more likely to respond to the side effects accordingly and therefore more likely to complete their treatment as planned.
Conclusion: The portal and the database enable us to capture side effects for all treatments currently given to patients at our department, potentially the whole country. As this is the first time an attempt to capture this much data is made in Denmark, it will hopefully facilitate research within oncology.
No conflict of interest.

1205 POSTER

Evaluation of the metastatic potential of human tumor cells by means of 3D culture on silicon microstructures

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Background: − The ability of cancer cells to spread and give rise to a secondary tumor is dependent of their physical interactions with microenvironment. Tumor cells must undergo elastic deformations and aberrant activation of the epithelial–mesenchymal transition (EMT). A better understanding of the role of cell mechanical properties will provide new insights in cancer progression and identification of new prognostic biomarkers and therapeutic targets. We investigate cell plasticity as an indicator of the tumor cell behaviour, strongly related to the metastatic potential.
Methods: − Silicon micromachined structures (SmS) were exploited as 3D microincubators (Carpignano F, PLOS ONE, 2012) able to host tumor cells. The 3D microstructure consists in periodic arrays of silicon walls separated by empty gaps, fabricated by electrochemical micromachining of a small silicon dice. After incubation, samples were washed, fixed overnight in 10% formalin and stained for fluorescence microscopy analysis. Experiments were performed in triplicate with human cell lines, with high (A375, MDA-MB-231, RPMI-7951) or low (MCF-7, CAPAN-1) metastatic potential. The K562 leukaemia cells were utilized as control.
Results: − Fluorescence microscopy analysis of the SmS populated by cells evidenced: a) cells with low metastatic potential are largely unable to grow on the SmS surface; only few of them can survive on top of the walls. Their nuclei showed a round shape typical of cell growing on flat surfaces; b) cells with high metastatic potential can grow on the SmS thanks to their ability to colonize the deep, narrow gaps between the silicon walls. These cells showed stretched nuclei aligned along the wall direction, proving that are deep inside the extremely limited empty spaces of the SmS.
Conclusions: − Data indicate that mechanical stiffness grades the metastatic potential (Swaminatan V, Cancer Res, 2011); on these basis, the less stiffed cytoskeleton/membrane of the cells grown inside the SmS can be related to their bio-mechanical ability to undergo dynamic changes in EMT. Applied to the study of circulating tumor cells (CTCs), the SmS could provide rapid and significant insights into functional readouts of EMT-oriented CTC subpopulations characterized by different levels of aggressiveness. Thus, SmS could be implemented in a lab-on-microchip clinically applicable to predict the metastatic potential. Work was partially supp. by Fondazione Cariplo, grant nº 2011–0308.
No conflict of interest.

1206 POSTER

Preclinical antitumor activity of a nanoparticulate SN38-polymeric micelle formulation in mouse xenograft models

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Background: Irinotecan (CPT-11) functions as a prodrug which is converted into SN38 (active metabolite of CPT-11) in liver or tumor tissues through carboxylesterases. In general, only 2−8% of CPT-11 can be converted into SN38 and to considerable patient-to-patient variability. Although SN38 is very effective against various human cancer cells, its extreme hydrophobicity also prevents the clinical use. In the current study, we demonstrated that SN38 was able to be efficiently incorporated into polymeric micelles (PM) fabricated using the synthesized block copolymers.
Material and Methods: Fifteen human cancer cell lines were testing and treated with CPT11, SN38, and SN38-PM respectively, and the cell viability was determined by MTT assay. The in vivo pharmacodynamics efficacy was performed in BALB/c nude mice. NCI-H460 (human large cell lung cancer) and RPMI-2650 (human nasal septum squamous cell carcinoma) were subcutaneously (sc.) implanted into mice and to develop xenografts tumor models.
Results: Compared with the IC_{50} of cytotoxicity concentration, SN38 and SN38-PM were 217-fold activity than CPT-11 in NCI-H460 cell and 1200-fold more potent than CPT-11 in RPMI-2650 cell. In NCI-H460 xenograft model, SN38-PM was administered to mice at doses of 20 mg/kg (iv., twice week) for three weeks, the tumor inhibition rate (TIR) was 87% at day 37. In contrast, for mice given CPT-11 at the dose of 50 mg/kg, 80% of TIR was achieved at the same time. In tumor growth delay (TGD), the mean tumor volume reaching to 1000 mm^3 was as compared with control group. The TGD of SN38-PM (iv., 20 mg/kg, twice week) were 28 days. In sc. xenograft of RPMI2650 tumor models, SN38-PM at doses of 20 mg/kg and 30 mg/kg (iv., twice week) for five doses, the TIR were 95% and 99% at day 40. On the other hand, treatment with CPT-11 at the dose of 20 mg/kg and 50 mg/kg, the TIR of RPMI2650 tumor were 54% and 80% respectively.
Conclusions: We have successfully developed a PM formulations that can efficiently incorporate with SN38 and markedly increase the solubility. Furthermore, SN38-PM exhibited significantly pronounced anti-tumor activities against both NCI-H460 and RPMI-2650 xenografts. These results suggest that SN38-PM has the potential to become a modality of anticancer treatments.
No conflict of interest.

1207 POSTER

Diffuse reflectance spectroscopy (DRS) for identification of breast cancer in lumpectomy specimen

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Background: Breast-conserving surgery (BCS) is an effective treatment provided adequate surgical margins can be obtained. Irradicality is a risk factor for an adverse clinical outcome. Even in highly specialized cancer centers often over 10% of BCS patients are left with a positive resection margin after initial surgery. Here we investigate whether DRS based on altered spectroscopic properties in malignant tissue can provide guidance in differentiating benign from malignant tissue.
Materials and Methods: The lamellae of 15 lumpectomy specimens were measured at the pathology department. Using an optical probe, spectra between 400 and 1600nm of macroscopically malignant, benign and borderline tissue were obtained. At each measurement location three optical spectra were acquired as well as histology. By fitting the spectra with a mathematical model fat and water content was registered.
Results: On the fifteen ex-vivo lumpectomy specimen a total of 95 locations were measured. Of these locations 56 were benign and 39 were malignant tissue. Comparing the shape of the tumor spectra with the benign spectra clear differences were seen, especially in the 1000–1200nm wavelength region where fat and water are the dominant absorbers. By calculating fat and water ratios for all 95 locations (Fat/Water >1 for benign and Fat/Water <1 for malignant tissue) malignant tissue can be distinguished from benign tissue with a sensitivity of 97% and a specificity of 92%. Based on this ratio not all of the locations were classified correctly in three patients. When these specimens were evaluated individually, in two of the three specimens all measurement locations were classified correctly when the cut-off of the ratio was shifted to a lower value. In a clinical setting where each patient is their own control and DRS spectra of suspicious tissue is compared to benign spectra of the individual patient even better results are to be expected.
Conclusions: DRS was able to distinguish benign tissue from malignant tissue based on fat and water content. This makes it a promising tool for the future.
Conflict of interest: *Corporate-sponsored research: Philips Research*

1208 POSTER

Transcatheter oily chemoembolisation (TOCE) in the treatment of patients with locally advanced adenocarcinoma of the stomach: First experience

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Purpose: To study the first results of new treatment for local advanced unresectable gastric cancer.
Materials and Methods: We performed 26 TOCEs in 18 pts with histologically proven adenocarcinoma of the stomach (T_{3-4}, N_{1-2}, M_{0-X}). TOCE of branches of the left gastric (LGA, n = 17), gastroduodenal (GDA, n = 5) and right gastric (n = 4) supplying the tumour was made using bolus injection of 5−10 mg mitomycin C (n = 14) or 40–100 mg irinotecan (n = 12) emulsified in 3−10 ml lipidiol. In 5 cases, when selective catheterisation of feeding arteries was impossible, we used redistribution embolisation of the right gastroepiploic and right gastric arteries with steel coils. Every TOCE was added with celiac arterial infusion of oxaliplatin, docetaxel, 5FU, gemcitabin in different combinations. The follow-up included clinical exemenation, repeat biopsy, CT and PET. In 8 pts, TOCEs was repeated with 1- mo interval.
Results: There were no treatment-related complications. The post-embolisation syndrome included mild upper abdominal pain and nausea; these symptoms disappeared within 1 day of symptomatic therapy.
After first TOCE partial tumour response was seen in 9 (50 %), stabilisation in 6 (33%), and progression in 3 (17%) pts. All 9 responders became resectable and were operated (R0 resection). Of them, 7 are alive 2−40 (mean 17.4) mo, 2 pts died in 7 and 26 mo from disseminated tumour progression. The 1-, 2- and 3 yr survival was 66%, 33 % and 33 % respectively.
At present three non-operated pts are alive during 2, 5 and 21 mo. Mean survival of 6 pts who died was 9.9 ± 2.3 mo.
Conclusion: TOCE of gastric arteries is a well-tolerated procedure that causes partial tumour response and promising down-staging effect in 50% patients with advanced unrespectable adenocarcinoma of the stomach.
No conflict of interest.

1209 POSTER

Spanish radiotherapy department experience with volumetric modulated arc therapy (VMAT)

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Introduction: Technology in Radiation Oncology is rapidly expanding. The Volumetric Modulated Arc Therapy (VMAT) designed by Elekta® is a more efficient way to administer Intensity Modulated Radiation Therapy (IMRT). This study reports the experience of a Spanish Radiotherapy Department by using this technique in several pathologies.
Patients and Methods: Between January 2010 and March 2013, we have analysed the experience in 171 consecutive radical radiotherapy treatments in 142 patients with 114 VMAT (66.67%) and57 IMRT step-and-shoot (33.33%).
All cases were planned with VMAT and Step-and-Shoot IMRT and dosimetric distributions have been compared and selected individually.
The proportion of cases that had been prescribed with each technique (VMAT/IMRT) regarding tumour localization was analysed by the application of a c2 independence test (1) = 19.00; $p < 0.001$.
To find difference between the techniques in terms of time, and monitor units (MU) per dose units we applied a multivariate analysis of covariance (MANCOVA).
Results: The most frequently treated pathologies were:
Prostate 49: 38 VMAT and 11 IMRT c2 (1) = 14.88; $p < 0.001$
Lung 20: 13 VMAT and 7 IMRT

Brain metastases 24: 15 VMAT y 9 IMRT
Head and Neck 22: 8 VMAT y 14 IMRT
Abdominal tumours 18: 15 VMAT y 3 IMRT c2 (1) = 8; $p < 0.01$.
Bone 7: 3 VMAT y 4 IMRT
Mean time (minutes per Gy) of treatment with VMAT = 1.92 (0.83) vs. IMRT Step and Shoot = 2.85 (1.17)
Mean Monitor Units per Gy (MU/Gy) with VMAT = 18.16 (10.61) vs. IMRT Step and Shoot = 25.34 (32.55)
Significant differences in time/Gy between the techniques were found F(1, 93 = 10.44; $p = 0.02$; h2 $p = 0.02$). Nevertheless, there were not significant differences in MU/Gy.
Conclusions: In all cases the dosimetric quality of the VMAT was similar to the IMRT Step-and-Shoot but the treatment time was shortened considerably.
In our series, VMAT is a more efficient therapeutic option in prostate and abdominal tumours, specifically in treatment time.
MU is not statistically different between both techniques in our series.
No conflict of interest.

1210 POSTER

Frameless stereotactic radiosurgery for brain metastases using image guided radiotherapy (IGRT)

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Introduction: Stereotactic radiosurgery (SRS) has become increasingly used for treatment of brain metastases. A non-invasive mask system plus Image Guided Radiotherapy (IGRT) is a very attractive and comfortable alternative for patients (Elekta® system).
Objective: To assess the clinical outcomes of frameless radiosurgery combined with IGRT for brain metastases.
Patients and Methods: In ONCOSUR and CROASA between January 2010 and December 2012 we have treated 16 patients (50% female) with 45 brain metastases and mean age of 53.63 years (33−68). A total of 21 treatments have been performed. Our GTV margin was of 2−3 mm.
We have evaluated clinical, therapeutic data and acute toxicity.
Results: Primary tumours were 7 breasts, 3 melanomas, 5 lungs, and 1 esophagus.
Only 6 patients were also treated with whole brain radiotherapy (WBRT).
The radiotherapy techniques used were: 15 Volume Modulated Arc Therapy (VMAT); 1 Intense Modulated Therapy Step and Shoot (IMRT S-S); 1 Dynamic Arc Therapy (DART); and 4 3D Conformal Radiotherapy (3DCRT).
The hypofractionated schemes that we used more often were: 6 Gy x 6 fractions (fx) (4 cases) and 10 Gy x 3 fx (6 cases). All patients received 2 fx per week.
A variable positioning accuracy of 1−4 mm has been reported for frameless stereotactic systems. In our series, IGRT repositioning mean accuracy was: X = 0.18 mm (0.01–0.44); Y = 0.23 mm (0.06–0.66); and Z = 0.20 mm (0.01–0.40).
Acute side effects were not detected.
With a mean follow-up of 10.35 months (2−30), 6 patients are alive, and 10 are dead. The causes of death were progression in: brain: 2 patients (no WBRT); lung: 3 patients; liver: 1 patient; unknown: 3 patients and general deterioration: 1 patient.
Conclusions: Frameless SRS is an effective and comfortable treatment in the management of brain metastases.
Non-invasive mask fixation system plus IGRT is associated with a high repositioning accuracy with no errors up to 3 mm.
No conflict of interest.

1211 POSTER

Establishing a clinical trial support system using open source software

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Background: To conduct an effective clinical study, reliable screening of the study candidates and information sharing of the study is important. IT technologies resolve these problems effectively. Specific software purchase or a service provider contract is needed but it is sometime difficult for academic institute due to the maintenance load and cost issues. As such, we have established a clinical study support system using an open source software (OSS) to meet the objective of solving the above issues.
Material and Methods: The system is based on Netcommons, an open source content management system (CMS), adding two implementations which are the eligibility check upon registration for subjects and information offering and sharing functions. Regarding the eligibility check function, we implemented mandatory and range check functions and examined measures to avoid non-qualified subjects registrations. Also implemented the interface which transfers the user information and registration details considering data coordination with other systems.
Results: The system operation started in our hospital server since 2011 and is now used as a registration system for multi institutions' trials on the Cloud server. The system is mainly operated for registration of the subjects for Phase 1 trial and early development of devices, and has been used in 7 trials registering 90 subjects. Recently, the information sharing functions utilizing CMS is also being used. The coordination with EDC developed by our hospital has also been implemented using data transfer interface.
Conclusions: In our hospital, the effective trial operation has become possible with the advanced IT introduction in subject registrations and information sharing. The rapid implementation of necessary functions for each clinical study is the strength of CMS allowing various allocations of information transfers and file sharing functions. Also, as the software that consists the system is OSS, modifications are possible with the introduced institutions. This indicates the possibility of the user community to come up with new ideas for improved functions and its actual implementations in the future. As such, with the wide use of the system, reasonable costs for clinical studies are expected by offering efficient clinical studies using IT technology in Academia.
No conflict of interest.

1212 POSTER

Does an automated self check-in process improve the quality and patient satisfaction associated with chemotherapy administration?

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Background: The Odette Cancer Centre (OCC) is the sixth largest cancer institution in North America and currently manages over 24,000 chemotherapy patient visits per year (and over 100 chemotherapy patients per day). We initiated an automated kiosk system whereby patients can 'actively' self-identify for check-in to the chemotherapy unit.
Materials and Methods: From January 1 to May 1, 2012, consecutive patients receiving >2 cycles of chemotherapy were randomly assigned to either radio-frequency identification (RFID) or barcode technologies to facilitate self check-in and time-in-motion studies. In parallel, the former manual check-in system (guided by OCC staff) continued for all patients. The primary outcome was the proportion of patients with more 3 or more scheduled appointments who used the self-check system at lest 3 times (compliance). Patient satisfaction was attained with a baseline and post-study survey instrument.
Results: The study accrued 81 patients (43 patients using RFID and 38 patients using barcode technology). Mean age was 59 (range 20 to 81 years). Sixty-four individuals completed baseline survey instruments at the time of analysis. Mean age of patients was 56 (range 21−81). The majority of patients at baseline had regular access to a computer (87.5%) and used the internet at least >1 hour/day (50%). With implementation of the study, 24 of 81 patients (29%) have used the kiosk only once. Of individuals with multiple scheduled chemotherapy appointments (at least 3), 50% assigned to the RFID group and 52.6% assigned to the barcode group used the kiosk at least 3 times ($p = 0.827$; Fisher's exact test). Thirty-eight patients completed patient satisfaction surveys; 95% found the system easy to use. More than half (53%) indicated the self check-in process would have positive effects on their overall cancer care, although only a third (34%) indicated that the efficiency of their care improved.
Conclusions: An automated check-in process is feasible for a diverse population of patients receiving chemotherapy. Multiple uses of the kiosk technology suggest appropriate uptake and retention of the technology. Continued use of the system was not different between RFID and barcode technologies. Patient satisfaction was high and indicated a positive contribution to the delivery of cancer care.
No conflict of interest.

1213 POSTER

Oncolex.org − a web based cancer encyclopedia for health care providers

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www.Oncolex.org is a free, comprehensive online resource for cancer diagnostics, treatment and supportive care. Oncolex contains extensive material for each cancer type including explanatory articles, illustrations,

animations, photos and video footage. As a resource in continual progress, it keeps track of novel procedures and technology transforming the field of cancer diagnostics and treatment.
Background: Few hospitals and medical centers have cancer specialists on site. Oncolex acts as an accessible resource for health care providers worldwide in need of specialized information when treating and informing their cancer patients. Acclaimed medical specialists in Norway and the US would like to share their knowledge, providing up-to date and detailed information on cancer care to health care professionals worldwide.
The accessibility of Oncolex will aid in increasing the quality of patient treatment, which again will ultimately increase cancer survival rates. The content of Oncolex is constantly being revised and reviewed, and as current information becomes available, it occurs on the site.
Content: Oncolex contains theoretical and practical information on the various forms of cancer, as well as descriptions of procedures within diagnostics, prognostics, surgery, drugs, radiation and adjuvant therapy. Details such as surgical instruments used and cell level histological analyses are included. All types of cancer and stages are covered, so health care providers can consult Oncolex when treating a patient with a possible cancerous disease.
Customizable search options are available on the site, and users can filter out specific information such as surgical procedures or radiation therapy.
Surgical treatments have been filmed at the Norwegian Radium Hospital using a custom made camera crane, capturing the details of the operation without disturbing the surgical team or contaminating the operating theatre.
Conclusions: Since 2006 the Norwegian version of Oncolex has been available, and more than a 1000 Norwegian health care providers consult the site on a daily basis (Norway has a total population of 5 million). In 2012 all texts and articles were translated in to English to supply information for a larger audience. More than 100 cancer specialists from the Norwegian Radium Hospital at Oslo University Hospital and MD Anderson Cancer Center in Houston have contributed to the content of Oncolex.
Oncolex aims to become one of the worlds preferred cancer resources online.
No conflict of interest.

1214 POSTER

Advances in data capture in oncology outpatients with modern mobile technology

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Introduction: The HITECH (Health Information Technology for Economic and Clinical Health) Act, enacted as part of the American Recovery and Reinvestment Act of 2009, was implemented to improve health and management of complex conditions like cancer through appropriate technology. Benefits of electronic health records, patient portals etc has been recognized in Oncology. The ease and portability of iPads (© 2013 Apple Inc, Cupertino, California) is attractive for use in outpatients. Compliance with HIPAA privacy is necessary; REDCap (Research Electronic Data Capture; REDCap Software − Version 5.1.3 − © 2013 Vanderbilt University) allows users to build and manage secure online databases.
Objectives: To assess the feasibility and acceptability of an iPad as an electronic self-report symptom assessment instrument in Oncology outpatients.
Methods: Consent obtained from participants. Electronic symptom assessment instrument on iPad given to the participants prior to their first Oncology visit. The instrument with 34 questions (symptoms, quality of life) was adopted from European Palliative Care Cancer Symptom Study. Responses downloaded to REDCap simultaneously. Printed assessment results given to the Oncologist for effective symptom management.
Results: Sample size = 50; Participation rate = 72%; Mean age = 65 yrs; Males = 64%; College education = 53%; Completion rate = 100%; Self-completed = 65%; Mean time to complete = 10 minutes.
Conclusions:
1. Self completion = 65% in an older population group with college education of 53%
2. Secure web-based data collection ensured compliance with patient privacy regulations
3. New technologies may offer practical comprehensive symptom assessment in complex illness

No conflict of interest.

1215 POSTER

Automating clinical protocol monitoring: A model from developing countries

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Background: Clinical Research is thought to be a luxury science that needs a lot of investment in implementing policies, protocols and building teams for taking care of patients and their close follow up. With aim of building the first autonomous clinical research unit we tried to reduce the number of staff needed for conducting clinical research and ensuring delivery of patients' best care. We will discuss using the mentioned system in the management of Retinoblastoma as model for other diseases conducted at our center.
Material and Methods: We have developed a standardized treatment protocols for Retinoblastoma diagnosis and treatment based on best available evidence. Clinical research specialist (CRS) job was initiated to handle the different processes in protocol development, monitoring and patients' enrollment. Electronic clinical research system was used to capture different protocol data and registering patients on studies. CRS started to extract data from hospital electronic and paper-based medical record system. The Clinical Research System was integrated with Electronic Medical Records (EMR) to automatically import new patients to the hospital cancer registry. Electronic Hospital Cancer Registry was sorted and revised collaboratively between many departments to distinguish tumours histology and topography. Patients with potential retinoblastoma lesions were also filtered by an electronic routine process from hospital EMR and sent weekly in automatic way to the CR who verifies diagnosis and put the patient on follow-up. With every visit or surgical operation the electronic routine process sends the details to be tracked in the patient clinical research profile.
Results: Clinical protocol management office Retinoblastoma service became fail-proof without missing patients with diagnosis. Moreover, All the visits of the patients were tracked in real time. Patients with missing investigations or data for some visits could be tracked promptly for instantaneous resolution of such incidences. Only one CRS job became needed for monitoring the whole process. The net result of this experience was proper patient monitoring for ensuring that best care is delivered to the patient and maximized control of clinical research subjects enrolled on clinical trials.
Conclusions: The above mentioned integration reduced the need for huge investments in complex processes and reduced the staff needed for implementing clinical research in limited resource settings. We believe that this experience can be replicated in other centers where resources could jeopardize the quality of care.
No conflict of interest.

1216 POSTER

The effect of telephone consultation and triage for outpatients with early breast cancer during chemotherapy

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Background: In recent years, there has been an increase in the number of cancer patients who receive outpatient chemotherapy. In order to detect adverse events early and provide appropriate care to outpatients, we have offered telephone consultation service for outpatients during chemotherapy since May 2011. We assessed the effect of telephone consultation and triage on unplanned hospital visits and admissions.
Material and Methods: Retrospective date was collected for patients with operable breast cancer who received primary systemic chemotherapy in our outpatient chemotherapy clinic. The chemotherapy regimen included anthracycline-containing regimen or anthracycline followed by taxane. Among patients with HER2-positive cancer, trastuzumab was also administered.
Results: Between May 2011 and March 2012, 166 patients were included. The median age was 51 years (range, 27−78), and all of patients were female. 73 patients (44.0%) were treated with anthracycline-containing regimen only, and 93 (56.0%) with anthracycline followed by taxane regimen. 52 patients (32.0%) accessed the telephone consultation service during chemotherapy, and the median number of service usage was 1 (1−30). A total of 139 complaints, frequently reported symptoms were pain (14.4%), fever (11.5%), chemotherapy-induced nausea and vomiting (CINV) (5.8%), and confirmation of dosing instruction for supportive care drugs (6.5%). Approximately three fourth of consultation subjects were concentrated during first 4 cycles of chemotherapy. After consultation, 12 patients were advised to visit the hospital, 2 of whom ended up with

hospitalization. Patients with telephone consultation had lower rate of unplanned hospital visits compared to patients with no consultation (7.2% vs 31.3%; P = 0.06); but trend toward that of unplanned admissions (1.2% vs 7.2%; P=.151). No treatment-related mortality was observed.
Conclusions: The telephone consultation may reduce unplanned hospital visits during outpatient chemotherapy and decreases the burden on busy hospital clinics. Further evaluation to assess safety and patients' satisfaction is needed.
No conflict of interest.

Poster Session (Sat, 28 Sep)
Surgical Techniques

1250 POSTER

Near-infrared fluorescence sentinel lymph node mapping in breast cancer: A multicenter experience

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Background: The sentinel lymph node procedure plays an important role in the diagnosis and treatment of breast cancer. Currently, blue dyes or radiotracers or a combination are used as standard of care. However, these modalities have several disadvantages, including the use of ionizing radiation and tattooing of the breast up till several months after blue dye injection. Near-infrared fluorescence (NIRF) imaging has the potential to improve the sentinel lymph node (SLN) procedure by facilitating percutaneous and intraoperative identification of lymphatic channels and sentinel lymph nodes. Indocyanine green (ICG) is currently the only FDA and EMEA approved NIRF probe that can be used as a lymphatic tracer. Previous studies indicated that a dose of 500 μM ICG is optimal for SLN mapping in breast cancer. The current multicenter study validates these results in a large patient cohort.
Material and Methods: 95 breast cancer patients planned to undergo SLN procedure were included at the Dana-Farber/Harvard Cancer Center (Boston, MA, USA) and the Leiden University Medical Center (Leiden, Netherlands) between July 2010 and January 2013. Patients underwent standard of care SLN procedure with lymphatic mapping using ^{99}Technetium-colloid, and in 33 patients patent blue dye was also injected. In addition, the optimal dose of 500 μM ICG (1.6 mL) was administered directly before surgical draping. For NIRF imaging the Mini-FLARE™ camera system was used, which is capable of displaying real-time NIR signal and visible image simultaneously.
Results: SLN mapping was successful in 94 of 95 patients using NIRF imaging or a combination of both NIRF imaging and radioactive guidance. A total of 175 sentinel lymph nodes (mean: 1.9, range: 1−5) were detected: 96% hot, 98% fluorescent, and 76% blue. In one patient, the SLN was found only by fluorescence imaging. Time between skin incision and detection of SLN was 8±4 minutes and was correlated to BMI (P <0.001). In all patients that were treated with patent blue, the NIRF signal in the SLN was detected through the axillary fat considerably earlier than blue staining. The NIRF signal of the SLN was on average 11.7±6.7 times higher than the surrounding axillary fat tissue. No adverse events related to ICG injection were noted.
Conclusions: This study demonstrates the safe and feasible introduction of NIRF imaging in order to detect the SLN in breast cancer patients with high identification rate using 500 μM ICG and the Mini-FLARE™ camera system.
Conflict of interest: *Ownership: FLARE™ technology is owned by Beth Israel Deaconess Medical Center, a teaching hospital of Harvard Medical School. It has been licensed to the FLARE™ Foundation, a non-profit organization focused on promoting the dissemination of medical imaging technology for research and clinical use. Dr. Frangioni is the founder and chairman of the FLARE™ Foundation. The Beth Israel Deaconess Medical Center will receive royalties for sale of FLARE™ Technology. Dr. Frangioni has elected to surrender post-market royalties to which he would otherwise be entitled as inventor, and has elected to donate pre-market proceeds to the FLARE™ Foundation. Dr. Frangioni has started three for-profit companies, Curadel, Curadel Medical Devices, and Curadel In Vivo Diagnostics, which may someday be non-exclusive sub-licensees of FLARE™ technology.*

1251 POSTER

Intraoperative ultrasound guided lumpectomy versus mammographically needle localization for breast cancer patients after neoadjuvant treatment

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Background: The use of intraoperative ultrasound (IOUS) to localize and guide breast cancer tumors excision has advantages over other techniques. It has been reported to improve negative margins and to reduce the resection of large excision volumes of breast. However, the use of IOUS has not been explored after neoadjuvant treatments (NAC). We aimed to compare IOUS guided surgery with needle localization (NL) guided surgery in breast cancer patients after neoadjuvant chemotherapy.
Material and Methods: In this study, patients with T1−3 and N0−2 who underwent NAC and where considered for breast conservative surgery after treatment were included in the study between July 2008 and April 2011. All patients had a clip placed at the beginning of systemic treatments for tumor localization after NAC. IOUS guided surgery was used in patients with a visible clip or tumor under ultrasound. If the clip was not visible under US, a NL guided surgery was performed.
Results: A total of 84 patients were included. IOUS was performed in 37 (44%) and in 47 (56%) a NL was performed. Mean age in IOUS was 59 years (range, 33−83) and in the NL was 52 years (range, 27−88), (p = 0.8). Tumoral volume at diagnosis measured by mammogram was 31.7 cc^3 in the IOUS group and 37.1 cc^3 in the NL group (p = 0.54). There were no statistically differences in the lumpectomy volume between groups (p = 0.84). Thirty-two patients (39%) had no tumor on the lumpectomy or microscopic foci of invasive tumor after NAC (11 patients in the IOUS and 21 patients in the NL group). When considering this group with better response to NAC, lumpectomy volume was smaller in the IOUS group 24.5 [SD 14] vs 41 [20] cc^3; p = 0.02. Tumor free margins were obtained in 95% with IOUS and in 94% in the NL group (p = 0.7).
There were no differences in rates of recurrences between groups with a median follow-up of 42 months (range, 24−57).
Conclusions: Compared to NL guided surgery, IOUS surgery lowers the volume of resection in patients with complete pathologic response or minimal microscopic disease after NAC. IOUS reduces the resection of healthy tissue without compromising margins and local recurrences. Breast conservative surgery can easily be achieved with IOUS guided lumpectomy in patients with good response after NAC.
No conflict of interest.

1252 POSTER

The SentiMag Study: Sentinel node biopsy with superparamagnetic iron oxide (SPIO) vs. radioisotope

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Background: The SentiMag study compares the 'gold standard' ^{99m}Tc with a new technique, which employs superparamagnetic iron oxide particles (SPIO) for localisation of sentinel lymph nodes. Aim of this study is to investigate the potential equivalency of the SentiMag® technique in comparison to the gold standard of sentinel lymph node biopsy (SLNB).
Materials and Methods: In a prospective, multicentre and multinational 2-arm study, 150 patients with histologically verified breast carcinoma are examined. For comparison, SLNs are marked initially with radioisotope following a 1- or 2-day protocol. Additionally, SPIO (Sienna+®) is injected at least 20 minutes before SLNB into the subareolar interstitial tissue, followed by 5 minutes massage. SLN-detection is carried out using a magnetometer (SentiMag®) and a gamma probe. Preparation and excision of lymph nodes is conducted using both techniques in a parallel manner. All lymph nodes marked with either tracer are excised.
Results: Interim analysis of 96 patients resulted in a detection rate concordance per patient of 98% (94/96). An average of 1.9 (radioisotope) and 2.0 (SPIO) lymph nodes were collected per patient. Nodal detection rate was 92% (173/188) for the radioisotope vs. 99% (185/188) for the SPIO tracer with magnetometer detection. The proportion of pathologically positive lymph nodes was 21/173 (12%) vs. 22/185 (12%). All pathologically positive lymph nodes detected with the conventional technique (radioisotope) were also detected with the new technique (SentiMag®).

Conclusions: The SentiMag® provides an easy technique which can be rapidly implemented into daily routine. Due to the simple handling, preoperative efforts can be reduced to a minimum. If further and consistent results prove its efficacy, this technique may ultimately replace the standard of care.
No conflict of interest.

1253 POSTER

Laparoscopic near-infrared fluorescence imaging of hepatic uveal melanoma metastases using indocyanine green: A technical note

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Background: Uveal melanoma is the most common primary intraocular tumor in adults and up to 50% of patients will develop liver metastases. Complete surgical resection of these metastases can improve 5-year survival, but only a few patients are eligible for a radical surgical treatment. Therefore, it is of great importance to select and treat these patients carefully, to prevent unnecessary laparotomies. Near-infrared fluorescence (NIRF) imaging using indocyanine green (ICG) is a promising technique to assist in the intraoperative identification of liver metastases in real time. However, all published cases concerning intraoperative detection of liver metastases using NIRF and ICG were performed in open procedures. A laparoscopic operation is preferable for patients with liver metastases from uveal melanoma, due to the high risk of multiple small metastases. The aim of this study was to introduce a novel, high definition, NIRF laparoscope during minimal invasive surgery for intraoperative identification of uveal melanoma liver metastases and to provide guidance during resection.
Methods: Two patients previously treated for uveal melanoma, both pre-operatively diagnosed with one solitary liver metastasis are presented. Patients received 10 mg indocyanine green (ICG) intravenously 24 hours before surgery (optimal timing based on a dose-finding study performed in 16 patients with colorectal liver metastases and an open imaging system). A high definition NIR fluorescence laparoscope (Karl Storz, Germany) was used to detect malignant liver lesions. After resection, ex-vivo imaging and fluorescence microscopy was performed for histological validation.
Results: In both patients, laparoscopic NIRF imaging using ICG successfully identified uveal melanoma liver metastases. A clear fluorescent rim around the tumor was observed. In patient 1, seven additional lesions in both left and right liver lobe, not seen with computer tomography (CT), were identified by inspection and NIR fluorescence imaging. In patient 2, one additional lesion, not identified by CT, magnetic resonance imaging, laparoscopic ultrasonography and inspection, was seen with NIR fluorescence imaging. Importantly, NIR fluorescence imaging provided guidance during resection of these metastases. A clear fluorescent rim around the metastases was seen with fluorescence microscopy.
Conclusions: This study describes the successful use of laparoscopic identification and resection of uveal melanoma liver metastases using NIR fluorescence imaging and ICG. This procedure is minimal invasive, and should be used as complementary to conventional techniques for the detection and resection of liver metastases.
No conflict of interest.

1254 POSTER

Liver metastases in close contact to supra-hepatic veins ablated under vascular exclusion

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Background: Liver metastases (LM) in close contact to suprahepatic veins (SHV) is a frequent cause of unresectability. Radical approach involving hepatic vein resection have been published using demanding grafting techniques for reconstruction. Otherwise experimental data have shown high resistance of SHV to heat. Intraoperative radiofrequency ablation (IRFA) with vascular exclusion (VE) may be a useful approach.
Material and Methods: Out of 358 patients operated for LM, 22 with LM close to a SHV treated by IRFA under VE with at least one year of follow-up were included in this retrospective study. Complications and outcomes are reported.
Results: There were 9 females and 13 males with median ASA of 2 (range: 1−3). All patients received IRFA with VE, combined or not with a parenchymal resection. One patient received two IRFA with VE. One patient received a 2-stage procedure. Median age was 67.5 years [range: 38−80]. Eighteen (81.8%) patients had a primary colorectal tumour and all except four received neoadjuvant chemotherapy.
Median number of metastases was 4.5 [range: 1−12]. They were bilateral for 17 patients. Median size of ablated lesions was 2 cm [range: 1−5.5]. Seven complications occurred (4 Grade IVa), and no mortality. At 4 months, no recurrence of ablated lesions was detected. Median overall survival for colorectal patients was 40 months 95% CI [17.5–not reached]. The OS at 2 years was 72.2%, 95% CI [45.6–87.4].
Conclusions: Resection of the metastasis only leaving clear margins is not so much a technical concern, but an oncological one, representing potential under-treatment. Indeed this resection is at high risk of leaving at least microscopic tumoral residue on the vessel's wall (R1 resection) increasing the risk of recurrence. To resect the lesion plus the vessel *en-bloc* is a good oncological solution, but this presents real technical difficulties for reconstruction. Despite some publications originating from transplant liver surgeons, resection of SHV followed by different grafting reconstructions has not gained widespread acceptance and cannot be advocated as a routine procedure. IRFA plus VE for LM in close contact to a SHV is a safe and effective technique which can extend the applications of liver metastases surgery.
No conflict of interest.

1255 POSTER

Extended indications for skin sparing mastectomy and immediate breast reconstruction without compromising oncological safety

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Background: Skin sparing mastectomy (SSM) and immediate breast reconstruction (IBR) is the treatment of choice for early breast cancer patients who need or desire a mastectomy. Considering SSM and IBR in patients after neoadjuvant chemotherapy (NAC) or after breast conservative recurrences is more controversial. The aim of this study was to evaluate the oncological safety and risk of complications in this group of patients.
Material and Methods: Outcomes from a multicentric prospectively maintained database of patients undergoing SSM and IBR from 2001 to 2011 were reviewed.
Results: SSM and IBR were performed on 261 breasts in 235 patients. Eleven (4.2%) patients underwent bilateral prophylactic SSM for high risk or mutation carrier, 7 (2.7%) patients underwent contralateral elective SSM at the same time of the breast cancer mastectomy, 22 (8.4%) patients were for local recurrences after breast conservative treatment (BCT) and 221 (84.7%) patients for a diagnosis of breast cancer who need or desire a mastectomy, including 15 patients (6%) who had received NAC. Tumor characteristic included 49 breasts (20%) with ductal carcinoma in situ, 167 breast (70%) with invasive ductal carcinoma, and 25 breasts (10%) with invasive lobular carcinoma. Pathological stage was 0 in 43 (16.5%) patients, I in 77 (29.5%) patients, II in 105 (40%) patients and III in 21 (8%).
IBR were performed with autologous tissue-latissimus dorsi (LD) in 3 (1%) patients, LD + implant in 76 (29%), and implants only in 182 (70%) patients. 45 (19%) patients had post mastectomy radiotherapy (RT) (15 with LD + implant and 30 with implants).
Complications after surgery were more frequent with autologous tissue than implants (27% vs 14%) $p = 0.013$, and this was not influenced by the pathological tumor stage ($p = 0.8$), NAC ($p = 0.6$) or RT ($p = 0.7$). Complications included 13 cases (5%) with partial skin flap necrosis and 15 with hematoma (5.7%). There was no delay in starting adjuvant treatment in any group.
Locoregional recurrence rate was 5.5%, 8 patients developed recurrence in the skin, 4 patients in the locoregional lymph nodes and one in the pectoral muscle; after median follow-up of 46 months (range 5–135). The 5-year disease free survival and 5-year overall survival was 88% and 96%, respectively.
Conclusion: Based on this study, SSM with IBR is an oncologically safe treatment regardless of tumor stage or neoadjuvant chemotherapy. Local recurrences are low and similar to conventional mastectomies series.
No conflict of interest.

1256 POSTER

Modified gastroesophageal anastomosis in proximal gastrectomy

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Background: Radical proximal gastrectomy is remaining to be a widely applied operative method, especially for gastric cancer, that involves mucosa and submucosa layer of the stomach wall. Postgastrectomy syndromes after proximal gastrectomy are still more or less unavoidable.

That is why, the selecting an ideal alimentary canal reconstructive pattern to elevate the quality of life has become more critical.
Methods: Three hundred twenty-four patients with upper third gastric and gastroesophageal cancers were admitted consecutively with curative intent in a clinic of National Cancer Institute of Ukraine, between May 2007 and May 2012. All patients were randomized in three groups by type of gastroesofageal anastomosis use during proximal gastrectomy (stapler anastomosis (SA), hand-sutured anastomosis by Ivor Lewis (HSA) or modified antireflux hand-sutured anastomosis (MAHSA)).
Results: Endoscopic control at 1 year follow-up of SA group showed reflux esophagitis with the following distributions: 40.6%, 30.2% and 13.2%; the same control in HSA group show 17.3%, 13.5 % and 8.6% for grade A, B and C respectively (according to Los Angeles Classification of Esophagitis). In contrast endoscopic control of MAHSA group showed reflux disease grade A and B only in 14.1% and 1.7% respectively.
The evaluation scores measured by the EORTC QOL gastric cancer-specific questionnaire (QLQ-25) for eating solid, liquid food and enjoying of meals were better in group MAHSA than in SA group patients: 2.1 ± 0.1; 1.3 ± 0.1 and 1.1 ± 0.05 vs 2.4 ± 0.2; 1.7 ± 0.2; 1.8 ± 0.2 respectively. The evaluation scores for acid indigestion or heartburn and acid or bile coming into mouth in main group MAHSA were 1.2 ± 0.08; 1.2 ± 0.08 whereas in groups HSA and SA they were 1.8 ± 0.1; 1.8 ± 0.2 and 2.2 ± 0.2; 1.8 ± 0.1 respectively ($p < 0.05$).
Conclusions: Our data showed that the presented modified method of esophagogastric anastomosis forming is a safe, easy to implement and effective in preventing the development of reflux after PGE for cancer of the upper third of the stomach.
No conflict of interest.

1257 POSTER

Oncoplastic breast-conserving surgery using latissimus dorsi miniflap

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Background: Breast-conserving surgery plus radiotherapy is firmly established as a good and safe option for most women with early breast cancer. Cosmoses after Breast-conserving surgery depend on two main factors; the site of the lesion and the breast volume excised in relation to total breast volume. Latissimus dorsi miniflap is one of the various autologous tissue reconstructions that can replenish loss of more than 25% of breast volume. The aim of our study is to evaluate the aesthetic outcome and complications of breast reconstruction using latissimus dorsi miniflap augmentation after wide local excision of the tumor combined with axillary lymph node dissection.
Patients and Methods: From January 2008 till January 2010 twenty eight patients with breast cancer were carefully selected from out-patient clinic of surgical oncology department, South Egypt Cancer Institute and underwent conservative breast surgery in the form of wide local excision with safety margin with immediate reconstruction using latissimus dorsi miniflap either by muscle only or musculocutaneous flap. Neoadjuvant chemotherapy was given in some patients to reduce the tumor size and after surgery; all cases received eligible adjuvant therapy. The aesthetic results were assessed independently by the patients and two surgeons. The aesthetic results have been ranked into three categories by the surgeons: good, satisfactory and fair and satisfaction of patients has been classified into three levels: deeply satisfied, satisfied and poorly satisfied. Follow-up of the patients ranging from 24 to 48 months (median 28 months) was done.
Results: Most of the patients (71.4%) were having T2 tumor, while (14.3%) of the patients had T1 tumor and (14.3%) had T3 tumor. Neoadjuvant chemotherapy was given for 14 patients with overall response rate about 76.7%. Wide local excision with safety margin with immediate reconstruction using latissimus dorsi mini-flap was done. Seventeen patients had reconstruction with muscle only, while 11 patients had reconstruction by musculocutaneous flap. A deeply satisfying cosmetic result was achieved in (82.1%) and none of them subsequently required mastectomy. After median follow up of 28 month, the progression free survival was 92.9% and the over all survival was 96.4%. No local recurrence was recorded.
Conclusion: Breast augmentation with autologous tissue comes into play by reducing the resultant deformity when the breast volume excised is significant. The Latissimus dorsi miniflap is the mainstay of oncoplastic breast surgery after partial mastectomy and it has low donor site morbidity, deep patient satisfaction with low and temporary postradiation effects.
No conflict of interest.

1258 POSTER

Oncoplastic surgery as an indispensible technique in breast conserving surgery

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Background: In breast cancer surgery more and more weight is lent to the cosmetic effects of operations whose aim is to decrease the psychic trauma of female patients and minimize mutilation resulting from the surgical treatment. The recent fundamental achievements in breast cancer surgery include the increasing use of breast conserving surgery, performing of breast reconstruction operations in such cases when breast conserving surgery is impossible and resignation from the excision of all the axillary lymph nodes in favour of sentinel node biopsy. This direction of changes in the treatment methods has begun to appear in Poland as well. Oncoplastic surgery is a new element of the therapy. It is the connection of classic oncological surgery associated with tumour resection with plastic surgery procedures. The essence of oncoplastic surgery is supplementing of the defect after tumour excision with healthy surrounding tissues. It is especially important in the case of an unfavourable proportion of a tumour size to the breast size, when a considerable tissue defect causes a negative cosmetic effect.
The aim of the study was to examine whether oncoplastic surgery has significantly increased the percentage of patients undergoing breast conserving surgery.
Material and Methods: 1468 patients with breast cancer were operated in the Oncological Surgery Department in 2010–2011. There were performed 648 simple amputations with sentinel node biopsy /SNB/, or axillary lymph node dissection /ALND/. Breast conserving surgery with SNB or ALND was conducted in 820 cases, including 58 oncoplastic operations. There was performed the translocation of breast tissues to suplement the defect after tumour excision with a margin in 45 patients, and subcutaneous amputation with a simultaneous prosthetic restoration was conducted in 13 patients.
Results: After introduction of oncoplastic surgery increase in the use of BCT techniques compared to simple mastectomy reached approximately 9%.
Conclusions: Oncoplastic surgery significantly increases the possibility of performing breast conserving surgery and thus constitute an indispensible technique which is a must for oncological surgeons specializing in breast cancer treatment. The survey of female patients' satisfaction revealed a high level of satisfaction from the aesthetic effects − 87%.
No conflict of interest.

1259 POSTER

Strategy for synchronous and multiple liver metastasis

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Background: Surgical indications for resection of synchronous metastasis from colorectal cancer (CRC) and the optimal timing of hepatectomy are still controversial and widely debated.
Patients: Synchronous and multiple metastatic liver tumours were detected in 57 since May 2005. Our treatment policy has been to perform hepatectomy first, if the resection can be done with no limit on size and number of tumours. However, if curative resection is not, chemotherapy is begun first and timing for the possibility of a radical operation is planned immediately. In 37 patients whose tumours were located only in the liver, primary tumour resection was performed first in 16 patients, and after tumour-decreasing by chemotherapy, operation was performed in 7 patients. In 20 patients in whom chemotherapy was performed first, after controlling the distant metastasis, hepatectomy was performed in 3 patients, and staged hepatectomy was performed in 10 patients.
Results: 1) Recurrence was detected after hepatectomy in 75.0% of simultaneous resection cases and in 70.0% of staged cases. In the recurrence cases, early detection (within 6 months) after tumour resection occurred in 58.3% of the simultaneous and 14.2% of the staged. 2) No differences in results of pre- and postoperative liver function tests were found, and duration of hepatectomy and blood loss were also similar. 3) Median survival time (MST) and 2-year survival rate were significantly better in the hepatic resection cases than in the non-operated cases. There was no significant difference in MST or 2-year survival rate between simultaneous and staged cases. 4) In 10 staged cases, length of chemotherapy had no effect on pre- or postoperative liver function test results, and survival curves.

Conclusion: The present data show that neoadjuvant chemotherapy does not increase the risk of postoperative complications or the surgical difficulties of hepatectomy for colorectal metastases.
No conflict of interest.

1260 POSTER

Randomized control trial for non-palpable breast lesions: Comparing radio-guided occult lesion localization (ROLL) vs. wire guided lesion localization (WGLL)

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Background: Non-palpable breast lesions have been localized using a variety of methodologies. Wire guided lesion localization (WGLL) has been employed for many years with successful outcomes. Recently, with the development of radio-pharmaceutical agents, radio-guided occult lesion localization (ROLL) has been implemented in actual worldwide practice. We conducted a study intended to determine the most effective method to localize and excise these non-palpable lesions in our countries biggest neoplastic referral center.
Material and Methods: A randomized control trial was designed and conducted in the National Cancer Institute of Colombia located in Bogota, from March 2006 to June 2011. We included 129 patients of which 64 (49.6%) were allocated to the ROLL group and 65 to the WGLL (51.4%). The intention was to compare effective lesion localization in these two groups of patients with lesions at risk evaluated by mammography or ultrasonography that previously had non-diagnosis percutaneous biopsy.
Results: In our study ROLL technique demonstrated a statistically significantly better median of centricity of the lesion (ROLL= 11.7; WGL = 15.4 p = 0.038). No differences were found for other variables studied between the two groups regarding the demographical characteristics, the surgical specimen, need of widening margins, surgical complications, difficulty of procedure and patient/surgeon satisfaction.
Conclusions: Using the ROLL technique is as equally as effective as WGLL in identifying the non-palpable lesions of the breast. In our study the ROLL technique demonstrated a better centricity of the lesions leading us to conclude that this technique could be applied as routine in localizing non-palpable breast lesions in centers of expertise.
No conflict of interest.

Table 1.

	WGL	ROLL	Total
Clinical and radiological characteristics			
Number of patients	65 (51.4%)	64 (49.6%)	
Age (standard deviation)	56.9 (9.6)	57.3 (10.7)	
Asymmetry	6 (9.23%)	8 (12.50%)	
Mass	28 (43.07%)	20 (31.25%)	
Microcalcifications	29 (44.61%)	35 (54.68%)	
Asymmetry and Microcalcifications	1 (1.53%)	0 (0%)	
Mass and Microcalcifications	1 (1.53%)	1 (1.56%)	
Outcome			
Localization rate	65/65 (100%)	62/64 (96.9%)	
Centricity (Median mm)**	15.4	11.7	
Minutes until skin closure	31.9 (12.5)	33.9 (15.1)	
Volume	20.7 mL (18.0)	18.3 mL (19.4)	
Weight	10.4 g (9.1)	9.3 g (8.1)	
Pain (VAS)*	3.7 (2.1)	3.0 (2.0)	
Difficulty (Likert) *	4.5 (1.4)	4.1 (1.5)	
Compromised borders	39 (60%)	38 (59.37%)	
Malignancy	11 (16.92%)	12 (18.75%)	
Patient satisfaction	63 (96.92%)	62 (96.87%)	
Surgeon Satisfaction	63 (96.92%)	63 (98.43%)	
Procedure complications			
Infection	1 (1.56%)	3 (4.61%)	
Seroma	0 (0%)	2 (3.07%)	
None	63 (98.43%)	60 (92.30%)	
Margin widening required	16 (24.61%)	12 (18.75%)	
Pathology			
Histology			
In situ Carcinoma	9 (13.84%)	5 (7.81%)	14 (10.85%)
Invasive Carcinoma	5 (7.69%)	7 (10.93%)	12 (9.30%)
Non proliferating lesions	15 (23.07%)	27 (42.18%)	42 (32.55%)
Proliferating lesions w/o atypia	25 (38.46%)	22 (34.37%)	47 (36.43%)
Proliferating lesions w/ atypia	11 (16.92%)	3 (4.68%)	14 (10.85%)
Total	65 (100%)	64 (100%)	129 (100%)

*Reported in medians (intercuartilic range).
**Sum Rank test, Z = −2.06, p = 0.038.

1261 POSTER

Lymphatic mapping and sentinel lymph node biopsy in an in-vivo porcine model using a novel magnetic technique

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Background and Objective: A novel magnetic technique for sentinel lymph node biopsy (SLNB) was developed and is currently being evaluated in an international multicentre trial (SentiMag). In this European collaborative project, we evaluated the optimal dose of magnetic tracer required for performing sentinel lymph node biopsy (SLNB). We also quantified the iron content of nodes and correlated this with readings with handheld magnetometer readings.
Materials and Methods: Local ethics approval was obtained (IR-CAD Ethical Committee, Strasbourg, France). SLNB was performed in anaesthetized pigs (Strasbourg, France) following the subcutaneous administration (deep to the third nipple in the inguinal mammary glands) of magnetic tracer (Sienna+, Endomagnetics Ltd) using a magnetometer (SentiMag, Endomagnetics Ltd.) to localize and excise groin lymph nodes. Procedures were undertaken bilaterally and using a range of different concentrations of magnetic tracer injected (0.1−2.0 ml). First hot spot measurements were performed within minutes post injection. Second hot spot measurements and SLN dissection were performed four hours post injection. Further ex-vivo counts were obtained with the handheld magnetometer. In addition, total quantity of iron in the SLNs was estimated using quantitative magnetometry (University of Twente, the Netherlands). High field ex-vivo MRI (14.1 T) and histological examination (H&E and Perl's staining) was undertaken to demonstrate the intra-nodal presence and distribution of magnetic dye.
Results: The magnetic dye drained from injection site to SLNs in the groin area in all cases. A total of 31 SLNB procedures (16 pigs) were successfully undertaken and 76 nodes (74 sentinel; 2 non-sentinel) were retrieved. Magnetic dye was proven to be present in the SLNs when measured with quantitative magnetometry, on MRI and on histological examination.
Conclusion: SLNB with the magnetic technique is feasible after subcutaneous injection of magnetic tracer, with all doses used. This magnetic tracer is ideally suited for SLNB.
No conflict of interest.

1262 POSTER

Adding imaging to the clinical picture improves BRONJ case adjudication and staging classification: Results of the "MISSION" study

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Background: Osteonecrosis of the jaw (BRONJ) is an adverse event of bisphosphonate therapy, which can significantly affect the quality of life of patients. Osteonecrosis of the jaw vary widely among studies and remain unclear. Recent data suggest that a defective definition and staging classification, based only on evidence of necrotic jawbone exposure, purulent discharge and pain could represent the main culprit of current under-diagnosis and inconsistent results of treatment.
Material and Methods: The Multicentre study on phenotype, defInition and claSSification of osteonecrosIs of the jaws associated with bisphosphONates (MISSION) was designed to investigate a well characterised large cohort of individuals diagnosed with BRONJ so to test their clinical and radiological phenotype against staging system of the American Association of Oral and Maxillofacial Surgeons (AAOMS), which relies on clinical data alone. The extent of jawbone involvement at computed tomography (CT) was measured based on the density of bone (osteosclerosis). Two patterns were analysed: focal sclerosis against diffuse sclerosis, with the former showing exclusive involvement of the alveolar bone process.

Thirteen European centres (the Institutions here represented plus UCL Eastman Dental Institute of London, Hospital 'S. Anna' of Como and the University of Pisa) contributed to MISSION collecting detailed clinical data of 799 individuals, the largest osteonecrosis cohort ever reported.
The main outcome measure was the proportion of individuals within the cohort who escape the standard AAOMS stage classification when CT is added to describe the extent of bone disease.
The local ethical Committee of each contributing Center approved the study protocol.
Results: Testing the present cohort against AAOMS staging system led to the adjudication of a total of 192 individuals (24.0%) as having non-exposed BRONJ (stage 0), and 605 with exposed BRONJ (stage 1 =72; stage 2 = 405; Stage 3 = 130). When bone disease extent as measured on CT was tested against each AAOMS stage, 57% of Stage 0 patients had already diffuse bone disease to the jaw despite the absence of frank bone exposure. In addition, more than half of AAOMS stage 1 patients had diffuse disease at CT, while 1/3 of AAOMS Stage 2 (35.1%) patients had focal disease at CT. Instead, inclusion of CT signs of bone involvement did not change distribution of AAOMS Stage 3 patients.
Conclusions: We have shown that clinical adjudication of ONJ patients based on current AOOMS staging system would potentially translate into underdiagnosis of stage 0 patients and defective treatment allocation for the entire population. The addition of imaging to the clinical picture of ONJ may become paramount in the future to anticipate diagnosis, categorize patients more consistently and offer successful treatments.
No conflict of interest.

1263 POSTER

Evaluation of surgical outcomes in conventional endoscopic thyroidectomy compared with single incision endoscopic thyroidectomy through the axillary approach for papillary thyroid carcinoma

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Background: Minimally invasive thyroidectomy has been researched extensively, and even now, the operative technique for this procedure is being further developed through research. Endoscopic thyroidectomy is performed by many techniques, using the axillary, breast, and anterior chest approaches. We have introduced single incision endoscopic thyroidectomy (SIET) as an alternative method for conventional endoscopic thyroidectomy (CET). The purpose of this study is to compare the surgical outcomes of CET and SIET for papillary thyroid microcarcinoma.
Material and Methods: This study included 118 patients with thyroid microcarcinoma who underwent CET and SIET through the axillary approach from Oct 2002 through June 2012. The surgical outcomes were retrospectively analyzed. The assessment included the size of tumor, operation time, complications, length of hospital stay, postoperative pain, and patient satisfaction.
Results: There was no conversion to conventional open thyroidectomy. The mean age of the patients was 42.3±7.6 years for CET and 38.0±9.0 years for SIET ($p = 0.551$). The mean size of the tumor were 0.5±0.23 cm in CET and 0.56±0.297 cm in SIET ($p = 0.051$). The operation time for SIET was not greater than that for CET (138.4±36.9 min vs. 128.3±36.55 min, $p = 0.794$). Postoperative pain was scored using the Visual Analog Scale (VAS). Postoperative pain was lesser in SIET than in CET (VAS 1: 4.7±1.7 vs. 3.7±1.2, $p < 0.001$; VAS 7: 2.6±1.9 vs. 2.0±1.4, $p < 0.04$). Cosmetic satisfaction was evaluated using a numeric system that ranged from 1 (extremely satisfactory) to 4 (not satisfied at all). Postoperative cosmesis appeared to have no difference between both groups (1.43±0.55 vs. 1.3±0.49, $p = 0.058$).
Conclusions: Endoscopic thyroidectomy is safe and feasible using both CET and SIET. However, SIET results in less postoperative pain with no increase in operation time. Although SIET has not been evaluated in a prospective clinical trial or large study, our results suggest that SIET reduces the postoperative pain by reducing the invasiveness of the procedure.
No conflict of interest.

1264 POSTER

A prospective study of surgical decompression and spinal reconstruction in vertebral metastases

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Background: The present prospective study aims to investigate the role of surgical decompression and spinal reconstruction in vertebral metastases.
Material and Methods: Patients with vertebral metastases were enrolled. Surgical approaches include laminectomy or laminectomy plus corpectomy. Pedicle screws stabilization was performed in all cases. Corpectomies and stabilization were performed via a single stage posterolateral approach. Expandable titanium cages were used to reconstruct spinal column after corpectomy. All patients were followed up until death.
Results: 21 patients (11 males, 10 females) with a mean age of 58 years were enrolled. 12 patients had a history of cancer, whereas vertebral metastases were first presentation of cancer in 9 patients. There were 3 cases in cervical spine, 14 in thoracic and 4 in lumbar spine. The most common primary cancers were lung, breast, colorectal and renal. Laminectomy and stabilization were performed in 3 cases, and corpectomy and cage reconstruction were performed in 18 cases. No peri-operative death or major complication was encountered. All patients were discharged to home or rehabilitation after surgery. Visual analog scale (VAS) pain score was significantly reduced from 8.8 to 3.2. In patients who had non-surgical treatment of vertebral metastasis, VAS decreased significantly from 8.3 to 3.1. There was no neurological deterioration after surgery. In patients with pre-operative neurological deficits, most patients (10/12) improved after surgery. Cobb angles were significantly reduced from 15 to 10 degree, and vertebral height was significantly increased from 28 to 34 mm after surgery. Mean survival was 5.3 months.
Conclusions: Surgical decompression and spinal reconstruction appeared to be safe in patients with vertebral metastases. Surgery reduced pain in patients with vertebral metastases, and likely to be more effective than non-surgical treatments alone. Surgery improved neurological deficit and spinal deformity.
No conflict of interest.

1265 POSTER

Diagnostic accuracy of preoperative CT scan and 18F-FDG PET/CT in patients with peritoneal carcinomatosis undergoing hyperthermic intraperitoneal chemotherapy (HIPEC) following cytoreductive surgery

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Background: The peritoneum is a preferred site of metastasis from several primary malignancies, and peritoneal carcinomatosis (PC) is one of the most significant negative prognostic indicators in patients with metastatic disease. A survival benefit has been observed for patients with PC from colorectal, ovarian, and gastric carcinomas treated by cytoreductive surgery (CRS) followed by intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC). In patients undergoing this treatment modality, the strongest determinant of outcome is the residual tumor extension after CRS. Unfortunately, PC can be difficult to diagnose preoperatively by imaging studies. The aim of our study was to evaluate the role of 18F-2-deoxy-fluoro-D-glucose positron emission tomography/computed tomography (PET/CT) scanning in detecting the presence and the extent of PC in patients with various malignancies.
Patients and Methods: A group of 47 patients (median age 61.4±11.5 years) with advanced or recurrent cancers (colorectal=26, ovarian=21, gastric=8, pseudomyxoma peritonei=3) scheduled for CRS and HIPEC underwent preoperative CT-scan and PET/CT. The results were expressed as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy. The negative (NLR) and positive (PLR) likelihood ratio were also obtained. The receiver operator characteristic (ROC) curves were drawn, and areas under the curve (AUC) were measured. The 95% confidence interval (95% CI) was also calculated, when appropriate. The results of CT scan and PET/CT were compared with the final surgical findings.
Results: The sensitivity, specificity, PPV, NPV, accuracy were 91%, 33%, 93%, 29% and 69% for CT-scan, and 82%, 67%, 95%, 33% and 71% for PET/CT, respectively. NLR and PLR were 0.27 (95% CI 0.07–1.09) and 1.37 (95% CI 0.76–2.44), while the AUC was 62 and 74 for CT-scan and PET/CT, respectively (p=NS).
Conclusions: In patients with PC undergoing surgery both PET/CT and CT showed low sensitivity, and thus they seem not to be a reliable tool in view of treatment planning. Our study demonstrates that PET/CT does not add substantially to CT scanning in the detection of this disease.
No conflict of interest.

1266 POSTER

Surgical management for gallbladder cancer

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The effect of radical resection in gallbladder cancer(GC) is still area of debate. Gallbladder carcinoma is rare and associated with dismal outcomes. Radical surgery is the only curative treatment and options for adjuvant therapy remain limited. Gallbladder cancer is a highly lethal disease. It is an aggressive disease with extremely poor outcome after surgical treatment and a poor prognosis. This study aimed to determine the factors influencing outcome of treatment in patients with gallbladder carcinoma and to identify the patients who might benefit from radical surgery and adjuvant therapy.
A retrospective analysis was conducted of 57 patients with the gallbladder carcinoma and the results of surgical treatment of patients with pathologically confirmed gallbladder cancer were identified. There were 57 cases (43 females, 14 males) with a mean age of 58 (range 36−84) years, treated surgically between 1995–2012.
57 patients were assessable for this study. Simple cholecystectomy was the only procedure performed in 44 of T2 and 4 of T3 cases. Radical cholecystectomy was performed as the primary procedure for 5 of the T2 and T3 cases in each. Palliative by-pass procedure or exploration was performed in 4 patients with unresectable tumours. Adenocarcinoma was the most frequent histological type and squamous cell carcinoma in 15 percent. The three-year survival rate was 70%(40 cases) and five-year survival rate was 30%(17 cases).
Favourable survival rate can be achieved after curative resection, even for selected patients with advanced disease. Adjuvant therapy may improve the survival of patients with gallbladder carcinoma. Gallbladder cancer continues to carry a poor prognosis. Very few patients underwent aggressive surgery. En bloc resection and lymphadenectomy may have stage-specific effects on survival. The only consistent curative therapy for gallbladder cancer is surgical resection. A subset of patients with peripancreatic positive nodes or invasion of adjacent organs seems to benefit from a synchronous pancreaticoduodenectomy. Radiotherapy and chemotherapy have not been found effective as an adjuvant or palliative therapy in gallbladder cancer. Because flat infiltrating gallbladder cancer and cancer with cholecystitis and numerous stones are difficult to diagnose preoperatively, we recommend taking frozen sections from patients who are of advanced age, have a long history of stones, or have a thickened gallbladder wall.
No conflict of interest.

1267 POSTER

Ruptured hepatocellular carcinoma in cirrhotic patients: Treatment options and survival outcome

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Background: Spontaneous rupture of hepatocellular carcinoma (HCC) is reported to be 3−15% of cases, with an increased incidence in Asian countries. It is considered the third leading cause of hepatocellular carcinoma-related death, after tumour progression and liver failure.
Materials and Methods: We retrospectively analysed data of 12 patients with ruptured HCC who were surgically or conservatively treated and evaluated the treatment modalities, the complications and the survival outcome.
Results: All the patients had histologic evidence of underlying cirrhosis. The median age of the patients was 65 years. There was a male predominance. Eight of these patients were hemodynamically unstable at presentation. Five patients had multifocal disease. Transcatheter arterial chemoembolisation was performed in 5 patients and 7 patients were subjected to emergency surgery. Patients with cirrhosis who received transcatheter arterial chemoembolisation had a median survival rate of 32 days. The patients who subjected to hepatectomy had higher survival rates 28.5% at 1 year.
Conclusion: The treatment of ruptured HCC should be individualised for each patient. Even though transcatheter arterial chemoembolisation is a promising treatment option still surgery is associated with better survival.
No conflict of interest.

1268 POSTER

Laparoscopic surgery of pancreatic endocrine tumors: Is there a benefit?

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Background: Although minimally invasive surgery is widely adopted for the treatment of many surgical diseases, results of laparoscopic procedures for pancreatic endocrine tumors (PET) are published only in small series. Objective of the study was to reveal and estimate the benefits of laparoscopic resection of PET and to compare it with the open approach by reviewing the available data.
Methods: Medline search for the words laparoscopic resection and pancreatic endocrine tumors was performed. 52 relevant papers were identified and studied from 2000 till 2012.
Results: Four non-randomized studies compared laparoscopic and open approach for resection of PET comprising totally 384 patients − 81 laparoscopic and 303 open. There were no cases of postoperative mortality. Mean operative time was estimated in three studies where there has been a significant difference ($p < 0.5$) in favor of open technique (121 min. vs 92 min) in one study, in favor of laparoscopic technique in the other study (188 min. vs 305 min.) and with no difference in the third study. Mean hospital stay was estimated in four studies, where it reached a significant difference ($p < 0.05$) in one study in favor of laparoscopic group (11 days vs. 14 days). Rate of postoperative pancreatic fistula was significantly higher in open group in two studies reaching up to 100% in comparison to only 14.2% in laparoscopic groups ($p < 0.05$).
Conclusion: Laparoscopic resection of PET is at least as feasible and safe as open surgery with possible benefits in terms of operative time, length of stay and rate of pancreatic fistula.
No conflict of interest.

1269 POSTER

Experience with the implant of vascular access devices by medical oncologist in a non-surgical scenery

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Background: Totally implantable central venous catheters are widely used in the management of patients (pts) with malignant diseases in order to facilitate drug delivery for the new therapeutic protocols. These are based on continuous administration and higher doses of chemotherapeutic agents with relative phlebitis problems and supportive treatment. Staff of our department, specially trained on the routinely implant of central venous accesses were in charge of the procedure. The technique was carried out under local anaesthetic in a special location of day hospital or in hospitalization environment, under strict aseptic measures without fluoroscopic control.
Material and Methods: From Sep 94 to March 2013, 1240 devices (port-a-cath systems [PS]) were implanted in 1212 pts, with age 50.5 yr (14−81) (mean, range), and K.I. 70% (50–100), female 738/male 474. Venous access: right interior jugular 715, left subclavian 245, right subclavian 252, left interior jugular 28. A thorax X-ray was performed after each procedure and in 168 pts prophylactic antibiotics were given.
Results: The venous access remained implanted a median of 438 days (1- +2210). Complications occurred in 195 placements (16%): Infections 87 (7%); deep venous thrombosis 50 (4%) Left placements 26, right placements 24; obstruction 7 (0.6%); malpositioned 25 (2%); fractures/migration 21 (1.7%); pneumothorax 4 (0.32%); local skin necrosis 7 (0.6%). Five hundred and twenty devices were removed, 347 (28%) after completing planned therapy and 173 (14%) due to complications [Infections (92), migration (22), malposition (12), venous thrombosis (26), obstruction (11) and skin necrosis (10)].
Conclusions: The best access route in order to avoid complications seems to be the right internal jugular vein. Our results are comparable with those obtained when the venous access is placed in the operating room, under fluoroscopic control and prophylactic antibiotics are administrated. This procedure, on top of being more comfortable for the patients is more affordable for the public health system.
No conflict of interest.

1270 POSTER

Needle oophoropexy: A new simple technique for ovarian transposition prior to pelvic irradiation

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Background: Irradiation of the pelvis in the treatment of cancers will result in ovarian failure unless the ovaries are shielded adequately. To protect

the ovaries, an oophoropexy may be performed. Our aim was to evaluate the feasibility, morbidity, and efficacy of laparoscopic ovarian transposition using a simple percutaneous needle technique.
Material and Methods: Fifteen patients (ten with rectal cancer and five with Hodgkin's disease) underwent the new laparoscopic oophoropexy technique. Laparoscopic releasing of the ovary was performed by cutting the utero-ovarian ligament followed by placing the ovaries on the anterior abdominal wall. A percutaneous straight needle was introduced through a 2-mm skin incision at the site of fixation. Repositioning of the ovaries was done on an outpatient basis without the need for readmission to the operating theatre.
Results: The technique was effective, reliable, and simple with no morbidities. Repositioning was performed simply in the outpatient clinic. At follow-up, 11 patients had evidence of ovarian function.
Conclusion: Percutaneous needle transposition of the ovaries is a simple, effective, reliable, and easy-to-perform technique. It has short learning curve and can be done by less experienced laparoscopic surgeons.
No conflict of interest.

1271 POSTER

From simple to complicated: The first 400 consecutive cases of oncologic robotic surgery

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Background: During the recent years, robotic surgery has known a tremendous growth although it is still not as widespread in general surgery as it was expected. However, the robot has changed the preferred approach even in oncologic surgery, in the centers that own the device. The aim of the present study is to globally assess the use of the robot for general oncology cases and to establish major indications.
Material and Methods: The first 400 consecutive cases of oncologic robotic surgery performed in our center were analyzed. The cases span on almost five years since the 1st of January 2008 until the 3rd of December 2012. Data was prospectively assembled in a Robotic Surgery Registry. Personal, clinical and surgical variables were recorded and analyzed using parametric and non-parametric tests under SPSS 16.0 software (SPSS Inc., Chicago IL, USA) for Windows. A p-value <0.05 was considered significant.
Results: In the study group there were 164 males (41%) and 236 females (59%) with an average age of 57 years (±12.53). The operations were performed by three main surgeons in stable surgical teams, with 30% of the cases performed in 2012. Indications included primary neoplasms, relapses and metastases of all major abdominal organs and some thoracic organs (thymus and esophagus). Only 17 patients needed thoracic surgery. 243 cases (60.8%) were pelvic surgery cases (gynecological cancers, rectal cancers, pelvic invasions or recurrences). In time, surgeons showed a stronger preference for pelvic robotic surgery compared to other indications ($p = 0.007$). A surgical complexity score showed a mild increase of the procedures' complexity in time and a correlation with the operative time ($p < 0.05$). Whilst pelvectomies where approached from the first year of experience, major hepatectomies and major pancreatic surgery were only addressed after an experience of 200 cases. There were only 11 conversions (2.8%) and 104 (26%) various Clavien-grade postoperative complications. The pathologic reports were satisfactory. Survival data was not available for all patients.
Conclusions: Robotic surgery in oncologic indications is feasible and safe. Pelvic cancers and pelvic recurrences are one of the most interesting indications due to a combination of factors favoring robotics: a narrow working space, complex procedures and difficult operating positions.
No conflict of interest.

Poster Discussion Session (Mon, 30 Sep)
Symptom Science

1300 POSTER DISCUSSION

Efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately emetogenic chemotherapy (MEC)

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Background: Targeting multiple molecular pathways is important for maximizing control of CINV. This is supported by antiemetic guidelines which recommend agents that target different pathways involved in emesis. NEPA is a fixed-dose combination of netupitant (NETU), a highly-selective NK_1 receptor antagonist (RA) and palonosetron (PALO), a pharmacologically and clinically distinct 5-HT_3 RA, that targets dual antiemetic pathways.
Materials and Methods: This multinational, randomized, double-blind, parallel group study (NETU-08−18; NCT01339260) evaluated the efficacy and safety of a single oral dose of NEPA (NETU 300 mg + PALO 0.50 mg) versus a single oral 0.50 mg dose of PALO in chemotherapy-naive patients receiving anthracycline-based chemotherapy. All patients also received oral dexamethasone (DEX) on Day 1 (12 mg in the NEPA arm and 20 mg in the PALO arm). The primary efficacy endpoint was complete response (CR: no emesis, no rescue medication) during the delayed (25–120 h) phase. Secondary efficacy endpoints included complete protection (CR plus no significant nausea), no emesis, and no significant nausea. Safety was assessed through reporting of adverse events, ECGs and cardiac troponin levels.
Results: 1455 patients were randomized. Treatment groups had comparable baseline characteristics with the overall population being predominantly female (98%) and white (80%), with a mean age of 54 years.
NEPA was superior to PALO for the primary CR endpoint as well as secondary efficacy endpoints during the delayed and overall phases following chemotherapy.

	Overall (0–120 h) % Patients	
	NEPA (N = 724)	PALO (N = 725)
Complete response	74.3*	66.6
Complete protection	63.8*	57.9
No emesis	79.8*	72.1
No significant nausea	74.6*	69.1

*p-value <0.05.

The type, frequency, and severity of AEs were comparable between groups. Most frequently reported treatment-related adverse events (TRAEs) for NEPA included headache (3.3%) and constipation (2.1%). The majority of adverse events were mild/moderate intensity and there were very few (0.7%) severe TRAEs for NEPA-treated patients. There was no evidence of any cardiac safety concerns for either NEPA or PALO.
Conclusions: NEPA is superior to PALO in preventing CINV following MEC. As a fixed-dose antiemetic drug combination it offers guideline-based prophylaxis with a convenient, single-day dose.
This study was sponsored by Helsinn Healthcare, S.A.
Conflict of interest: *Advisory board: Grunberg: Helsinn Healthcare, Eisai, Merck, AP Pharma, Redhill Biopharma Aapro: Helsinn Healthcare. Other substantive relationships: Rossi, Rizzi and Borroni: Employed by Helsinn Healthcare*

1301 POSTER DISCUSSION

Improved control of nausea and vomiting (CINV) with a fixed-dose combination of netupitant and palonosetron (NEPA) following highly emetogenic chemotherapy (HEC): Results from a pivotal study

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Background: Further progress in preventing CINV will require the introduction of novel agents with improved efficacy for nausea as well as vomiting. NEPA is a fixed-dose combination of netupitant (NETU), a new NK_1 receptor antagonist (RA) and palonosetron (PALO), a pharmacologically and clinically distinct 5-HT_3 RA.
Materials and Methods: This randomized, double-blind, parallel group study (NETU-07−07) in 694 chemotherapy-naive patients undergoing cisplatin-based HEC compared 3 oral doses of NEPA (100 mg, 200 mg and 300 mg NETU + 0.5 mg PALO) with oral PALO 0.50 mg, all given on day 1. A standard IV ondansetron (OND) 32 mg + 3-day aprepitant (APR) regimen was also included as an exploratory arm. All patients received oral dexamethasone (DEX) days 1−4. The primary efficacy endpoint was complete response (CR: no emesis, no rescue medication) during the overall (0–120 h) phase.
Results: Treatment groups were comparable: male (57%), median age 55. Most frequent cancers were respiratory (27%) and head & neck (21%). Median cisplatin dose: 75 mg/m^2.
All NEPA doses met the primary endpoint of superior overall CR rates compared with PALO (87.4%, 87.6%, 89.6% for $NEPA_{100}$, $NEPA_{200}$, and $NEPA_{300}$, respectively vs 76.5% PALO) with the highest NEPA dose studied ($NEPA_{300}$) showing an incremental benefit over lower NEPA doses for all efficacy endpoints. $NEPA_{300}$ was also more effective than PALO for all secondary efficacy endpoints: no emesis, no significant nausea and complete protection (CR plus no significant nausea) rates during the acute, delayed and overall phases.

	Overall (0–120 h) % Patients		
	$NEPA_{300}$ (N = 135)	APR+OND* (N = 134)	PALO (N = 136)
No emesis	91.1	87.3	76.5
No significant nausea	89.6	85.8	79.4
Complete protection	83.0	78.4	69.9

*Exploratory arm.

The type, frequency, and severity of AEs and % of patients who developed ECG changes were comparable between groups.
Conclusions: NEPA, a convenient single-day oral combination targeting dual antiemetic pathways, is superior to PALO for preventing CINV. $NEPA_{300}$ was more effective than PALO for all efficacy endpoints including nausea control following HEC. All NEPA doses were well tolerated with a similar safety profile to PALO and APR.
This study was sponsored by Helsinn Healthcare, S.A.
Conflict of interest: *Advisory board: Gralla: Helsinn Healthcare Hesketh: Helsinn Healthcare. Other substantive relationships: Rossi, Rizzi, and Palmas: Employed by Helsinn Healthcare*

1302 POSTER DISCUSSION

Prevention of chemotherapy-induced nausea and vomiting (CINV) over repeated chemotherapy cycles: Results of a phase 3 trial of NEPA, a fixed oral dose combination of netupitant and palonosetron

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Background: Safe, effective and convenient antiemetic regimens that preserve benefit over repeated chemotherapy (CT) cycles are key for enhanced cancer treatment. This study tested a single oral dose of a fixed combination, NEPA (netupitant (NETU), a highly selective NK_1 receptor antagonist (RA) and palonosetron (PALO), a pharmacologically distinct 5-HT_3 RA) over up to 6 CT cycles. Recent trials have demonstrated the safety and efficacy of NEPA in a single cycle of highly (HEC) or moderately (MEC) emetic CT. Therefore, this study (NETU-10−29; NCT01376297) was intended to assess the safety and describe the efficacy of NEPA over multiple cycles of HEC and MEC. Major efforts were made in this study to retain patients (pts) on trial as many multi-cycle antiemetic studies are of questionable validity due to high patient drop out.
Materials and Methods: This multinational, randomized, double-blind, active-controlled, parallel group study assessed the safety and efficacy of a single oral dose of NEPA (NETU 300 mg + PALO 0.50 mg) given only on day 1 of repeated cycles of HEC or MEC with oral dexamethasone (DEX) [days 1−4 (HEC) or day 1 (MEC)]. A 3-day regimen with oral aprepitant (APR) + PALO + DEX was included as a control in an unbalanced 3:1 (NEPA:APR) randomization. Safety was assessed primarily by adverse events; efficacy by complete response (CR: no emesis, no rescue medication).
Results: 413 pts were randomized with 309 (NEPA) and 103 (APR) included in the efficacy analysis. Groups were comparable with: male (50%), mean age 57, 24% HEC, 76% MEC. Percent of all patients remaining on study (balanced among groups) and overall CR rates by cycle are in the table:

Cycle #	% Pts remaining on study	% CR	
		NEPA+DEX	APR+PALO+DEX
1	100%	81%	76%
2	92%	86%	81%
3	85%	91%	87%
4	76%	90%	88%
5	52%	92%	86%
6	41%	91%	86%

The type/frequency of AEs were comparable for both groups. The most frequent patient-reported treatment-related AEs (TRAEs) for NEPA included constipation (3.6%) and headache (1.0%); there was no indication of increasing TRAEs over multiple cycles. The majority of TRAEs were mild or moderate; few were serious (1.3% NEPA, 0% APR).
Conclusions: With 75% of patients completing 4 CT cycles, it can be concluded that NEPA, a convenient single-dose oral antiemetic targeting dual pathways, was well tolerated and highly effective over multiple cycles of HEC/MEC.
This study was sponsored by Helsinn Healthcare, S.A.
Conflict of interest: *Ownership: None. Advisory board: Gralla: Helsinn Healthcare Jordan: Helsinn Healthcare and Merck Balser: Roche Pharma. Board of directors: None. Corporate-sponsored research: None. Other substantive relationships: Rizzi, Borroni, and Rossi are employees of Helsinn Healthcare*

1303 POSTER DISCUSSION

A randomized phase III trial of palonosetron plus dexamethasone (day 1) versus palonosetron plus dexamethasone (day 1−3) in the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy, not including a combination of anthracycline plus cyclophosphamide

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Background: The objective of this trial was to evaluate the efficacy of palonosetron plus dexamethasone (day 1) single administration for the prevention of chemotherapy induced nausea and vomiting (CINV) in patents receiving moderately emetogenic chemotherapy, not including a combination of anthracycline plus cyclophosphamide (non-AC MEC).
Methods: This trial was conducted as a multi-center, randomized non-inferiority phase III trial. Patients who received non-AC MEC as the first line chemotherapy were randomized by minimization for palonosetron (0.75 mg, IV) plus dexamethasone (9.9 mg, IV) administered before that

chemotherapy (PALO + DEX day1 arm) and PALO + DEX day1 plus day2−3 dexamethasone (8 mg, IV or PO) (PALO + DEX day1−3 arm).
Primary endpoint was complete response (CR; no emesis and no rescue antiemetics) during the overall 5-day study period. The difference of CR rate in overall between two arms and 95% confidence interval (95% CI) were calculated by logistic regression model which includes chemotherapy, sex and age as covariates. Non-inferiority margin was estimated as 15%, and the degree of lower limit of 95% CI in the difference of CR rate in overall was verified whether it include less than 15%.
Results: From April 2011 to March 2013, 305 patients who received non-AC MEC were randomized. Oxaliplatin-containing regimen was the most common non-AC MEC regimen (72.8%), followed by irinotecan-containing regimen (13.4%), carboplatin-containing regimen (12.1%), and other regimens (1.7%). Overall CR rate was 68.2% in PALO+DEX day1 arm (n = 151) and 64.7% in PALO+DEX day1−3 arm (n = 154). PALO+DEX day1 was non-inferior to PALO+DEX day1−3 (difference 3.6%, 95% CI, −6.6% to 13.9%; $p = 0.0002$). There were no differences between two arms on CR rate in acute and delayed phase (Table).

	CR (%)		
	Overall: 0–120 h	Acute: 0−24 h	Delayed: 24–120 h
PALO+DEX day 1	68.2	95.3	68.9
PALO+DEX day 1−3	64.7	94.7	66.0

Conclusions: This is the first report of the study that demonstrated the prevention of CINV induced by non-AC MEC. PALO+DEX day1 was non-inferior to the standard regimen: PALO+DEX day1−3 for the prevention of CINV induced by non-AC MEC. In conclusion, the administration of dexamethasone on day2 and 3 can be omitted in the prevention of CINV for patents receiving non-AC MEC.
No conflict of interest.

1304 POSTER DISCUSSION

Skeletal-related events in patients with solid tumors receiving denosumab or zoledronic acid by baseline pain status: Results from three phase 3 trials

R. Von Moos[1], A. Stopeck[2], K. Fizazi[3], C. Cleeland[4], J.E. Brown[5], S. Oudard[6], L. Costa[7], H. Wang[8], A. Braun[9]. *[1]Kantonsspital Graubünden, Chur, Switzerland; [2]University of Arizona, Arizona Cancer Center, Tucson, USA; [3]University of Paris Sud, Institut Gustave Roussy, Paris, France; [4]University of Texas M.D. Anderson Cancer Center, Division of Internal Medicine, Houston, USA; [5]St James's University Hospital, Cancer Research UK Clinical Centre, Leeds, United Kingdom; [6]Université Paris Descartes, Hôpital Européen Georges Pompidou, Paris, France; [7]Hospital de Santa Maria, Instituto de Medicina Molecular, Lisboa, Portugal; [8]Amgen Inc., Global Biostatistical Science, Thousand Oaks, USA; [9]Amgen Inc., Global Development, Thousand Oaks, USA*

Background: Pain is often a consequence of bone metastases in patients with solid tumors, and may precede skeletal-related events (SREs) (Saad, et al, J Urol 2010). Previous integrated results from three phase 3 trials demonstrated superiority of denosumab compared with zoledronic acid (ZA) for preventing SREs in patients with breast, prostate, or other solid tumors. Here, we asked if it was possible to identify patients who would benefit, or not benefit, from bone-targeted treatment on the basis of clinical pain symptoms at baseline.
Materials and Methods: Patients with solid tumors and bone metastases including breast and prostate cancers and other solid tumors received either SC denosumab 120 mg and IV placebo (n = 2775) or IV ZA 4 mg (adjusted for renal function) and SC placebo Q4W (n = 2768) in the double-blinded treatment phase. Time to first on-study SRE and to first and subsequent SRE were evaluated in patients with no/mild pain or moderate/severe pain at baseline as measured by the Brief Pain Inventory − Short Form (BPI-SF).
Results: Among patients with no/mild pain at baseline, 828 (31%) patients had experienced an SRE at the time of primary analysis compared with 1000 (40%) among those with moderate/severe pain at baseline. Denosumab significantly delayed time to first SRE compared with ZA in patients with no/mild baseline pain (HR = 0.84 [95% CI: 0.73, 0.96]; p = 0.01) and in patients with moderate/severe baseline pain (HR = 0.83 [95% CI: 0.73, 0.94]; p = 0.003). The time to first and subsequent SREs was similarly significantly delayed compared with ZA in the no/mild baseline pain group (RR = 0.81 [95% CI: 0.70, 0.92]; p = 0.002) and in the moderate/severe baseline pain group (RR = 0.82 [95% CI: 0.73, 0.93]; p = 0.001).
Conclusions: In a combined analysis of three phase 3 trials of patients with solid tumors and bone metastases, the presence of pain at baseline was not a reliable predictor of response to bone-targeted therapy. In this analysis, denosumab significantly delayed time to first and multiple SREs compared with ZA. This difference in treatment effect was similar in magnitude regardless of patients' pain status at baseline.
Trials sponsored by Amgen, Inc. ClinicalTrials.gov registration numbers NCT00321464, NCT00321620, NCT00330759.
Conflict of interest: *Advisory board: RvM-Amgen, Novartis, Roche, Merck Sharp Dome (MSD), Bristol-Meyers Squibb (BMS) AS-Amgen KF-Amgen JEB-Amgen, Novartis, Bristol-Meyers Squibb SO-Janssen, Novartis, Bayer, Pfizer, Sanofi LC-Amgen, Novartis, Roche, Janssen. Corporate-sponsored research: RvM-Amgen, Roche (unrestricted research grant) AS-Amgen, Novartis. Other substantive relationships: RvM-Amgen, GSK, Roche (speaker homoraria) AS-Amgen, GSK (honoraria) KF-Amgen (speaker honoraria) CC-Amgen (consultant) JEB-Amgen (consultant) HW-Amgen (employee, stockholder) AB-Amgen (employee, stockholder).*

1305 POSTER DISCUSSION

Risk factors for developing osteonecrosis of the jaw (ONJ) in patients receiving denosumab or zoledronic acid for bone metastases: Results from three phase 3 trials

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Background: The use of antiresorptive therapies such as denosumab or zoledronic acid (ZA) for patients with metastatic bone disease reduces the risk of skeletal-related events (SREs) but is associated with a risk of osteonecrosis of the jaw (ONJ). Here we report risk factors for the development of ONJ for the blinded treatment phase of three phase 3 clinical trials comparing the two agents for reduction of SREs.
Materials and Methods: Patients (n = 5677) with bone metastases from solid tumors or multiple myeloma received either SC denosumab 120 mg and IV placebo or IV ZA 4 mg (adjusted for renal function) and SC placebo Q4W in the double-blinded treatment phase of each trial. Study exclusion criteria included prior/current ONJ or osteomyelitis of the jaw, planned invasive dental procedure, or non-healed oral or dental surgery. Patients who received $\geqslant$1 active dose during the blinded treatment phase were included in this analysis for up to 44.5 months of denosumab exposure and 41.3 months of ZA exposure. Oral assessments were conducted at baseline and every 6 months thereafter by the investigator or other qualified examiner. Potential ONJ events were independently adjudicated by a blinded committee of experts.
Results: In combined data from three phase 3 trials, 63 patients in the denosumab group and 44 patients in the zoledronic acid group had adjudicated positive events of ONJ. Most patients who developed ONJ had recognized oral risk factors, among which tooth extractions were the most frequent (Table). Additional risk factors for ONJ, including concurrent chemotherapy, anti-angiogenesis medications, corticosteroid treatment, and their impact on clinical outcome, will be presented.

Table: Risk factors for developing adjudicated positive events of ONJ in three phase 3 trials

Risk factor	n (%)	
	Denosumab (n = 63)	ZA (n = 44)
History of tooth extraction, poor oral hygiene, and/or use of dental appliance	54 (85.7)	38 (86.4)
Tooth extraction	37 (58.7)	30 (68.2)

Conclusions: In combined data from three trials comparing denosumab with zoledronic acid, development of ONJ was associated with recognized risk factors encompassing oral factors. Trials sponsored by Amgen, Inc. ClinicalTrials.gov registration numbers NCT00321464, NCT00321620, NCT00330759.
Conflict of interest: *Advisory board: JEB-Amgen, Novartis, Bristol, Myers SquibbFS-Amgen, Novartis AS-Amgen KF-Amgen DH-Amgen RDB-*

Novartis, Amgen. Corporate-sponsored research: FS-Amgen, Novartis AS-Amgen, Novartis DH-Amgen RDB-Novartis, Amgen. Other substantive relationships: JEB-Amgen (consultant)FS-Amgen,Novartis (honoraria) AS-Amgen, GSK (honoraria) KF-Amgen (speaker honoraria)ID-Amgen, Novartis, GSK, Medtronic (consulting and honoraria), Roche, TEVA, Riemser (honoraria) HW-Amgen(employee and stockholder) AB-Amgen(employee and stockholder).

1306 POSTER DISCUSSION

Effect of skeletal-related events on pain interference in patients with solid tumors and bone metastases

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Background: Patients with metastatic bone disease who experience a skeletal-related event (SRE; including pathological fracture [PF], surgery [SB] or radiotherapy to bone [RB], or spinal cord compression [SCC]) often have increased pain. Using data from patients with solid tumors enrolled in three identically designed phase 3 trials, we evaluated how pain interferes with the emotional well-being (affect) and physical function (activity) of these patients.
Materials and Methods: In these completed phase 3, double-blind, double-dummy, placebo-controlled trials, patients were randomized (1:1) to receive denosumab (120 mg SC) or zoledronic acid (4 mg IV, adjusted for renal function) every 4 weeks (ClinicalTrials.gov NCT00321464, NCT00321620, and NCT00330759; sponsor Amgen Inc.). Data from patients with solid tumors in the 2 treatment arms (n = 5543) were pooled for this post-hoc analysis. Pain interference (overall, emotional, and physical) was assessed using the Brief Pain Inventory (BPI)-Short Form (0: no interference to 10: interferes completely) at baseline and each study visit. The impact of 1st on-study SREs, starting 28 days before the SRE, was assessed using a stratified Cox proportional hazards model adjusting for SREs as time-dependent covariates.
Results: On-study SREs were reported for 1925 patients (923 PF; 829 RB, 119 SCC, 54 SB). PF, RB, and SCC were associated with significantly greater risk of pain interference overall; the impact of SB was also greater, but not significantly so (Table). Results were similar for pain interference with emotional well-being. All SRE types were associated with significantly greater risk of pain interference with physical function.

Table: Effect of 1st on-study SREs on time to ⩾2-point increase from baseline in pain interference score*

Pain interference	PF	RB	SCC	SB
Overall (n = 4911)				
HR (95% CI)	1.30 (1.13, 1.51)	2.29 (1.98, 2.66)	2.60 (1.84, 3.68)	1.70 (0.97, 2.98)
P-value	0.0004	<0.0001	<0.0001	0.06
Emotional well-being (n = 4819)				
HR (95% CI)	1.27 (1.10, 1.46)	2.44 (2.12, 2.80)	2.02 (1.41, 2.91)	1.28 (0.73, 2.23)
P-value	0.0012	<0.0001	0.0001	0.39
Physical function (n = 4535)				
HR (95% CI)	1.40 (1.21, 1.62)	2.29 (1.96, 2.67)	2.42 (1.69, 3.46)	2.14 (1.20, 3.81)
P-value	<0.0001	<0.0001	<0.0001	0.01

*Includes patients with baseline BPI score ⩽8.

Conclusions: In general, pain interference was increased in patients who experienced on-study SREs. Effective treatments that prevent SREs may reduce pain interference with patients' emotional well-being and physical function.
Conflict of interest: *Ownership: none. Advisory board: R. von Moos − Amgen Inc., Novartis, Roche, Merck Sharp Dome (MSD), and BMS. C. Cleeland − Genentech, BMS, Exilixis, Merck, J & J, and Amgen Inc. J.J. Body − Amgen Inc. J.E. Brown − Amgen Inc., Novartis, and Bristol, Myers, Squibb. G Marx − Amgen Inc., AstraZeneca, and Sanofi. Board of directors: none. Corporate-sponsored research: R. von Moos − Amgen Inc. and Roche. C. Cleeland − Genentech. Other substantive relationships: R. von Moos − speaker honararia from Amgen Inc., GSK, and Roche. J. J. Body − lecture fees from Amgen Inc. and Novartis. J.E. Brown − consultancy for Amgen Inc. Y. Zhou, A. Balakumaran, and Y. Qian − employees of and hold stock/stock options in Amgen Inc.*

1307 POSTER DISCUSSION

Difficulties in meeting accrual and obtaining adequate follow up in palliative trials: Results from an intergroup randomized trial of single vs multiple fractions (Fx) for re-irradiation (RE-RT) of painful bone metastases (PBM): NCIC CTG SC.20

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Background: The optimal RE-RT dose and fractionation schedule for PBM is uncertain.
Methods: Patients (pts) with PBM after previous radiation (RT) to the same site were stratified by previous Fx schedule and pain response and randomized to 8 Gy in 1 Fx or 20 Gy in 5 Fx. The primary endpoint was overall response rate (RR) at 2 months using the International Consensus schema (Chow 2002) which combines Brief Pain Inventory worst pain score and opioid analgesic use. We tested if 8 Gy was non-inferior (NI), analyzed by intention to treat (ITT) and a per-protocol (PP) sensitivity analysis excluding those who were ineligible, inevaluable or received non-allocated therapy. Sample size was calculated using an expected RR of 70% with 20 Gy and a NI margin of 10% (i.e. upper boundary of 1-sided 95% CI for the RR difference). Patients reported adverse events (AEs) by questionnaire on Day 14.
Results: Between 01/2004 and 06/2012, we enrolled 850 pts from 9 countries. The median age was 65 years old, 59% were male, The Karnofsky performance status was 50 or more in all pts and 17% had no response to prior RT. The median follow-up was 12.2 months (range 0.03 to 15.6 months). The median survival was 8 months with no differences detected between arms (HR = 0.96; P = 0.67). Most common cancers were prostate (27%), breast (26%) and lung (22%). Before the 2 month assessment, 98 (11%) pts died. By ITT, the 2-month RR was available in 66% (557/850) and was 119/425 (28%) with 8 Gy and 136/425 (32%) with 20 Gy (P = 0.2); the upper boundary of the 95% CI for RR difference = 9.2% and is less than the pre-specified NI margin. By PP analysis, 2-month RR was available in 521 and was 117/258 (45.3%) with 8 Gy and 135/263 (51.3%) with 20 Gy (P = 0.17); the upper boundary of the 95% CI for RR difference = 13.2%, which exceeds 10% non-inferiority boundary. Among the 263 pts with a response at month two, 36 had pain progression (16 with 8 Gy and 20 with 20 Gy); the HR for freedom from progression (20 Gy vs. 8 Gy) among these pts was 1.05 (95% CI: 0.55 to 2.04). Day 14 AEs differing by treatment were: lack of appetite (P = 0.01), vomiting (P = 0.001), diarrhea (P = 0.02) and skin reddening (P = 0.002); all were worse with 20 Gy.
Conclusions: In pts with PBM receiving RE-RT, the 2-month RR obtained with 8 Gy is non-inferior to 20 Gy when assessed by ITT but findings were not robust to a PP sensitivity analysis. When choosing between options tested, trade-offs exist between pain response and acute toxicity.
No conflict of interest.

1308 POSTER DISCUSSION

Efficacy and safety of anamorelin HCl in NSCLC patients: Results from a randomized, double-blind, placebo-controlled, multicenter phase II study

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Background: Cancer cachexia is a multifactorial syndrome, characterized by decreased body weight (BW) and muscle mass/strength, and associated with worsened morbidity/survival. Anamorelin HCl (ANA), an orally active

ghrelin receptor agonist with orexigenic and anabolic activity, is in development for treating non-small cell lung cancer (NSCLC)-associated anorexia/cachexia.
Materials and Methods: We conducted an international, randomized, double-blind, multicenter Phase II trial to evaluate the effect of ANA on BW and handgrip strength (HGS) (NCT00622193; sponsored by Helsinn). Safety endpoints included adverse event (AE) profile and overall survival; secondary endpoints included IGFBP-3 and Quality of Life (MDASI). Patients with Stage IIIB or IV NSCLC, ECOG performance score $\leqslant 1$, and candidates for treatment with carboplatin/paclitaxel ($\pm$ bevacizumab) were eligible. Patients were randomized 1:1:1 to receive either 50 mg ANA, 100 mg ANA, or placebo (PL) once daily for 12 weeks.
Results: 226 patients were randomized and treated (N = 76 for 50 mg ANA; N = 73 for 100 mg ANA; N = 77 for PL), and 215 patients with at least 1 post-baseline efficacy assessment comprised the Modified Intent-To-Treat (MITT) population for efficacy analysis. A beneficial effect on weight was observed as early as 1 week after ANA treatment. Over 12 weeks, the 100 mg ANA group gained an average of 0.14 kg in BW from baseline, compared to mean losses of 0.3 kg and 1.32 kg for the 50 mg and PL groups, respectively (mean treatment difference between 100 mg ANA and PL was 1.47 kg; $p = 0.0005$). For HGS, the mean treatment difference between 100 mg ANA and PL was 0.58 kg, but was not statistically significant. ANA was safe and well-tolerated in this study, and AEs of anorexia, nausea, and fatigue were reported in fewer ANA-treated than PL-treated patients. There was no statistically significant effect on long-term overall survival in the 50 mg or 100 mg ANA groups compared with PL. ANA also increased IGFBP-3, a marker of drug activity ($p < 0.0001$ for both treatments vs placebo). MDASI total and domain scores improved in the 100 mg ANA group, but were not statistically significant.
Conclusions: ANA significantly increased BW, had a neutral effect on survival, and showed an overall favorable safety/tolerability profile. Directional improvements in HGS and QoL were also observed. These data support further investigation of ANA for treating NSCLC anorexia/cachexia.
Conflict of interest: *Corporate-sponsored research: J. Temel, S. Bondarde, and M. Jain received funding from Helsinn to conduct this study. Other substantive relationships: S. Allen and W. Mann are employees of Helsinn, which funded this study.*

1309 POSTER DISCUSSION

Do methylprednisolone 32 mg provide pain relief, improve fatigue and appetite in cancer patients using opioids? A randomized, controlled trial

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Background: Corticosteroids (CS) are used as co-analgesics in cancer pain patients. In a systematic review we concluded that CS may have a moderate analgesic effect in cancer pain, but with 'very low' level of evidence. Therefore, this randomized study was conducted to compare the analgesic efficacy of CS to placebo. Secondary aims were to evaluate the effects in analgesic consumption, patient satisfaction, fatigue and appetite.
Material and Methods: Adult cancer patients with average pain last 24 hours $\geqslant 4$ (NRS 0−10) despite ongoing opioid treatment were recruited from five palliative centres in Norway. After randomization, the patients received methylprednisolone 16 mg twice daily or placebo for seven days in a double-blind design. Primary outcome was average pain intensity on day seven (NRS 0−10); secondary outcomes were analgesic consumption (oral morphine equivalents (OME)), overall satisfaction (NRS 0−10), fatigue, and appetite (EORTC QLQ-C30 (0–100)). Sample size estimation required 22 patients in each group to show a clinical significant difference of 1.5 (NRS 0−10) with a $p < 0.05$ and a power of 0.90.
Results: A total of 592 patients were screened from April 2008 to January 2012. Fifty patients were recruited, 47 completed the study. Forty seven patients had metastatic cancer disease; mean Karnofsky index was 66 (0–100), and mean analgesic consumption 218 mg OME. On day seven there were no differences in average pain intensity (CS: 3.6, (CI: 2.8−4.4); placebo 3.7 (3.0−4.4)) or in change in opioid consumption (day seven versus baseline: CS 1.19 (1.00–1.38); placebo 1.20 (0.90–1.51)). CS improved both fatigue (CS: −17 (−27 − −6); placebo 3 (−5−11) ($p < 0.01$)), and appetite (CS: − 24 (−38 − −11); placebo 2 (−8−11) ($p < 0.01$)). Overall satisfaction was 5.4 (4.1−6.7) in the CS versus 2.0 (0.7−3.3) in the placebo group ($p < 0.01$).
Conclusions: Methylprednisolone 32 mg daily did not improve pain or decrease analgesic consumption in cancer patients with advanced disease using opioids. The patients treated with CS reported better treatment satisfaction and clinically significant improvement in fatigue and appetite compared to the placebo group.
Funding: Telemark Hospital Trust
No conflict of interest.

1310 POSTER DISCUSSION

Health-related quality of life in small-cell lung cancer: a systematic review on reporting of methodological and clinical issues in randomized controlled trials

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Purpose Small-cell lung cancer (SCLC) represents approximately 15% of all lung cancers and increasingly health-related quality of life (HRQOL) of SCLC is evaluated in randomized controlled trials (RCTs). The objective was to evaluate the adequacy of HRQOL methodology reporting in SCLC RCTs and its possible impact on clinical decision making.
Material and Methods: A MEDLINE systematic review was performed in RCTs. Eligible RCTs implemented patient-reported HRQOL assessments and oncology treatments for adult SCLC patients. Included studies were published in English between January 1991 and December 2012, with sample size $\geqslant 100$ and patient age $\geqslant 18$.
Results: Thirty RCTs out of seventy-nine studies were classified as eligible, involving over 10,000 patients. HRQOL was a secondary endpoint in 29 RCTs of which 53% reported no significant difference in overall survival (OS). A benefit of HRQOL was reported in 85% of the positive-outcome trials, and in 44% of the negative-outcome trials. Significant improvements in HRQOL were seen when standard platinum-based regimens were compared with: a) irinotecan and carboblatin, b) ifosfamine, carboplatin, etoposide and vincristine. A priori hypothesis on the expected overall HRQOL outcome was defined in 27% of the RCTs. Baseline HRQOL assessment was stated as mandatory in 14% of the RCTs. Tests of statistical significance were applied in 90% of the RCTs and missing data were discussed in detail in 30% of the trials.
Conclusions: While the overall reporting of HRQOL was of acceptable standards, some improvement in reporting RCTs could be encouraged. HRQOL assessment in SCLC RCTs clearly provides major added information in studies where no OS difference is found, but more importantly provides valuable information for these treatments where better HRQOL was associated with OS benefit.
No conflict of interest.

1311 POSTER DISCUSSION

Understanding quality of dying in a hospital

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Background: Quality of dying (QOD) is a multi-dimensional concept that includes physical, psychosocial and existential experiences, life closure, death preparation, circumstances of death, and experiences of care. We studied how relatives of cancer patients who had died in a hospital experienced QOD regarding these dimensions.
Material and Methods: Between June 2009 and February 2011 each adult cancer death at non-IC units in a university hospital was followed by an invitation to relatives, sent 10−13 weeks later, to answer a questionnaire. Relatives were asked to rate QOD overall on a 0−10 numeric rating scale; furthermore, they valuated their experiences in the different domains of QOD on verbal scales, which were merged into 2 answer categories before analysis. Data were analyzed with students' t-tests and linear regression analysis.
Results: In the study period, 259 cancer patients died; of 246 patients (95%) relatives could be traced, and 123 participated (50%). Of patients, 60% was male, mean age was 65 years (sd 13), and mean duration of final hospital stay was 12 days (sd 14). The mean score for QOD 6.3 (sd 2.8). QOD scores were higher when the final stay had been longer and relatives were younger. Adjusted for these characteristics, QOD scores were associated with almost all domains, but most strongly with experiences of care. In this domain the most important variables were

those related to participation in decision making (R^2 0.17) and to outcomes of care (R^2 0.21). QOD scores were higher when relatives were satisfied about patient's and relative's involvement in decisions on medical treatment (Mean QOD 6.8 vs 5.4 and 6.8 vs 5.2); when relatives had been informed of the imminence of death (6.7 vs 5.3); when they judged physician's efforts to relieve suffering, and nursing care as sufficient (6.8 vs 4.0 and 6.7 vs 4.0); and when the patient had primarily been approached as a person (7.0 vs 4.9).
Conclusions: On average, relatives rate QOD in hospital was moderately good. Experiences of care are more important in explaining variance in QOD scores than physical, psychosocial, or existential experiences, or circumstances of death. Therefore, improvements in end of life care can be achieved by clinical staff through being present, providing information, listening, and shared decision making.
No conflict of interest.

Poster Session (Mon, 30 Sep)
Symptom Science

1312 POSTER

Haemoglobin outcomes with biosimilar epoetin alfa in the management of chemotherapy-induced anaemia in cancer patients: first results from OnCoBOS, a French observational study

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Background: OnCoBOS is an ongoing, national, prospective, multicentre, observational study of the use of biosimilar epoetin alfa (Binocrit®) for the treatment of chemotherapy-induced anaemia (CIA). Here we present an evaluation of haemoglobin (Hb) outcomes in 444 patients treated (2000 scheduled) in France.
Patients and Methods: We analysed 444 cancer patients with CIA treated with biosimilar epoetin alfa in 75 centres in France. Data were collected at treatment start and 3−4 weeks (W3−4) and 12 weeks (W12) later. Hb outcomes assessed included the proportion of patients achieving a Hb increase of $\geqslant$1 and $\geqslant$2 g/dL, and the mean Hb change from baseline in the subsets of patients with a baseline Hb $\leqslant$9 and 9.1−10 g/dL.
Results: Median (range) age was 67 (18−93) years and 59.3% of subjects were male. Mean±SD Karnofsky score was 77.9±13.2. 77.5% of patients had solid tumours, including lung (22.1%), breast (13.4%), and colorectal cancer (12.8%), mainly stage 3 or 4 (59.3%); and 22.5% had haematological malignancies including non-Hodgkins lymphoma (55.0%) and multiple myeloma (24.0%), again mainly stage 3 or 4 (77.7%). Overall, 64% of patients had metastatic disease. Mean±SD Hb at biosimilar epoetin alfa initiation was 9.6±0.9 g/dL. Mean±SD biosimilar epoetin alfa starting dose was 32793±5147IU/week; the dose at W12 was 32605±6359IU/week. At W3−4 11.9% of patients received intravenous iron. Mean±SD Hb increased to 10.6±1.4 g/dL at W3−4 and 11.2±1.5 g/dL at W12 ($p < 0.001$ vs baseline). In patients with a baseline Hb $\leqslant$9 and 9.1−10 g/dL, the mean Hb change from baseline at W12 was 2.1 and 1.4 g/dL, respectively. 74.8% of patients achieved a Hb increase $\geqslant$1 g/dL during the study, and 47.8% achieved a Hb increase $\geqslant$2 g/dL. 81.3% of patients were able to continue their chemotherapy without delays or dose reduction. Only three patients experienced an adverse drug reaction, none of which were serious.
Conclusions: These data indicate the real-life clinical effectiveness and safety of managing CIA with biosimilar epoetin alfa (Binocrit®). The results reflect the ability to safely correct anaemia and maintain Hb, in line with current recommendations, using a weekly dose regimen. In agreement with European recommendations, treatment with an erythropoiesis-stimulating agent was not restricted to patients with metastatic disease.
Conflict of interest: *Corporate-sponsored research: J.D, O.S, JC.L, A.T, C.D, JC.I, H.O and G.B − This study is sponsored by Sandoz Biopharmaceuticals. Other substantive relationships: C.A-O and RF.S are employees of Sandoz Biopharmaceuticals*

1313 POSTER

Prospective observational study on chemotherapy-induced nausea and vomiting (CINV) for cancer patients who were to receive moderately and highly emetogenic chemotherapy (MEC and HEC) and primary care medical staffs' perception on CINV by the CINV Study Group of Japan

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Background: There has been no nationwide survey on CINV and validation of the guideline made in Japan after introduction of NK-1 receptor antagonist to the market. The aim of the study is to investigate occurrence of CINV in cancer patients (pts) who are to receive chemotherapy for the first time, and primary care medical staffs' perception on CINV for their pts.
Methods: A nationwide survey on CINV was conducted by the CINV Study Group of Japan. 108 institutions participated in the study which was approved by the review board. The written consent was obtained from the pts. A 7-day diary for CINV was provided to the pts prior to MEC and HEC to record daily occurrence and severity of CINV and an amount of food intake. Acute and delayed CINV was defined as nausea and vomiting which developed within or after 24 hours after the start of chemotherapy, respectively. The medical staffs also filled out questionnaires to estimate their pts' CINV.
Results: A total of 2068 pts were registered from April 2011 to December 2012. The number of pts' diary paired with their staffs' report was 1925 after pts received HEC or MEC. Underlying diseases were gastrointestinal (651 pts), lung (429 pts) and breast cancer (433 pts), and gynecological (215 pts) and hematological malignancy (197 pts). There were 883 males with a median age of 65 (range: 19−87) and 1042 females with a median age of 59 (range: 21−87). MEC was given to 710 pts as was HEC to 1215 pts. Acute vomiting was noted in 13 pts with MEC as was in 66 pts with HEC, while delayed vomiting was experienced in 88 pts with MEC and 101 pts with HEC, respectively. Acute nausea was experienced in 49 pts with MEC and in 250 pts with HEC, while was noted delayed nausea in 278 pts with MEC and in 542 pts with HEC, respectively. Combination of 3 antiemetics was given along the guideline to 81% of the pts with CDDP-based regimen and 64% of those with non-CDDP regimen of HEC. The staff estimated that the incidence of acute CINV was 58% and that of delayed CINV was 80% of the pts when pts of HEC and MEC were combined.
Conclusions: Chemotherapy-induced vomiting was well controlled, but delayed nausea remained to be high in both HEC and MEC, and needs further investigation. Non-CDDP regimen of HEC had a high incidence of developing acute CINV, indicating that other treatment modality should be studied. Surprisingly medical staffs overestimated the incidence of CINV suggesting that antiemetic treatment for CINV given to the pts was quite appropriate by the fact that 2/3 to 4/5 of the pts with HEC had received a combination of 3 antiemetics recommended by the Japanese guideline.
No conflict of interest.

	HEC(n = 1215)		MEC(n = 710)
	CDDP-based regimen (n = 666)	non-CDDP based regimen (n = 549)	
2 antiemetics*	129 (19%)	195 (36%)	509 (72%)
3 antiemetics**	537 (81%)	354 (64%)	201 (28%)
Acute			
nausea	55 (8%)	195 (36%)	49 (7%)
vomiting	14 (2%)	52 (9%)	13% (2%)
Delayed			
nausea	283 (42%)	259 (47%)	278 (39%)
vomiting	61 (9%)	40 (7%)	88 (12%)
Medical staff's estimation			
acute CINV	352 (53%)	436 (79%)	325 (46%)
delayed CINV	581 (87%)	411 (75%)	546 (77%)

*: 5HT3 receptor antagonist + dexamethasone. **: * + aprepitant.

1314 POSTER

The efficacy of palonosetron compared with granisetron in preventing chemotherapy-induced nausea and vomiting: A randomized study

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Background: Chemotherapy-induced nausea and vomiting (CINV) are among the most problematic symptoms for patients (pts) with cancer. 5-HT_3 receptor antagonists such as palonosetron (PAL) and granisetron (GRA) are the current standard of care for the prevention of acute CINV. This study aims to assess the efficacy and safety of PAL versus GRA in pts treated with chemotherapy.
Material and Methods: Eligible pts were randomized to receive iv PAL 0.25 mg (GrpA) or GRA 3 mg (GrpB), 30 minutes before theinitiation of chemotherapy on day 1. All pts were also given dexamethasone iv 8 mg before PAL or GRA. Aprepitant was used for pts who received highly emetogenic chemotherapy. The primary efficacy endpoint was to determine the complete response rate (CRR) for acute and delayed emesis. The secondary endpoints were to identify the safety of both medicine and the rescue medication rate. This study was approved by the institutional Research Ethics Board.
Results: A total of 177 pts were assessed in this study.Eightysix pts (45% female) were in the GrpA and 91 pts (41% female) were in the GrpB study arms. The mean age was similar between the two groups (54±12 vs. 56±11; p = 0.245). Gender distribution, the use of cisplatin and the use of a highly emetogenic protocol were indifferent between the groups. For acute emesis, CRR was 73% in the GrpA and 74% in the GrpBgroup (p = 0.492). The rate of rescue medication was similar between the two groups (22% for GrpA and 19% for GrpB; p = 0.706). The most common side effects were diarrhea, constipation, dizziness, headache and fatigue. The frequencies of these side effects were similar between the two groups (p < 0.05 for each variable). In the sub-group analyses that were performed for patients who received cisplatinum and a highly emetogenic chemotherapy regimen, the rates of acute and delayed emesis as well as the rescue medication rates were not different between the two groups (p = 0.136 and p = 0.341, respectively).
Conclusion: Both PAL and GRA have provided similar CRR for patients with CINV in acute and delayed emesis. Moreover, both PAL and GRA could safely be used and they demonstrated similar side-effect profiles, either.
No conflict of interest.

1315 POSTER

Risk factors for severe complications during febrile neutropenic episodes in patients with solid tumors

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Background: Febrile neutropenia (FN) is a frequent complication during chemotherapy in solid tumors, and to identify those patients (pts) with higher risk of developing severe complications during FN episodes is important. Here we aimed to characterize those risk factors for severe complications during FN episodes in pts with solid tumors, admitted for intravenous antibiotics.
Material and Methods: It is a retrospective study of all consecutive pts admitted with FN between May/2008 and May/2012. Eligibility criteria included: age ⩾16 y, the diagnosis of FN (documented axillary temperature greater than 37.8ºC, and neutrophil count <500/mm^3 or expected to fall below 500/mm^3) as an adverse event of chemotherapy for a solid tumor. Potentially life-threatening complications during FN episodes were collected and univariate and multivariate logistic regression analyses were performed to assess the relationships between risk factors and these complications.
Results: 333 FN episodes in 295 pts with solid tumors were studied. Median age was 57 y (16−88), 150 female (51%). Most frequent primary sites included: breast (15%), lung (14%), bone/soft tissues (13%), colorectal (10%), stomach (9%), head & neck (8%) and testis (5%). 31 pts (10%) presented more than 1 FN episode. No GCSF primary prophylaxis was prescribed in 282 pts (85%). At admission, median neutrophil count was 690/mm^3, and the median MASCC score was 19 (7−26). Infection sites were identified as pulmonary (19%), urinary tract (11%), abdominal (10%), bloodstream (8%) and soft tissues (8%), and regarding etiology, Gram-negative bacilli could be isolated in 56 (16%) and Gram-positive cocci in 26 FN episodes (8%). All pts were admitted with a median duration of hospital stay of 10 d (0–106 d). Overall, a severe complication as a consequence of FN was detected in 248 episodes (74%), being hypotension (47%), ICU admission (35%), renal failure (30%), respiratory failure (19%) and altered mental state (17%) the most common (>10%), and 46 pts died (14%). A univariate analysis revealed age ⩾60 y (OR 3.1, 95% CI 1.8−5.5, p 0.0001), controlled cancer (OR 0.5, 95% CI 0.3−0.9, p 0.01), previous COPD (OR 4.5, 95% CI 1.7–11.5, p 0.0016), presence of symptoms (OR 2.2, 95% CI 1.3−3.7, p 0.0063) or dehydration (OR 4.6, 95% CI 2.6−8.3, p < 0.0001) and regular or bad general condition (OR 3.3, 95% CI 1.9−5.7, p < 0.0001) as risk factors for complications. On multivariate analysis, only dehydration (OR 4.1, 95% CI 2.2−7.5, p < 0.0001), previous COPD (OR 3.7, 95% CI 1.3–11.0, p 0.0171) and age ⩾60 y (OR 2.5, 95% CI 1.4−4.6, p 0.0027) were associated with severe complications. The multivariate model correctly classified 75% of all FN episodes as complicated.
Conclusions: Severe complications were common during febrile neutropenic episodes in pts with solid tumors. COPD, age ⩾60 yo and dehydration represent clinically significant risk factors for severe complications in FN pts.
No conflict of interest.

1316 POSTER

Anamorelin's effect on bone mass: beyond the expected outcomes in non-small cell lung (NSCLC) cancer cachexia

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Background: Cachexia is a serious complication of cancer, characterized by decreased body weight and muscle mass/strength, and associated with poor survival. Another consequence of cancer is bone loss (a form of secondary osteoporosis), a major risk factor for fractures. Previously, we reported a Phase II study where anamorelin (ANA), an investigational ghrelin receptor agonist with orexigenic and anabolic activity, significantly increased lean body mass (LBM) and functional performance over 12 weeks. Beyond these cachexia-focused endpoints, we present here post-hoc analysis on bone mass (BM), which support additional benefits of ANA in cancer patients.
Materials and Methods: 82 patients with advanced cancers, ECOG performance score ⩽2 and weight loss ⩾5% within 6 months were enrolled in a Phase II trial (NCT00219817/NCT00267358) sponsored by Helsinn. Patients received placebo (PL, N = 36) or 50 mg anamorelin (ANA, N = 38) once daily for 12 weeks. Body composition (BM, LBM, fat mass and total body mass) by dual-energy X-ray absorptiometry and plasma inflammatory cytokines (CRP, IL-6 and TNF-α) were measured at baseline, 4, 8 and 12 weeks.
Results: At baseline, BM was comparable between groups. Over 12 weeks of treatment, BM continuously decreased in PL patients, while BM loss stopped at Week 4 in ANA patients and then stabilized. At Week 12, mean BM loss from baseline was statistically significantly greater in the PL vs. ANA patients (−0.05±0.103 kg vs. −0.02±0.09 kg, respectively; p = 0.0176). Inflammatory cytokines are important in bone remodeling and cachexia, and ghrelin has been shown to have anti-inflammatory properties. Accordingly, temporal decreases (~45% for CRP and IL-6 and ~25% for TNF-α at Week 12) were noted in ANA- compared to PL-treated patients. While not statistically significant, this generally uniform pattern of a directional decrease in ANA-treated patients was not noted in PL-treated patients.
Conclusions: Decreased BM with bone fractures are major medical concerns for cancer patients. In this study, 50 mg ANA treatment for 12 weeks significantly prevented the loss of BM compared to PL patients; trending decreases in pro-inflammatory cytokines after ANA administration may also be related to maintaining BM and improving cachexia-related endpoints. Since interventions to increase bone content typically require 1 year of exposure, a longer treatment duration may be needed to confirm these observations and could result in bigger increases in BM.
Conflict of interest: *Corporate-sponsored research: J.M. Garcia received funding from Helsinn to conduct this study and is a consultant for Helsinn and Aeterna Zentaris Inc. Other substantive relationships: S.M. Zabbatino is an employee of Medpace. M. Lu, E.M. Duus, and J. Friend are employees of Helsinn, which funded this study.*

1317 POSTER

Short post-infusion scalp cooling time still prevents docetaxel-induced alopecia

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Background: Chemotherapy-induced alopecia (CIA) is a common side effect and its pathobiology remains unravelled (Paus et al. Lancet Oncol 2013). Scalp cooling is practiced to reduce CIA, but optimum post-infusion cooling times (PICT) are unknown. Our previous study showed an unchanged and excellent prevention of CIA during 3-weekly docetaxel chemotherapy after a reduction of PICT from 90 to 45 minutes (vd Hurk et al. Support Care Cancer 2012).
Material and Methods: The objective of this prospective multicentre trial (SCALP3, number NTR1856) was to compare the proportion of hair loss between patients who were randomised between PICTs of 45 or 20 minutes and who received docetaxel (75 or 100 mg/m^2). Secondary outcomes were wig and head cover use, pattern of hair loss, quality of the remaining hairs and tolerance of scalp cooling. Multivariate analyses will be performed to identify patient and chemotherapy characteristics associated with the result, including age, type of hair, liver function, infusion times and previous chemotherapy. Scalp cooling was performed using the Paxman system.
Results: Patient inclusion has been finalised (n = 130), 57% of the patients were men, 11 patients will be excluded from analyses. Proportions of hair loss are not known yet, but preliminary results show that a 45 minutes PICT resulted in 79% of the patients (n = 53) not requiring a wig or head cover, versus 73% in the 20 minutes PICT group (n = 44). Data collection is ongoing for 22 patients in both treatment arms. During the conference final results will be presented, including associated characteristics.
Conclusion: Scalp cooling prevents docetaxel-induced hair loss, even when the PICT is shortened to 20 minutes. Therefore the PICT seems not to be determined by the half life time of the cytotoxic agent. It cannot be excluded that shorter PICTs positively contribute to the efflux of cytotoxic agents from the hair follicle cells into the blood stream, thereby questioning any PICT. The shorter PICT is a major advantage in time investment for patients but also for logistics at day care units. Scalp cooling should be offered on a routine basis when docetaxel monotherapy is given, also in men. The proportion wig use after 45 minutes PICT is in accordance with our previous trial.
Knowledge on the influence of scalp cooling time and the reached temperature on the results will possibly be obtained more accurate and quicker with a new research model in which the patient is her or his own control. This work was supported by Sanofi Aventis.
No conflict of interest.

1318 POSTER

Impact of a two-drug combination regimen for cancer-related cachexia on nutritional, anabolic/metabolic, physical activity, anti-infammatory and quality of life variables

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Background: Cancer progression is characterised by loss of lean body mass (LBM), inflammatory status, metabolic derangements and poor quality of life (QL) which result in cancer-related anorexia/cachexia syndrome (CACS). The aim of the present study was to test the safety and efficacy of a combination treatment (including nutraceuticals, i.e. quercetin, alpha lipoic acid and curcumin) with carnitine + celecoxib for the treatment of CACS. Primary efficacy endpoints were: increase of LBM, resting energy expenditure (REE) and improvement of QL, particularly fatigue. The following were assessed as secondary endpoints: physical performance (tested by grip strength and 6-min walk test, 6MWT), appetite, chronic inflammatory variables (IL-6 and CRP), Performance Status (PS) and Glasgow prognostic score (GPS).
Patients and Methods: Outpatients with advanced cancer at different sites with CACS (i.e. loss of body weight >5% of the pre-illness (or ideal) weight in the last 3 months) received L-carnitine 4 g/day plus Celecoxib 300 mg/day plus nutraceuticals /antioxidants, i.e., quercetin 300 mg/day, lipoic acid 300 mg/day, carbocysteine 2.7 g/day, curcumin 2 g/day (i.e.400 mg/day of active curcuminoids extract (Meriva, Indena, Milan, Italy). Treatment duration was 4 months.
Results: From June 2011 to October 2012, 80 patients with advanced cancer (all stage IV) at different sites were enrolled: 70 completed the treatment and were evaluable (mean age 65±9.6, range 32−82 years). Ten patients did not complete the treatment for death due to disease progression. Results showed a significant increase of LBM and a significant improvement of QL (by EORTC-QLQ-C30), and particularly fatigue (by MFSI-SF). Moreover, an improvement of physical performance assessed by 6MWT as well as a decrease of inflammatory parameters (IL-6 and CRP), ECOG PS and GPS was observed. The treatment was very well tolerated (no grade 3−4 toxicities occurred) and no patient discontinued the treatment due to severe adverse events.
Conclusions: The results of the present study showed that a combined treatment with anti-inflammatory, anabolic/metabolic agents plus antioxidants was able to improve the main nutritional, metabolic and physical activity variables as well as QL of cachectic cancer patients with an optimal safety and cost-benefit profile, so that it may be suggested in the clinical practice as treatment for CACS.
No conflict of interest.

1319 POSTER

A phase II/III, randomized, double-blind, placebo controlled study to investigate the efficacy of a probiotic VSL#3®, on chemotherapy-induced diarrhoea in cancer patients receiving fluoropyrimidines and or irinotecan (interim analysis)

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Background: Chemotherapy induced diarrhoea (CID) is a common side-effect and its treatment is non-specific. VSL#3 a safe supplemental product has shown to be effective in prevention of radiation-induced diarrhoea. Primary end point of this study is to see effect of study medication (VSL#3) or placebo on grade III or IV diarrhoea.
Material and Methods: This Phase II/III double blind placebo controlled study was approved by Institute Ethics Committee and all subjects signed informed consent prior to enrolment. 121 evaluable patients in each arm are needed to demonstrate reduction in grade III or IV CID from 30% in placebo to 15% in study group with 80% power and α value of 0.05. The trial medications were in the form of a sachet for oral use.
VSL#3: It contains 900 billion viable, lyophilized bacteria, 4 strains of *Lactobacillus*, 3 strains of *Bifidobacterium* and 1 strain of *Streptococcus thermophilus.*
Placebo: Identical sachets containing cornstarch. The daily dose is 1 sachet bid. Eligible subjects received either sachets for atleast 14 days before starting chemotherapy and continued till two weeks after the end of cycle 3. CTCAE 3.0 was used for assessment of diarrhoea. We also randomly collected serum (for VEGF, clusterin) and stool (for calprotectin) sample before and at the end of study from subset of study subjects.
Results: Interim results for primary end point are presented after evaluation of 202 subjects without unblinding. Ten patients (10.42%) in group1 and 4 (3.8%) in group 2 developed grade III or IV diarrhoea (p = 0.07). Biomarkers data given in table 1 clearly shows that levels either increased or remained same in group 2 compared to significant reductions in group 1 at the end of treatment.
Conclusion: Interim analysis suggests that incidence of grade III and IV diarrhoea in two groups is significantly lesser than expected and possibly because of this difference between the 2 groups is not evident. However, the biomarkers analysis suggests that levels of biomarkers reduced significantly during treatment in one of the groups (group =1).
Clinical Trial Registry number: CTRI/2009/091/001042
No conflict of interest.

	Mean value		
	Group 1	Group 2	P value
VEGF (pg/ml)			
baseline, N = 15&14	1253±335	1203±273	0.60
end of study, N = 15&14	899±408	1465±285	<0.001
Calprotectin (mg/kg)			
baseline, N = 11&12	395±328	610±114	0.11
end of study, N = 11&12	293±245	605±123	0.001
Clusterin (μ/ml)			
baseline, N = 10&6	156±15	153±18	.83
end of study, N = 10&6	63±17	166±15	0.001

1320 POSTER

Use of erythropoiesis-stimulating agents and comparison of different products for the treatment of chemotherapy-induced anaemia (CIA)

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Background: It is unclear if the most recent recommendations for more conservative use of ESAs to treat CIA are reflected in real-world clinical practice. In addition, there is a paucity of data on the relative effectiveness of biosimilar ESAs and other available ESAs in this setting.
Patients and Methods: This was a retrospective, single-centre audit of the treatment of CIA with ESAs at the largest oncology centre in Spain, and included patients treated by multiple physicians. It included a total of 284 patients with mostly solid tumours, treated with Binocrit® 40,000 IU QW (n = 116) or 30,000 IU QW (n = 14), darbepoetin alfa 500 μg Q3W (n = 99), darbepoetin alfa 300 μg Q2W (n = 2), darbepoetin alfa 150 μg QW (n = 45), or epoetin beta 30,000 IU QW (n = 8).
Results: Overall, the most common tumour types were NSCLC (30%), breast (12%), ovarian (6%) and bladder (5%). 27% of patients received ESA treatment for 4 weeks, and 42% received >4 weeks' treatment. The mean overall haemoglobin (Hb) at start of ESA treatment was 9.3 g/dL; 19% of patients had Hb <8.5 g/dL at the start of treatment, and 42% had Hb <9 g/dL. The mean overall Hb level at the end of treatment was 10.8 g/dL; 54% of patients had Hb in the range 10−12 g/dL, and 68% achieved a Hb >10 g/dL. Comparisons were performed of Hb outcomes according to the different ESA treatments given to patients. There were no significant differences ($p > 0.05$) between the groups in terms of Hb levels at the start of ESA treatment, Hb levels achieved at the end of ESA treatment, and the highest Hb level achieved on ESA treatment. No drug-related adverse events were recorded.

ESA	Mean treatment duration (weeks)	Mean Hb at start of treatment (g/dL)	Mean maximum Hb achieved (g/dL)
Darbepoetin 150 μg QW	4.98	9.0	11.2
Darbepoetin 300 μg Q2W	4.50	9.4	10.6
Darbepoetin 500 μg Q3W	4.68	9.3	10.7
Epoetin beta	6.50	9.6	11.3
Binocrit 30,000 IU	4.57	9.1	10.4
Binocrit 40,000 IU	4.20	9.3	10.7

Conclusions: The use of ESAs in our centre could be described as conservative and safe, and reflects the most recent ESA label change and recommendations for more moderated ESA use in patients with CIA (i.e. use the lowest possible dose and duration of treatment necessary to avoid transfusions). Our data indicate that Hb outcomes are similar for the different ESA products in a real-world clinical practice setting.
No conflict of interest.

1321 POSTER

Nutritional assessment: Who should report and how?

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Background: Malnutrition is common but likely under-diagnosed and adversely affects quality of life and survival. Recognition will improve care and facilitate timely and appropriate nutritional interventions. Local and national diagnostic criteria have been imprecise. Standardized guidelines have been developed to standardize a reliable nutrition assessment tool to identify and grade severity of malnutrition. We aimed 1) to identify prevalence and severity of malnutrition among inpatients who consulted a Registered Dietitian (RD) 2) to compare Nutrition Therapy assessments (NTA) and physician Electronic Medical Records (EMR) notes for diagnosis and severity of malnutrition.
Material and Methods: This study was a quality improvement project. Data included consecutive nutrition therapy assessments in 2009 made by a Registered Dietitian. RD used a standard assessment tool with 6 criteria to assess nutritional status; unintentional weight loss, BMI, visual muscle wasting, nutrient intake, wounds, and laboratory values e.g., pre-albumin, albumin, and transferrin. ⩾2 criteria had to be present for malnutrition. Weight loss (WL) was: moderate if 1−2% WL in 1 week, 5% in 1 month, 7.5% in 3 months, or 10% in 6 months; severe if >2% WL in 1 week, >5% in 1 month, >7.5% in 3 months, or >10% in 6 months. Physician notes were reviewed as to whether malnutrition was reported and/or graded.
Results: 213 NTA were reviewed for 116 patients. Median age 65 years (range 19−94); 57% male; 84% cancer diagnosis. Most common cancers were gastrointestinal 26%, genitourinary 26%, and respiratory 16%. 78% had metastatic disease. 147 (69%) NTA were eligible for RD assessment. Most often requested by physician/physician assistant (51%), dietetic technician (21%), or nurse (18%). Of the 147 NTA, most 99 (67%) identified malnutrition per RD; 55% of them had moderate/severe malnutrition. Malnutrition was usually noted by unintentional WL (59%), low nutrient intake (58%), and low serum albumin (54%). WL was severe in 68%. 60% of physician notes did not document nutritional status; 28% reported moderate/severe malnutrition.
Conclusions:
1. Clinically important (moderate/severe) malnutrition was highly prevalent (42%).
2. Weight loss, albumin level, nutrient intake were the most common malnutrition criteria used by RD.
3. Most physician notes did not formally document malnutrition.

No conflict of interest.

1322 POSTER

Oral nutritional support can shorten the duration of parenteral hydration in end-of-life cancer patients: A randomized exploratory trial

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Background: Varied symptoms such as anorexia and vomiting reduce oral intake in end-of-life cancer patients. Thus, nutritional support or artificial hydration needs to be initiated in clinical practice. However, these procedures jeopardize patients' quality of life (QoL). The amino acid jelly Inner Power® (IP) does not contain any fat and is easy to drink owing to its taste and semisolid form, proving useful for exhausted people. We conducted a randomised trial to compare the efficacies of IP and a liquid enteral nutrient Ensure Liquid® (EL) in terminally ill cancer patients.
Material and Methods: We randomly assigned patients to 3 arms. We started nutritional support for patients when their oral intake decreased to less than 10% of the normal amount. Patients received nutritional support in 3 arms as per their intakes: EL, supported by EL; IP, supported by IP; and EL+IP, support with EL followed by IP. When the amount of oral intake decreased despite nutritional support, patients received parenteral hydration (500–1000 ml/day). This regimen was continued until patients' death. We recorded the duration of nutritional support, the duration of parenteral hydration, and the amount of oral intake. Primary endpoint was drip infusion in vein (DIV)-free survival, which is defined as the duration from the initiation of nutritional support to the administration of parenteral hydration. Secondary endpoints included overall survival, the duration of parenteral hydration, the duration of nutritional support, adverse events, and QoL.
Results: Twenty-seven patients were enrolled in the study, of which 21 were included in intention-to-treat analysis (EL:IP:EL+IP, 8:5:8). Median age of the subjects was 69 years. Primary tumor sites were the lung (n = 6), hepatobiliary (n = 5), breast (n = 4), colorectal (n = 3), head and neck (n = 2), and cervix (n = 1). There was a significant difference between the 3 arms with regard to DIV-free survival (EL, IP, and EL+IP time was 0.5, 6.0, and 4.5 days, respectively; $P = 0.050$). Overall survival was 7, 9, and 8 days in the EL, IP, and EL+IP arms, respectively. The IP arm showed better QoL scores for fatigue and global health and low occurrence rates of adverse event in nausea.
Conclusions: IP can shorten the duration of parenteral hydration in terminally ill cancer patients and does not affect their survival.
No conflict of interest.

1323 POSTER

Transdermal fentanyl vs oral oxycodone+naloxone prolonged release: Efficacy in pain control for stage IV cancer patients

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Background: The Breakthrough cancer Pain (BTcP) is a transitory exacerbation of pain that occurs on a background of otherwise stable pain in an oncologic patient receiving chronic opioid therapy. The management of BTcP episodes require on-demand opioid (e.g., immediate-release morphine or rapid-onset fentanyl) in addition to the baseline (regular) opioid therapy. The aim of this study is to assess the pain control in metastatic cancer patients receiving either transdermal fentanyl or oxycodone+naloxone prolonged release tablets, through the evaluation of the frequency of BTcP episodes in these patients.
Methods: An observational study to assess the frequency of BTcP episodes in patients with metastatic disease receiving either transdermal fentanyl (25 mcg/h every 72 hours) or oral oxycodone+naloxone prolonged release tablets (30 mg/die). Rapid onset fentanyl (buccal or nasal at equidoses) were provided as rescue medication for Breakthrough pain. Patients were asked to record when they took additional medication for incident pain.
Results: Baseline characteristics = N patients: 132; men: 60%; mean age: 61.05 years; ECOG 1: 70%. Main location of the primary tumor: breast (44%), lung (25%), colon/rectum (17%), head and neck (14%). 60 patients were treated with transdermal fentanyl 25 mcg/h (45%), 72 with oxycodone+naloxone prolonged release tablets 30 mcg/die (55%). In the fentanyl group, patients used more on-demand opioid than the oxycodone+naloxone group (54% vs 42%; $p = 0.0005$) and a sizeable proportion of patients required upward titration of opioids (47% required at least one fentanyl dose change and 27% at least one oxycodone+naloxone dose change; $p < 0.05$).
Conclusions: Clinical practice confirms significant improvement in preventing BTcP episodes in metastatic disease with oral oxycodone+naloxone compared to trandermal fentanyl. Furthermore, we observed that the efficacy of the patch is shorter than 72 hours (in a range between 4 h − 60 h) and that in some clinical occurrences (e.g., hyperhidrosis, altered thermoregulation) transdermal opioids are less effective than oral formulations.
No conflict of interest.

1324 POSTER

Current emesis patterns of chemotherapy and antiemetic treatments in Western Europe

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Background: Cytotoxic treatments and supportive care to prevent chemotherapy-induced nausea and vomiting (CINV) vary across key cancers and countries in Western Europe, which may influence patient outcomes. This study describes the latest use of chemotherapies and antiemetic regimens in clinical practice across five countries.
Methods: For this study IMS Oncology Analyzer™ (OA) was used, a patient database collected through a quarterly physician panel survey. OA reports on patient case history information related to the treatment of patients across all cancer types. The most recent data (January-December 2012) in France, Germany, Italy, Spain and UK was used.
Results: From a total sample of 58,619, 37,444 patients were identified as being treated with chemotherapy. Among them, 22,145 (59.1%) received an antiemetic. 73.5% of patients were ⩾56 y. Overall, patients were mainly diagnosed with Colorectal (14.9%), Breast (11.7%) and Non-hogdkin lymphoma (NHL) (11.6%). 36.7% of patients received high-emetogenic chemotherapy (HEC), 41.2% moderate-emetogenic chemotherapy (MEC) and 21.5% low/minimal-emetogenic chemotherapy (LEC) −0.6% not specified-.
In HEC, 71% of chemotherapies contained a platinum compound. The antiemetic treatment used the most was Ondan±Dex (30.9%) and 25% of HEC patients received Aprepitant. HEC were mainly used in Non-small cell lung cancer (22.1%) and Breast (17.3%). In MEC, 19% of chemotherapies contained an anthracycline and cyclophosphamide. The main antiemetic treatment was still Ondan±Dex (28.6%) and only 5.4% of patients received Aprepitant. MEC were mainly used in Colorectal (30%) and NHL (23.9%). In LEC, 19% of chemotherapies contained a taxane. Only 1.3% of patients received Aprepitant. The anti-emetic treatment used the most was Dex (14.9%). LEC were mainly used in Multiple Myeloma (20.8%) and Pancreas (17.5%).
Focusing on Breast cancer, HEC and MEC were mainly used in Stage II and III (75.1% and 59.6% respectively), whereas LEC were mainly used in Stage IV (61.9%).
Conclusions: Nearly 60% patients treated with chemotherapy received a treatment for CINV in Western Europe. Over 75% of patients received a HEC or MEC. Emetogenic level of chemotherapies used depend on the tumor types but also on the stage of the disease; aggressive chemotherapies can be used mainly in early stages as in Breast cancer. Usage of setrons and aprepitant differ also across countries, key cancers and types of chemotherapy.
Ondan: ondansetron, Dex: dexamethasone
No conflict of interest.

1325 POSTER

Comparison of CKD-EPI, MDRD and Cockcroft-Gault to estimate baseline renal function in patients with head & neck and thoracic cancers

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Background: Estimation of renal function is essential in patients (pts) treated with cisplatin (DDP). We aimed to compare the estimated glomerular filtration rate (eGFR) according to different methods and also to verify the incidence of acute renal failure (ARF) after DDP in pts diagnosed with head & neck and thoracic cancers.
Materials and Methods: Uniinstitutional, retrospective and exploratory study. All pts were >18 y, diagnosed with head & neck or thoracic cancer, and were treated with DDP, at least for one cycle. DDP was administered in NS 500 mL in 60 min, following NS 1000 mL, KCl 25 mEq, $MgSO_4$ 100 mg and manitol 20 g. Baseline eGFR was calculated using Cockcroft-Gault (CG), Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. ARF was defined as elevation of serum creatinine ⩾0.3 md/dL, or more than 50%.
Results: 157 pts were included: median age 58 y (26−78), 68% male. Lung (61%), larynx (13%), oral cavity (8%) and oropharynx (8%) were the most common primary sites. Median weight was 60 kg (36–107), and BMI 22.7 kg/m^2 (13.2–39.3). First DDP cycle was administered to all 157 pts, the second to 154 pts, the third to 127 pts and 91 pts received the fourth one. Median DDP dose was 80 mg/m^2 for all cycles. Median baseline serum creatinine was 0.75 mg/dL (0.46–1.76) and it increased to 0.78 (0.40–1.51, p = 0.044, t-test), 0.80 (0.42–1.68; p = 0.005) and 0.77 (0.41–1.69, p = 0.075) after each DDP dose. At baseline, median eGFR (ml/min/1.73 m^2) was 86 (34–175)(CG), 107 (44–226)(MDRD) and 100 (45–145)(CKD-EPI). Considering normal eGFR as >90(CG), >125 (MDRD) and >100 (CKD-EPI), according to ROC analysis, the agreement between MDRD and CG was fair (k=0.291) and between MDRD and CKD-EPI was moderate (k=0.553). Bland-Altman analysis revealed that CG overestimates eGFR in comparison to MDRD (+19) and to CKD-EPI (+11). Overall, the incidence of ARF was low: 9 pts (6%), 11 pts (8%) and 1 pt (1%) after first, second and third cycles, respectively.
Conclusions: In comparison to MDRD, both CG and CKD-EPI overestimate eGFR, and the agreement between these equations is not good. CG should be used with caution as the reference eGFR in these pts.
No conflict of interest.

1326 POSTER

A probability/risk matrix of febrile neutropenia to select patients for G-CSF primary prophylaxis

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Introduction: Current guidelines suggest a risk threshold of 20% for G-CSF primary prophylaxis (PP) in patients with solid tumors. Individual factors that increase the risk of FN are considered when chemotherapy

yields a medium rate of FN (10−20%). This recommendation does not address the qualitative impact of FN. A probability/risk matrix could improve the prevention of severe episodes.
Patients: An ambispective study of cases with solid cancer and FN was carried out in 15 Spanish hospitals between 2006–2013. The risk factors (RF) that were available before chemotherapy initiation were used to create a vulnerability index (VI): low risk (0 RF), medium risk (1−2 RF) and high risk (⩾3 RF). We classified the cases on a 3x3 table, according to the probability of FN (<10%, 10−20%, >20%) and the VI.
Results: We reviewed 734 cases of FN. We found 207 complications (28.5%) and 27 deaths (3.7%). The independent baseline predictors of complications were COPD (OR 2), cardiovascular disease (OR 2.4), ECOG PS ⩾2 (OR 2.6) and palliative setting (OR 1.4). Rates of complications and deaths according to the VI and the predicted myelotoxicity are shown in Table 1. Of note, the use of G-CSF PP increased in parallel to the expected myelotoxicity of the regimen: 6%, 21% and 61% ($p < 0.0001$), but not in relation to the VI.
Conclusions: This study identified risk factors for severe neutropenic complications and mortality before chemotherapy initiation, with potential implications for prevention. It remains a priority to classify the patients on basis of the likelihood of FN and their individual vulnerabilities.
No conflict of interest.

Table 1. Complications and deaths

VI % FN	Low risk	Medium risk	High risk	n	p-value
Complications					
<10%	4/20 (20%)	35/97 (36%)	13/17 (76%)	134	<0.0001
10−20%	27/165 (16%)	65/239 (27%)	34/50 (68%)	454	<0.0001
>20%	14/84 (17%)	13/53 (25%)	2/3 (67%)	140	0.1
Deaths					
<10%	0/20	4/97 (4%)	6/17 (35%)	134	0.006
10−20%	1/165 (1%)	10/239 (4%)	3/50 (6%)	454	0.01
>20%	0/84	1/53 (2%)	2/3 (67%)	140	0.08

1327 POSTER

Effect of food and age on the pharmacokinetics of NEPA (a fixed-dose combination of netupitant and palonosetron) in healthy volunteers

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Background: The incidence of cancer is highest among the elderly and chemotherapy-induced nausea and vomiting has an adverse impact on their quality of life and compliance with therapy. NEPA, an oral fixed-dose combination of netupitant, a new NK_1 receptor antagonist (RA), and palonosetron, a pharmacologically distinct 5-HT_3RA, targets dual antiemetic pathways with a single-dose administration. This trial assessed the effect of food and age on the pharmacokinetics (PK) of NEPA.
Material and Methods: This was an open-label, randomized, two-way, cross-over trial (EudraCT 2010–020436−20). NEPA (300 mg netupitant + 0.5 mg palonosetron) was administered to healthy volunteers (⩽45 years) after an overnight fast of ⩾10 hours (fasted condition), or following a high-fat breakfast (fed condition). Cross-over took place after 28 days. A parallel group of healthy volunteers (⩾65 years) received NEPA in the fasted state. PK parameters of netupitant and palonosetron were calculated in the fasted and fed condition, as well as in elderly and younger volunteers in the fasted condition. Safety and tolerability were evaluated.
Results: 24 adult (22−45 years) and 12 elderly (66−79 years) volunteers were enrolled in the study. Food had no effect on the PK of palonosetron. In the fed state, netupitant maximum plasma concentration and overall plasma exposure increased by 18% and 16%, respectively, compared with the fasted condition (C_{max}: 635.0 vs. 539.3 μg/L and AUC_{inf}: 21271 vs. 18344 h*μg/L, respectively). This increase in netupitant exposure is not considered clinically relevant. Compared to younger, elderly volunteers showed an increased exposure to netupitant [C_{max}: 36% (735.4 vs. 539.3 μg/L); AUC_{inf}: 25% (22913 vs. 18344 h*μg/L)] and to palonosetron [C_{max}: 10% (839.5 vs. 760.1ng/L); AUC_{inf}: 37% (44414 vs. 32445 h*ng/L)], which was not considered clinically relevant. All reported treatment-emergent adverse events (TEAEs) were of mild and moderate intensity. TEAEs were more frequent in elderly volunteers (91.7%), as well as in the fed vs. fasted condition (47.8% vs. 34.8%). Overall, most common TEAEs were constipation (47%) and headache (33%). No deaths and no serious adverse events occurred during the study.
Conclusion: The changes in the PK profile of NEPA are not considered clinically relevant and, consequently, dose adjustments are not expected with regards to food and age. Overall, NEPA was safe and well tolerated.
This completed study was sponsored by Helsinn Healthcare SA.
Conflict of interest: *Other substantive relationships: SC, CL, MG: Helsinn Healthcare SA employees KK: The trial was sponsored by Helsinn and conducted at the Clinical Research Organization which received payment for the conduct of the trial. The co-author was an employee of the respective CRO at the time of the conduct of the trial.*

1328 POSTER

Prevalence of iron deficiency in severe anemia for cancer patients visiting the emergency unit for acute onset symptoms

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Background: Anemia in cancer is a common biological abnormality and etiological research is often not conducted. Iron deficiency is rarely explored. The objective is to determine the prevalence of absolute (A) or functional (F) iron deficiency (ID) in severe anemia for cancer patients.
Materiel and Methods: All cancer patients who visited the emergency unit for acute symptoms were included prospectively during 3 months if hemoglobine level was <10 g/dl. Three groups were defined using serum ferritin (SF (ng/ml) and transferrin saturation (TSAT): Absolute ID: TSAT<20% and SF<30; status unknown for ID (UID) (functional ID): TSAT<20% and SF>30 ng/ml and a group without ID (WID): TSAT >20%.
Results: Severe anemia was observed for 85 patients; 5% of the patients had AID. Asthenia and dyspnea were reported in 76% and 62% of the patients, respectively. A gastrointestinal localization was found for only 50% of the patients with AID. Anemia had another cause than ID in 19%. ID status was difficult to define for 76.5% of the patients (CS<20%, SF>30). For 66% of the patients in UID, inflammatory syndrome (C reactive protein >60 mg/l) might explain the functional ID, but for the remaining patients (34%), there are probably other explanations for the TSAT less <20%.
Conclusions: Absolute ID was rarely observed in cancer patients visiting for acute onset symptoms. There are more than 3/4 of the patients with an ID status difficult to determine and the reticulocytosis response after an iron supplementation could be of help for diagnosis and understanding the underlying mechanisms.
No conflict of interest.

1329 POSTER

Factors associated with mortality rates of patients with advanced cancer admitted to a specialized intensive care unit

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Background: Cancer patients often need intensive care to recover from drug- related toxicities, infections or other clinical complications. Proper selection of cancer patients who could benefit from such care would spare resources and avoid overtreatment of patients with poor prognosis. We aim to evaluate the prognostic factors associated with mortality rates of these patients during hospitalization in an Intensive Care Unit (ICU) and within 30 days after hospital discharge.
Material and Methods: All cancer patients with advanced solid tumors admitted in an ICU of a comprehensive cancer center were retrospectively evaluated in a 6-month period. We extracted the following data from the last medical visit before hospital admission: tumor type, performance status (PS), body mass index (BMI), renal and liver function, hemoglobin, cancer treatment, and number of days from the last cancer therapy. Results of laboratory tests at ICU admission were also collected. A multivariable logistic regression model was performed to evaluate potential predictors of mortality during hospitalization and after 30 days from hospital discharge. Variables were considered statistically significant if two-sided *P* values <0.05.
Results: From May 2012 to Oct 2012, 627 patients were admitted to ICU and 338 were eligible. Median age was 60.0 years; 257 (76.0%) were metastatic. Gastrointestinal was the most common primary site (30.2%). Half of patients had a poor PS (ECOG⩾2) and 16.6% were malnourished (BMI⩽18.5). Any degree of renal and liver impairment was found in 33.8% and 7.1% of patients, respectively. One-fourth (20.4%) had received two or more lines of therapies against cancer. The mortality rate was 38.8% during ICU period and 59.2% when considering the whole hospitalization. Of the 132 discharged patients, the 30-day mortality rate was 21.2%.

The multivariable analysis demonstrated that hypoalbuminemia (OR=3.93; 95%IC: 1.58–9.79) and high levels of arterial lactate (OR=1.84; 95%IC: 1.03–3.30) collected at ICU admission were significantly related to death during hospitalization.
Conclusions: In this large retrospective analysis, the mortality rate of patients with advanced cancer admitted to a specialized ICU is high, what shows the poor prognosis of these patients. Hypoalbuminemia and high level of arterial lactate at ICU admission were associated with death during hospital recovery. The indication of ICU to cancer patients should be carefully discussed.
No conflict of interest.

1330 POSTER

Chemotherapy-induced neutropenia and febrile neutropenia during chemotherapy for gynaecologic malignancy

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Background: Chemotherapy-induced neutropenia seemed to be a relevant problem in clinical practice. Febrile neutropenia (FN) seemed to be one of medical emergency in cancer treatment. In this study, we investigated chemotherapy-induced neutropenia recently performed in patients with gynaecologic malignancy.
Methods: Between January 2009 and December 2011, we examined our reported chemotherapy-induced neutropenia using the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0. We analysed the incidence and clinical features of chemotherapy-induced neutropenia (grade4: absolute neutrophil count <500 /μL) and febrile neutropenia in patients with gynaecologic malignancy.
Results: During this period we administered over 1614 infusions (29 regimens) to 291 patients with gynecologic malignancy. Median age was 60 years (24−84). Neutropenia occurred in 147 (50.5%) patients over 378 (23.4%) chemotherapy cycles. Febrile neutropenia occurred in 20 (6.9%) patients over 25 (1.5%) cycles. FN occurred after cycle 1 in 14 (56%) cycles. Mean duration of neutropenia and fever was 3.6 (1−12) and 3.4 (1−9) days respectively. The source of fever was unexplained by exam or cultures in 15 (60.0%) cycles. 5 patients (25%) had bowel resection history. There were two neutropenic-related death cases. Neutropenia was associated with elderly age (over age 70) ($p < 0.0001$), less than five previous chemotherapy cycle ($p = 0.02$), disseminated disease ($p = 0.03$), platinum-based regimens ($p < 0.0001$), taxan-containing regimens ($p < 0.0001$) and combined therapy ($p < 0.0001$). Febrile neutropenia was associated with poor performance status ($p < 0.0001$), no previous chemotherapy ($p < 0.05$), disseminated disease ($p < 0.0001$) and distant metastatic disease ($p = 0.03$). Both neutropenia and febrile neutropenia were not related with bone marrow metastases or previous radiotherapy.
Conclusions: By estimating risk factor of febrile neutropenia such as performance status and progression of disease, safe management of chemotherapy-induced neutropenia may be possible in patients with gynaecologic malignancy.
No conflict of interest.

1331 POSTER

Evaluating the impact of a new oncology consultant ward round

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Background: Regular consultant ward rounds have been shown to reduce length of stay and improve discharge planning for patients. The Royal College of Physicians advises regular morning consultant led ward rounds for medical patients. Balancing the competing demands of outpatient activity and inpatient oncology specialist care has been difficult in our hospital. Previously there was no timetabled consultant ward round for oncology inpatients at our hospital. Inpatients were managed primarily by oncology specialist trainees, qualified in internal medicine, with ad-hoc review by their named consultant. A regular consultant ward round was introduced for the first time on the 7/1/13. Each consultant was timetabled to give a twice weekly morning ward round, on a rolling rota. Whilst based on the ward they provided cover for all inpatients, regardless of tumour site.
Materials and Methods: To evaluate this intervention, a retrospective case note analysis was undertaken. This included all patients admitted under oncology for the two months preceding and succeeding the new ward round. For each patient the admission date, time to first consultant review, number of consultant reviews, time to discharge after consultant review and discharge date was identified. A staff survey also took place before and after the new consultant ward round. Statistical analysis was performed using Mann-Whitney U or Chi-Squared tests.
Results: 85 patient episodes meeting the inclusion criteria were under the care of oncology between 7/11/12 and 7/3/13. Case notes were available for 63 episodes (74%). The average length of stay significantly decreased from 11 days to 3.5 days ($p < 0.05$). The time to discharge after first consultant review also significantly decreased from 6 days to 2 days ($p < 0.05$). The number of consultant reviews and time to first consultant review remained unchanged (p= not significant). The percentage of patients receiving a consultant review increased, from 54.3% to 71.4%, though this was not statistically significant. However it is likely such a large increase is clinically significant. Medical and nursing staff satisfaction assessed by an online questionnaire and free text survey also improved following the new ward round.
Conclusion: This study suggests that a regular consultant ward round improves length of stay for patients, possibly through more patients having a consultant review and by expediting treatment and discharge decisions after such a review. Further robust work is needed to establish exactly how this is achieved and how best to make the new ward round a permanent feature logistically.
No conflict of interest.

1332 POSTER

Randomized trial to explore indisetron tablets for preventing chemotherapy-induced nausea and vomiting (CINV)/acute-onset diarrhea induced by IRIS/FOLFIRI: An exploratory trial -HGCSG0704-

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Background: Indisetron is a serotonin (5-hydroxytryptamine type 3: 5-HT_3) receptor antagonist that also antagonizes 5-hydroxytryptamine type 4 receptors. Indisetron tablets showed the non-inferiority to ondansetron tablets in terms of efficacy for preventing chemotherapy-induced nausea and vomiting (CINV). Preclinical data administered with irinotecan showed indisetron significantly reduced the stool frequency in mice and inhibited the colonic peristalsis in dogs. We designed a pilot study compared the efficacy and tolerability of indisetron for irinotecan-induced diarrhea, nausea, and vomiting with granisetron.
Material and Method: This study was a pilot, multicenter, randomized, open-label, comparative trial (HGCSG0704). Advanced colorectal cancer patients treated with FOLFIRI or IRIS (Irinotecan + S-1) with or without bevacizumab were enrolled in this study. Treatment: Arm A: indisetron tablets po day1. Arm B: granisetron iv day 1. The primary endpoints were the incidence of acute-onset diarrhea and complete protection from vomiting. Secondary endpoints were complete protection from nausea, rate of no rescue therapy and tolerability. Nausea, vomiting and other adverse events (AE) were evaluated using Common Terminology Criteria for Adverse Events, version 3.0.
Results: Between May 2008 and July 2012, 33 patients (pts) were randomized. The study was closed prematurely due to poor accrual. Arm A: 16 pts, arm B 17 pts. Median age A: 68 yrs (55−76), B: 66 yrs (47−78): ECOG PS 0/1: A: 12/4, B: 14/ 3pts. There was no significant difference of the incidence of acute-onset diarrhea between both groups (18.8% [95% CI −0.2–39.5] in A vs 35.3% [95% CI 10.7–59.9] in B, $p = 0.44$). The proportion of pts with complete protection from vomiting was 87.5% in A and 88.2% in B (p=1.00). Similarly, complete protection from nausea and rate of no rescue therapy did not have a significant difference (50.0% in A and 41.2% in B, $p = 0.73$). Severe AE as nausea and vomiting were also similar between two groups. No severe AE induced by 5-HT3 receptor antagonist were observed in both groups.
Conclusions: Although indisetron showed effective and feasible results for preventing CINV induced by regimen containing irinotecan, the proportion of acute-onset diarrhea induced by irinotecan had not improved in indisetron group. Because there were small numbers in this study, the significant difference was not recognized. However, Group A tends to be a low incidence of the diarrhea. Therefore, it may be necessary to prove it in the clinical trial with the larger number.
Conflict of interest: *Advisory board: Yakult Honsha Co., Ltd. Taiho Pharmaceutical Co., Ltd. Chugai Pharmaceutical Co., Ltd. Merck Serono Pharmaceutical Co., Ltd. Pfizer. Novartis. Sawai. Ono Pharmaceutical. Daiichi Sankyo Co., Ltd. Takeda Pharmaceutical Co., Ltd. Otsuka Pharmaceutical Co., Ltd. Bristol-Myers Squibb Co. Corporate-sponsored research: Taiho Pharmaceutical Co., Ltd. Lilly. Novartis. Yakult Honsha Co., Ltd. Daiichi Sankyo Co., Ltd. Merck Serono Pharmaceutical Co., Ltd. Takeda Pharmaceutical Co., Ltd. Kureha. Other substantive relationships: Synergy International, Inc.*

1333 POSTER

Results of ultrasonic stimulation in oncological patients with leucopenia

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The purpose of the study: Studying the role and assessment of efficiency of ultrasonic stimulation of spleen in oncological patients during chemotherapy complicated with leucopenia.
Objectives: Evaluate the effectiveness of ultrasonic stimulation of spleen in patients with leucopenia receiving polychemotherapy. Suggest indications and terms of ultrasonic stimulation of spleen in leucopenia.
Materials and Methods: The study included 113 patients with a diagnosis of a malignant tumor, complicated by leucopenia receiving specialized treatment in chemotherapy department of National Cancer Research Center in 2010–2011. From the total enrolled patients 24 (21%)- patients were diagnosed breast cancer, 26 (23%)- ovarian cancer, 13 (11.5%)- cervical cancer, 8 (7%)- brain tumors, 7 (6%) − non-Hodgkin's lymphoma. All patients before the beginning of next course or during chemotherapy had complication in the form of reduction in the total number of leukocytes. Indicators of leucocytes ranged from 1.8 to 3.2 and averaged $2.4 \pm 0.03 \times 10?/l$. To activate the production of white blood cells used ultrasonic stimulation of the spleen (USS) 1−2 times per day, 3−6 procedures without the use of corrective and immunostimulatory drugs. Ultrasonic stimulation of the spleen was prescribed in case of reducing the number of leucocytes below $3.0 \times 10?/l$. The effectiveness of treatment was assessed after the third procedure.
Results: In the study of peripheral blood on the third day after the start of the USS were detected increase in the number of white blood cells from 4.5 to $6.0 \times 10?/l$ and up to $11 \times 10?/l$ after treatment ($p < 0.05$). After the stimulation of the spleen in the period from 1 to 6 days 113 (100%) patients had recovery of white blood cells that allowed for a special anti-cancer treatment.
Conclusions: The study shows the usefulness and actuality of the method for further study of the ultrasonic stimulation at leucopenia in oncological patients receiving chemotherapy.
This method can be recommended as an effective and economically unhindered method for stimulating leucopoiesis.
No conflict of interest.

1334 POSTER

Qualitative assessment of dysgeusia in early breast cancer patients undergoing anthracycline or taxane-based standard chemotherapies

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Background: Taste alternations (TAs) during chemotherapy are common and significant complaints of cancer patients potentially leading to poor compliance, malnutrition and decreased quality of life. Although chemotherapy regimens with different toxicity profiles may vary in their impact on TAs, research on this topic has not extensively examined. Therefore, the standard prevention and treatment have not been established. Here we conduct a prospective study to assess not only the prevalence but also the quality of TAs in chemotherapy-naive patients receiving 2 distinct worldwide standard therapies.
Patients and Methods: Japanese female patients with early breast cancer who undergo 4 cycles of FEC (5-fluorouracil, epirubicin and cyclophosphamide) or TC (docetaxel and cyclophosphamide) regimen as adjuvant setting were prospectively enrolled. Patients completed a daily questionnaire, which measures dysgeusia and related adverse effects by using CTCAE criteria. In addition, alternations of 5 basic tastes were qualitatively monitored with 5-category scales consisting of very strong (+2), strong (+1), normal (0), weak (−1) and very weak (−2). These data were collected from 24 and 18 patients who received FEC and TC, respectively.
Results: (1) To assess the sequential alteration of dysgeusia, 21 days of single cycle were separated to 5 short periods; day 1−2, 3−5, 6−8, 9−14 and 15 or later. The frequency of grade 2 dysgeusia in each period was 29%, 25%, 29%, 21%, 8% and 38%, 44%, 56%, 56%, 25% in 1st and 4th cycle of FEC, respectively. On the other hand, TC showed 0%, 44%, 50%, 33%, 0% and 17%, 50%, 58%, 42%, 8% in the same setting. These results suggest that the onset of TAs induced by FEC is prompt and the symptoms prolong with accumulation. In contrast, the adverse symptoms caused by TC may appear more frequent but transient.
(2) The character of TAs developed clearly until 2nd cycle of both regimens. The average score of 5 basic tastes (salty/sweet/umami/sour/bitter) in the 2nd cycle of FEC and TC were 0.48/0.38/−0.43/0.29/0.33 and −0.41/−0.35/−0.59/−0.35/−0.12, respectively. These results support the idea that each taste sensations except umami are emphasized during FEC, while they are potentially diminishing during TC.
Conclusions: This study demonstrates that the features of TAs may differ definitively between anthracyclin-based FEC and taxane-based TC regimen. Further research has yet to be required focusing on individualized management strategies for TAs depending on the type of chemotherapy.
No conflict of interest.

1335 POSTER

Palonosetron plus dexamethasone for the prevention of nausea and vomiting in patients with locally advanced head-neck squamous cell cancer (HNSCC) treated with radiotherapy plus concomitant administration of cisplatin

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Background: Nausea and vomiting still represent relevant issues in patients treated with cisplatin (>50 mg/mq): an unsatisfactory emetic control could negatively affect the patients' compliance with potential detrimental effects in terms of treatment's efficacy. In this study we have evaluated the efficacy of single dose IV palonosetron (0.25 mg) plus dexamethasone (8 mg IV day 1 plus 8 mg PO dd.2−3) in patients with locally-advanced HNSCC treated with standard fractionation radiotherapy (total dose from 66 to 70 Gy) plus concomitant administration of cisplatin 100 mg/m^2 every 21 days.
Material and Methods: From March 2010 to January 2013 we consecutively recruited 43 pts with locally advanced HNSCC. Main characteristics of pts were as follows: M:F 34:9, median age 62.3 yrs (range 54−73 yrs), median ECOG PS 1 (range 0−1). 10 pts (23%) were still alcohol consumers. Primary end points were: Complete Response (CR: no vomiting and no rescue therapy) and Complete Control (CC: CR and no more than mild nausea). These endpoints were evaluated during the acute (0−24 h), the delayed (25–168 h) and overall (0–168 h) phases. A safety evaluation of this antiemetic protocol was also planned.
Results: All recruited patients were evaluated for efficacy and safety. During the acute phase, CR and CC were reported in 84% and 81% of patients, respectively; 86% and 81% of patients achieved CR and CC during the delayed phase; in the overall phase, 81% and 79% of patients experienced CR and CC, respectively. This antiemetic regimen was really well tolerated: 12 pts (28%) experienced G1−2 constipation easily managed by the administration of common laxatives; in 3 pts (7%) was reported G1 headache.
Conclusions: In this study the combination of palonosetron and dexamethasone has proven to be effective and safe to prevent chemotherapy-induced nausea and vomiting in patients with locally-advanced HNSCC treated with radiotherapy plus concomitant cisplatin 100 mg/m^2 administered every three weeks.
No conflict of interest.

1336 POSTER

The efficacy of low dose transdermal fentanyl in opioid-naive cancer patients with moderate and severe pain

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Background: Little was known about the efficacy of low doses of transdermal fentanyl patch(TDF) in opioid naive patients with moderate to severe cancer pain.
Methods: The study was conducted open-label, prospective design from April 2007 to February 2009 in seven tertiary cancer hospitals and 98 patients were enrolled. TDF was started with low dose formulation(12.5 μg/h) and adjusted according to clinical situation. Pain intensity, used TDF doses, adverse events were monitoring over 4 weeks. Data were analyzed by intent-to-treatment(ITT) principle.
Results: Of 98 enrolled patients, sixty-four(65%) patients completed the study. The median pain intensity decreased from 6.0 to 3.0

(p<0.0001) at the follow-up visit. The efficacy of low dose TDF on pain relief was consistently maintained after considering various variables such as sex(p<0.0001), age(p<0.0001), metastasis(p=0003), previous treatment(p<0.0001) and regardless of baseline pain intensity(p<0.0001). The decrease of pain intensity were significantly larger in severe group than in moderate group(mean±SD; 5.10±2.48 vs 2.48±1.56, p<0.0001). There were no differences between two intensity groups in the TDF dose (27.8 μg/h vs 24.8 μg/h, p = 0.423) and mean time (7.5 days vs 7.9 days, p = 0.740) for pain control.
Conclusion: Low dose TDF was effective treatment in cancer pain patients with moderate to severe intensity. Future randomized trials on efficacy of TDF in severe pain and/or optimal starting dose are warranted.
No conflict of interest.

1337 POSTER

Suppression of bone resorption by denosumab is better measured with CTX than with alkaline phosphatase

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Aim: Study design. This was a single centre study to determine the efficacy of a single injection of denosumab in 20 patients with solid tumors, to expand this experience to serum CTX and in other common metastatic tumors. The study ran from 1.6. 2012 to 1.11.2012.
Patients: Patients with radiological evidence of lytic or mixed bone metastases were enrolled into the study as well as patients with a bone isotope scan confirming diffuse bone metastases (N = 20).
Methods: On the morning of dosing, patients received a s.c. injections of 120 mg denosumab. Chemotherapy within 21 days following denosumab treatment, was allowed.
Patients were followed for at least 7 to 28 days; blood samples for alkaline phosphatase and serum CTX were scheduled on days 1, 2, 3, and 4, and then weeks 1, 2, 3. The data were recorded whenever the patient accepted this exam.
Results: The results from this study show that denosumab, a monoclonal antibody with high affinity and specificity to inhibit osteoclasts, was effective in decreasing bone resorption rapidly and for a sustained period of time in patients with all tumor types metastatic to bone. Bone resorption suppression was extensive based on changes from baseline in the measured biochemical markers, notably serum CTX. Normalisation of this bone resorption markers occurred within 4 to 21 days following single s.c. dose of denosumab in 18 out of 19 patients. Bone-specific alkaline phosphatase levels were only mildly and lately suppressed, confirming that denosumab does not have a direct effect to inhibit osteoblasts.
Conclusions:
1. The effect of denosumab can be easily followed by measuring serum CTX and the use of alkaline phosphatase can no longer be uphold.
2. CTX decreased with denosumab even in zoledronic acid pretreated patients.

No conflict of interest.

1338 POSTER

Predicting adverse outcomes after cisplatin administration in head & neck and thoracic cancer

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Background: Renal failure after cisplatin(DDP)-based chemotherapy is a harmful adverse event. Although different equations are used to estimate glomerular filtration rate (eGFR), there is no evidence supporting superiority of one over another in cancer patients (pts). We compared three equations: Cockroft-Gault (CG), Modification of diet in renal disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) in a population of cancer pts, after one cycle of DDP. We aimed to investigate if a decrease in eGFR using these equations could predict negative endpoints: death, dialysis or acute kidney failure (ARF).
Materials and Methods: Uniinstitutional, retrospective and exploratory study. All pts were >18 y, diagnosed with head & neck or thoracic cancers, and were treated with DDP, at least for one cycle. Acute renal failure (ARF) was defined as elevation of serum creatinine ⩾0.3 mg/dL, or more than 50%. We defined treatment-related deaths if they occurred in the first 28 days after DDP exposure.
Results: 157 pts were analysed. First DDP cycle was administered to all pts, the second to 154 pts, the third to 127 pts, and 91 pts received the fourth one. Median DDP dose was 80 mg/m^2 for all cycles. At baseline, median eGFR (ml/min/1.73m^2) was 86 (34–175)(CG), 107 (44–226)(MDRD) and 100 (45–145)(CKD-EPI). After first DDP administration, according to ROC analysis, cutoff values of eGFR reductions were calculated as follows (ml/min/1.73m^2): 10 (CG; sensitivity 78%, specificity 72%, AUC 0.816, 95% CI 0.74–0.88, p = 0.0001), 8 (CKD-EPI; 72%, 76%, 0.75, 0.67–0.82, 0.0003)and 20 (78%, 89%, 0.83, 0.76–0.90, 0.0001), respectively. No differences regarding ROC curves in detecting the studied outcomes were seen: CG vs. CKD-EPI (p = 0.971), CG vs. MDRD (p = 0.529) and CKD-EPI vs. MDRD (p = 0.556). Overall, 4 treatment-related deaths were observed and 14 pts developed ARF. Decreased renal function estimated by any of the studied equations was able to predict negative outcomes, with OR 9.0(CG, 95% CI 2.8–29.2, p < 0.0001), OR 33.0(MDRD, 95% CI 9.3–116.3, p < 0.0001) and OR 8.45 (CKD-EPI, 95% CI 2.8–25.6, p < 0.0001).
Conclusions: Decrease in renal function estimated by all three equations (CG, CKD-EPI and MDRD) seemed to predict negative outcomes (ARF, dialysis and 28-day mortality) after one cycle of DDP-based chemotherapy in patients with head & neck and thoracic cancers.
No conflict of interest.

1339 POSTER

Pneumocystis jiverocii infection during chemotherapy in solid cancer patients

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Background: Pneumocystis pneumonia (PCP) is an opportunistic infection caused by the ascomycetous fungus Pneumocystis jiroveci. Pneumocystis pneumonia (PCP) is common in patients with HIV infection but may also occur in patients with other causes of immunodeficiency, including hematologic and solid malignancies. Although solid tumors carry a lower risk of PCP than do hematologic malignancies, the incidence of PCP in solid tumor patients is increasing. Many studies on the risk factors of PCP in this patient group have been conducted. However, few data have been reported exploring PCP during systemic chemotherapy in solid cancer patients.
Material and Methods: We retrospectively analyzed 24 HIV-negative patients diagnosed with PCP between April 2005 and February 2013 during systemic chemotherapy for solid tumors.
Results: The median age at the time of diagnosis of PCP was 63.7 years (range 46−82) and the majority of patients (81.9%) did not have comorbidities. In terms of purpose of chemotherapy, 23 patients (95.8%) received chemotherapy for locally advanced or metastatic/recurrent disease and 1 (4.2%) had adjuvant chemotherapy after curative resection. Of 23 patients, 7 (29.2%) had non-small cell lung cancer and 4 (16.7%) breast cancer. All patients had a median of 2 metastatic lesions (range 0−4). The most common site of metastasis was brain. At the time of diagnosis, 6 patients (25.0%) were receiving first-line chemotherapy and 11 (45.8%) more than third-line chemotherapy. The proloned use of steroids was found on 17 patients(70.8%). The mean white blood cell, platelet and albumin level was 5,736, 1,205×10^3/uL and 3.1 mg/dl, respectively. The mean pressure of O_2 measured by arterial blood gas analysis was 51.3 mmHg. On analysis for disease evaluation at the time nearest to diagnosis of PCP infection, only 5 patients (20.8%) revealed tumor response to chemotherapy. After the diagnosis of PCP infection, most patients(21/24, 87.5) were treated with sulfamethoxazole and trimethoprim accompanied with steroid. Almost half of the patients (13/24, 54.2) experienced failure of therapy for PCP leading to death.
Conclusion: We reported PCP infection during systemic chemotherapy in solid cancer patients. Patients may have a relatively poor tumor response to chemotherapy at the time nearest to diagnosis of PCP infection. A prospective or matched controlled trial is needed to confirm this finding.
No conflict of interest.

1340 POSTER

Hair preservation results of scalp cooling in >3000 patients − The Dutch Scalp Cooling Registry

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Background: Chemotherapy-induced alopecia (CIA) is a frequently occurring side effect of cancer treatment. Scalp cooling can prevent CIA

and is practiced in more than 70 out of 100 Dutch hospitals. Here the results of the Dutch Scalp Cooling Registry from 2006 and onwards are presented. The main objective is to study the proportion of patients with satisfactory hair preservation after scalp cooling for each currently used chemotherapy schedule. Wetting the hair before scalp cooling is of particular interest, because it is applied in several Dutch hospitals. It has been shown to lower the scalp skin temperature, but it might be an extra burden for the patient and it is unknown whether it affects the result.
Methods: Patients who received scalp cooling with Paxman cooling devices in 55 Dutch hospitals participated in our prospective registry. Scalp cooling was performed from 30 minutes before the chemotherapy infusion until 90 minutes after stopping the infusion. Nurses registered information on type, dose and infusion time of chemotherapy. Patients completed questionnaires on the result of scalp cooling and reported age, gender, type of hair, hair length and quantity, chemical manipulation (dyeing, waving, colouring), wetting the hair before scalp cooling, and previous chemotherapy. Logistic regression analysis will be used to examine all above mentioned factors that might be associated with the scalp cooling result. The main outcome is whether a patient wore a wig or head cover.
Results: From 2006, more than 3000 scalp cooled patients have been included in the Registry. During the conference scalp cooling results will be presented for the currently used main types and doses of chemotherapy. Furthermore, associated factors will be discussed.
Conclusions: This study is by far the largest in the literature about scalp cooling. Our Registry is invaluable for informing patients and medical professionals about the scalp cooling result they may expect for a particular type and dose of chemotherapy. Besides, studying associated factors will ultimately lead to a more patient-tailored approach. The Registry also adds to improving the results by evaluating scalp cooling methods between hospitals.
No conflict of interest.

1341 POSTER

Familiarity, opinions, experiences and knowledge about scalp cooling − a Dutch survey among breast cancer patients and oncological professionals

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Background: Scalp cooling is applied to reduce chemotherapy-induced alopecia (CIA). The aim of this study was to investigate patients' familiarity and opinions and oncological professionals' attitude and knowledge about scalp cooling in the Netherlands.
Methods: (Ex)breast cancer patients, nurses and medical oncologists (MDs) from scalp cooling and non-scalp cooling hospitals were asked to fill out questionnaires.
Results: The questionnaires of 177 breast cancer patients, 49 nurses and 100 MDs were eligible for analysis. In scalp cooling hospitals, the majority of MDs (80%, n = 52) and nurses (81%, n = 30) were satisfied with the results, as were patients who had scalp cooling (61%, n = 52). In these hospitals, 41% of the MDs and 63% of the nurses perceived their level of knowledge insufficient to inform patients about the effectiveness and safety of scalp cooling. The most important reason of MDs to not apply scalp cooling was doubt about effectiveness and safety. Severe problems in implementing scalp cooling were reported by three professionals. Scalp cooling had been offered to a minority of eligible patients, especially men had been excluded. Patients were often unfamiliar with scalp cooling before breast cancer diagnosis. Twenty out of 51 scalp cooled patients (39%) reported an insufficient result and most of them (72%) reported CIA to be moderately or very bothersome. With an expected chance for hair preservation of 35%, 36% of the patients would like to use scalp cooling in case of future chemotherapy treatment, which was 54% at a success rate of 50%.
Conclusions: Much room for improvement has been shown for both patients' familiarity and oncological professionals' knowledge about scalp cooling, which will apply for other countries too. Sharing knowledge about results and safety of scalp cooling and patients' experiences with CIA will improve patient counseling and availability of scalp cooling. The results of this survey have led to the development of a national standard on chemotherapy-induced alopecia and scalp cooling.
This study was supported by the Dutch Pink Ribbon Foundation.
No conflict of interest.

1342 POSTER

Feasibility and acceptability of an interactive mobile phone application for early detection of patient reported symptom distress in prostate cancer

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Introduction: For immediate and continuous dialogue between patients and caregivers new approaches in modern technology are encouraged today. In cooperation with a Swedish health management company, we developed an interactive mobile phone application for the assessment of symptom distress, evidence-based self-care advice and an alerting function of severe symptoms with instant access to professionals in real time. By using this technique patients can communicate symptoms with instant support while cared for out-side hospital but at the same time reassured that their condition is monitored by the professionals. The objective of this study was to evaluate the feasibility and acceptability of the application for patients with prostate cancer during radiotherapy and for the involved health care staff.
Material and Methods: Evidence-based symptoms and related self-care advices were implemented in the application after literature review and interviews with patients and health care professionals. Nine patients diagnosed with prostate cancer undergoing radiotherapy treatment were recruited to test the application for two weeks. The patients reported in the electronic symptom questionnaire daily. After the two weeks they were interviewed about their experience. Nurses directly involved in the care and treatment of the participating patients were interviewed at the end of study.
Results: Overall, patients and nurses reported positive experiences of using the mobile phone system. The patients considered the application helpful and easy to use although there were some suggestions for further development of the electronic questionnaire. Most of the patients had read the self-care advice and found them useful. The alerting system was activated in several cases; the nurses found it useful to identify and manage problematic symptoms early and the patients felt safe and well cared for. Some of the nurses considered the monitoring system time-consuming and made suggestions for improvement.
Conclusions: Both patients and nurses could see the potential for using the mobile application in clinical practice. The system enables the involvement of the patients and the alerts showed problematic symptoms promoting timely interventions. The results support further development and testing of the system in full-scale.
No conflict of interest.

1343 POSTER

Complementary and integrative medicine improved quality of life, depression, anxiety and fatigue levels in cancer patients on active oncology treatment

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Background: Complementary/integrative medicine (CIM) is being integrated more frequently in conventional clinical and academic institutions as part of the treatment of cancer patients. The influence of those therapies on quality of life (QoL), depression, anxiety and fatigue on the short- and long-term was tested prospectively in this study.
Patients and Methods: CIM treatments are given as part of the service at Rambam Health Care Campus, Haifa, Israel, for oncology patients. According to a 'waiting list', patients were referred to six weekly treatments of one of the therapies: art therapy, music therapy, Reiki, Shiatsu, guided imagery, healing, cranio-sacral therapy or oil anointing. Hospital Anxiety and Depression Scale (HADS) and the Brief Fatigue Inventory (BFI) were completed every two weeks and QoL-EORTC-Q30 questionnaire every six weeks during the treatment sessions and six weeks after the end of treatment.
Results: Over a two-year period, 162 patients entered the study and 135 completed therapies sessions. There were 86% women, 60% on chemotherapy and 24% on radiotherapy treatments. Global QoL ($p < 0.001$) and parameters on the functioning scale and symptoms scale of EORTC-Q30 questionnaire showed significant improvement, which was also seen in median scores of BFI from 4.57 to 3.76 ($p < 0.001$), HADS-Anxiety from 8.27 to 6.83 ($p < 0.001$), and HADS-Depression from 7.12 to 6.16 ($p < 0.001$) after 12 weeks. Main improvement was during the treatments and for six weeks after. No significant difference was seen in use of opioids, anxiety-depression medication, steroids or epo-treatment, and haemoglobin levels were maintained without significant change.
Conclusion: A short intervention of CIM therapies improved QoL of cancer patients. The improvement lasted even six weeks following treatments.
No conflict of interest.

1344 POSTER

Polyprenol in cancer cachexia management

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Background: Many patients with advanced cancer undergo a wasting syndrome associated with cancer cachexia. Patients with cachexia generally have a short survival time, respond poorly to palliative chemotherapy and immunotherapy. A number of cytokines (TNF-apha, IL-1,IL-6, interferon-gamma) and proteolysis-inducing factor (PIF) have been proposed as mediators of the cachectic process. Dolichyl Phosphate (Dol-P) plays an essential role in cytokine synthesis and protein processing. The present study was carried out to present evidence that Dol-P is rate limiting factor in pathogenesis of cachexia using a 'urinary dolichol test' and polyprenol (PP) supplement in nutrition.
Methods: Urinary dolichol (Dol) concentrations were studied in 64 patients with cachexia with good performance status and life expectancy >1 to 2 months, treated with megestrol acetate >480 mg/day (group 1), 48 patients with poor performance status and short life expectancy, treated with prednisolone 50 mg/day (group 2). Nutrition of 30 and 25 patients in both groups contained PP 2 mg/day. Samples were taken from fresh urine and assayed by HPLC. Radioimmunoassay was used to measure cytokins and PIF.
Results: Mean urinary Dol concentration in patients from group 1 (45.9±4.8 mkg/mmol) as well as in group 2 (62.3±9.5erbfts;mkg/mmol) was significantly higher ($p < 0.001$) than that observed in patients without weight loss (19.8±2.2 mkg/mmol). Urinary Dol increase was shown to be correlated with weight loss in cachexia: 2 mkg/mmol = 1 kg. PP in nutrition caused a significant fall in production of IL-1in group 1 (from mean 74.8 pg/ml to 26.3 pg/ml, $p < 0.001$) and a fall in the proportion of patients excreting PIF (from 90% to 27%, $p < 0.001$).
Conclusions: Dol concentration in urine of cancer patients with cachexia is dictated by performance status and life expectancy. Dol-P dependent disorders in cachexia are established as a possible step in mechanism of weight loss in advanced cancer and as a new target for therapy and nutrition. Modulating effect of Dol-P substitute polyprenol on IL-1and PIF opens up possibilities for cachexia management.
No conflict of interest.

1345 POSTER

Does wetting hair during scalp cooling decrease scalp skin temperature?

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Background: Hair is frequently wetted before scalp cooling in order to improve its effect. Whether this actually improves the prevention of chemotherapy-induced alopecia (CIA) remains to be seen. If wetting improves scalp cooling results a lower scalp skin temperature may be expected. We have investigated whether scalp skin temperature was reduced by wetting the hair.
Material and Methods: Experiments were performed on 29 healthy subjects with a Paxman cooling device. Scalp skin temperatures were measured with thermocouples. To document tolerance a graded scale has been used; zero in case of no discomfort at all and 10 for feeling very uncomfortable. As theoretically wetting of one side may cause a lower temperature of the other side, scalp cooling was also performed without wetting. The scalp was first cooled with dry hair. After a warming up period of 30 minutes to normalize the scalp skin temperature, the cooling procedure was repeated, whereby only one half of the scalp was wetted.
Results: Lower scalp skin temperatures were observed on the wetted side compared to the dry side. The initial great differences between the scalp skin temperature of the dry and the wet side decreased. After 30 minutes this difference was 4.5ºC,(95% C.I. 3.8−5.1, $p < 0.001$). The inter-individual differences in scalp skin temperatures after 30 minutes were considerable, both in dry (range 13.9 −26.9ºC) as in wet hair (range 0.3 −20.8ºC). Only for a short period, till about 15 minutes after the start of scalp cooling, the feeling of discomfort was considerable higher when the hair was wetted.
Conclusions: This is the first study, as far as we know, that demonstrates that wetting of hair before scalp cooling actually results in lower scalp skin temperatures. This substantial lower scalp skin temperature may be relevant to the prevention of CIA as there are indications that a number of scalp cooled patients do not obtain the required scalp skin temperature to prevent CIA. The initial increased feeling of discomfort caused by wetting will be no problem if hair wetting leads to less CIA.
Scalp skin temperature is substantially decreased if hair is wetted before scalp cooling. Wetting hair lowers scalp skin temperatures more rapidly which may lead to shorter pre-infusion cooling times. Further research is needed to determine if wetting leads to less CIA.
No conflict of interest.

1346 POSTER

Skeletal muscle density predicts prognosis in metastatic uterine sarcomas: an observational pilot study

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Background: Several studies have shown that skeletal muscle mass, skeletal muscle density and adipose tissue are linked to progression free survival (PFS) and overall survival (OS) in lung and gastro intestinal cancer. Because prognostic factors are not well defined in metastatic uterine sarcomas (MUS), another approach is required. Our aim was to analyze whether body composition parameters have a prognostic role in MUS.
Materials and Methods: Adipose tissue, skeletal muscle mass and skeletal muscle density (SMD) were assessed with computed tomography imaging by measuring cross-sectional areas of the tissues and mean muscle Hounsfield Units (HU). High level of HU reflects high SMD and high quality of muscle. As there is no defined threshold for SMD, we chose the one that had the best sensitivity: 29.5 HU. The population was dichotomized in two groups according to this value. OS and PFS were estimated using Kaplan–Meier method and compared with the log-rank test.
Results: In the 79 patients, median age was 56 years (range: 32−74). Histology: leiomyosarcoma (n = 53), undiffenciated sarcoma (n = 16), endometrial stromal sarcoma (n = 4), unknown (n = 6). OS was correlated with SMD: the median OS in the 24 patients with high SMD (5 years) was twice that in the 55 patients with low SMD (2.4 years) ($p = 0.04$). At 2 years OS was 58% (95% CI: 45%-70%) versus 81% (95% CI: 61%-93%) respectively for low and high SMD. Despite a trend for a better PFS for the group with a high level of SMD, the difference was not statistically significant. No associations between OS or PFS and adipose tissue or muscle mass were found.
Conclusion: High muscle density is associated with improved outcome in metastatic uterine sarcoma and could be part of a prognosis scores based on body composition parameters enhancing metastatic uterine sarcomas management. This hypothesis has to be confirmed in a prospective way.
No conflict of interest.

1347 POSTER

Palliative chemotherapy in patients with malignant bowel obstruction

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Background: Malignant bowel obstruction (MBO) is a frequent complication of gastrointestinal (GI) and gynecological cancers. It is often associated with advanced stages of disease and high tumor burden, and hence a marker of poor prognosis. It is unknown whether palliative chemotherapy (CT) can alter this unfavorable scenario.
Material and Methods: Retrospective, single institution analysis of 36 patients' chart data, hospitalized at the Instituto do Cancer do Estado de São Paulo (ICESP) from 2009 to 2013 due to MBO. All patients (pts) were not candidates for surgical intervention and were submitted to palliative CT. Primary objective was median survival after CT, estimated by Kaplan–Meier method. Secondary objectives were relief and failure rates of obstruction after CT, and toxicities associated with CT. Possible prognostic factors were analyzed by log-rank.
Results: Pts median age was 53 years (22−71). They were mostly females (67%), ECOG-PS >2 (94%), with gastrointestinal primaries (69%) and without previous systemic treatment (64%). Anemia was frequent (median hemoglobin 10.8 mg/dL, 5.3–15.6) as well as malnutrition (mean albumin 3 g/dL, 1.8−4.3). Normal bowel function after CT was achieved in 23 pts (64%) (median 13 days, 3−39), however 30% recurred MBO within one month (mo). Median overall survival was 1.97 months. About one third (36%) of pts experienced grades 3 or 4 toxicity. On univariate analysis the only factor associated with better outcome was reversal of MBO (5.8 vs. 1.2 mo, p 0.001). There was no correlation of serum albumin, creatinine, hemoglobin or ECOG with prognosis.
Conclusions: In this mostly treatment naive population no apparent clinically significant survival benefit was associated with CT. Its role in the reversal of MBO is unclear, as pts may have recovered normal bowel function with clinical measures alone. When considering palliative CT for pts with MBO, which is associated with other known poor prognostic

markers (such as anemia and malnutrition), patient selection is critical to avoid exposure to unnecessary toxicity and provide better quality of life.
No conflict of interest.

1348 POSTER

Complementary and integrative medicine therapy for chemotherapy induced peripheral neuropathy in breast cancer patients

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Background: Peripheral neuropathy is a known side effect of several chemotherapeutic drugs, mainly paclitaxel. When severe it can lead to significant disability and discontinuation of therapy with the offending drug. Neuropathy can be long lasting and recovery can take months and is often not complete. As patients feel that 'Western' medicine has little to offer as remedy, many turn to different types of complementary and integrative medicine (CIM) thrapies. In an attempt to evaluate CIM's efficacy we assessed the improvement in patients' neuropathy after treatment at our institution's CIM centre.
Methods: Thirty consecutive breast cancer patients files were retrospectively evaluated. Neuropathy was graded before and after treatment and was categorized to grade 1−2 and grade 3−4 according to the treating physician's follow up. Type of neuropathy was also recorded. Additional data gathered included patients' age, disease stage, presence and location of metastasis and chemotherapy used with total doses. All patients were treated with acupuncture on a weekly basis according to the CIM's protocol for neuropathy.
Results: Two patient's records were lacking sufficient information and not included in the analysis. The remaining patients had stage Ia-IV breast cancer with 4 patients (14%) having metastatic disease. Patients were treated with various agents including paclitaxel, docetaxel, doxorubicin, cyclophosphamide, trastuzumab and tamoxifen. Twenty one (75%) patients had grade 1−2 neuropathy and 7 (25%) had grade 3−4 neuropathy. Types of neuropathy included sensory neuropathy in 21 (75%) patients, proprioceptive neuropathy in 7 (25%) patients and unknown in 2 (7%) patients. Symptomatic improvemnt was recorded in 11 (39%) patients, with 82% improving after 3 months and 18% after 6 months from starting acupunture therapy.
Conclusions: Thirty nine percent of the cohort patients demonstrated symptomatic improvement, for either sensory or proprioceptive complaints, after acupuncture therapy. Most responders improved 3 months from starting therapy and while on continued oncological therapy. Shortcomings of this study include its retrospective nature and the heterogeneity of the oncological treatment patients were receiving. However, this high response rate indicate that acupuncture might offer a relief to patients and justifies further studies.
No conflict of interest.

1349 POSTER

Early treatment discontinuation and switching in 1st line metastatic breast cancer: Impact of symptom burden in a real world sample

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Background: Treatment options in 1st line metastatic breast cancer (MBC) vary and may include chemotherapy, targeted and hormone therapy. Some patients (pts) discontinue or switch therapies, perhaps due to treatment related toxicities. The current study examined the association of symptom burden with early treatment discontinuation or switching (EDS) of 1st line therapy of MBC in real-world settings.
Materials and Methods: Data were abstracted from medical records of pts at 9 community oncology practices. Eligible pts had stage IV MBC with start of 1st line therapy 1/2004 to 6/2012, were $\geqslant$18 years old, and had $\geqslant$1 Patient Care Monitor (PCM) survey, an 86-item survey of cancer-related symptoms, during 1st line. Age, race, HER2 and hormone status, oral and infused agents, dates of diagnosis, treatment, progression, and death were recorded. EDS was defined by direct indication of early stopping in the record, and by treatment duration $\leqslant$6 weeks or regimen change without evidence of disease progression. Cox regression of EDS with time varying covariates was used to examine the impact of 23 separate symptoms, a multivariate (MV) model with multiple symptoms, and an overall composite symptom burden score based on individual symptoms.
Results: 797 pts were included, with mean age of 58.4 years, 62.1% White; with 340 on Chemotherapy (CT), 349 on CT + Targeted therapy (T) and 108 on Hormone therapy only (H). Overall, EDS occurred in 197 (24.7%) pts, with rates highest among CT (27.9%), followed by T (26.1%) and H (11.5%). Cox regression showed that 22 of 23 symptoms each increased the risk of EDS. Across several MV models, 4−6 symptoms were retained, each reflecting distinct symptom clusters (e.g., hair loss, fatigue, numbness/tingling, mouth sores/ulcers, diarrhea). In the composite symptom burden score (median 6; range 0−22) analysis, overall symptom burden was found to be significant (HR = 1.13, $p < 0.0001$), indicating a 13% increased risk of EDS with each additional symptom. Pts with 10+ symptom score had a significantly increased risk of EDS (HR = 4.03, $p < 0.0001$) compared to pts with <5 symptom score. Pts with 15+ symptom score had the highest risk of EDS (HR = 5.12, $p < 0.0001$).
Conclusions: Pts treated with CT or T for 1st line MBC had higher rates of EDS than pts on H. The likelihood of EDS increased as the number of symptoms increased. Additional research is needed to evaluate impact of symptoms on other pt outcomes, including overall survival.
Conflict of interest: *Other substantive relationships: The study was sponsored by Genentech, Inc. A. S. Masaquel, D. Lalla, and O. D. Abidoye are employed by Genentech/Roche and have stock or stock options at Genentech/Roche. L.S. Schwartzberg has received honoraria from Genentech/Roche.*

1350 POSTER

Patient-proxy agreement of health-related quality of life (HRQOL) measurements in low-grade glioma patients

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Background: HRQOL has become an important outcome measure in clinical trials of glioma patients. Utilizing patient-by-proxy HRQOL assessment might increase data availability, provided that patient and patient-by-proxy ratings show high levels of concordance, which we aim to investigate in this study. Based on Sneeuw et al (1997), we hypothesized that 1) concordance levels are relatively high in cognitively intact patients, and 2) decrease in cognitively impaired patients, with proxies being more negative on patients' HRQOL.
Material and Methods: We analyzed cross-sectional data on HRQOL of 281 Dutch low-grade glioma (LGG) patients with stable disease who participated in a study comparing cognition and HRQOL after radiotherapy versus no radiotherapy. Proxy rating was assessed via the SF36 and EORTC BN20 in 246 patients. Data on the cognition were collected on a subgroup of 195 patients. The Bland-Altman limit of agreement (LA), mean difference (MD) [proxy minus patient], concordance correlation coefficient (CCC) and the percentage difference (PD, +/− 0, 5, or 10 points) were used to assess patient-proxy agreement. To investigate the effect of cognitive function on agreement we defined patients to be cognitively impaired (n = 66) or cognitively intact (n = 129) based on their neuropsychological performance and investigated the level of agreement via LA and MD.
Results: Patients were more negative in rating their HRQOL than their proxies in general except for the SF36 scale role emotional and social functioning and the BN20 scale future uncertainty, motor dysfunction, headaches, seizures and drowsiness. We found no statistically significant difference in MD except for the SF36 scale general health ($p = 0.03$) and BN20 scale visual disorder ($p = 0.04$). Results from the LA revealed a fairly high agreement between the patient and proxy rating in all HRQOL domains. However, a slightly poorer agreement was observed for the physical component summary (PCS) [LA; −13.63–11.03). The CCC was fairly high overall in all HRQOL domains (ranging from 0.37 to 0.80). The CCC for PCS was (r = 0.69) and mental component summary (MCS) was [r = 0.55]. The percentage of perfect agreement (PD +/− 0 point) ranged from 8.54% (general health) to 76.83% (hair loss). The PD for the PCS and MCS for a +/− 5 points and +/- 10 points was 76.42% and 65.85%, and 93.0% and 87.40%, respectively. The magnitude of the MD in the cognitively intact patient group was overall smaller and agreement by LA higher in the cognitive intact group.
Conclusion: Preliminary results suggest that there was overall a high level of agreement between patient and proxy rating of patient's HRQOL but a larger mean difference was observed in the cognitively impaired patients. Contrary to our hypothesis, patients tended to rate their HRQOL more negatively. Future research will focus on the validity of using complementary HRQOL assessments provided by proxies for patients with declining cognitive functioning.
No conflict of interest.

1351 POSTER

Internal and external validation of a fatigue prognostic score for overall survival (OS)

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Background: Fatigue is an adverse reaction related both to disease and treatment in cancer patients (pts). We previously found (ESMO2012, lecture 15450) that the F score was able to discriminate pts in "Good", "Intermediate" and "Poor" risk groups. We present the results of an internal and external validation of our model.
Methods: Patients included in the PROCHE program between 2008 and 2011 at the HEGP hospital (Paris, France). Pts were contacted before each chemotherapy (CT), and F experienced since the last cycle was collected (patient's reported outcome from CTC-NCI grading: 0=none, 1=mild, 2=moderate, 3=severe, 4=3+long-term condition). Scores were calculated as weighted means of F over the whole CT period and during the 2 and 4 first cycles. OS was calculated from CT initiation to death or censured at last contact. Cox regression covariates: age, tumor localization, disease setting and continuous or categorized Fatigue score. Patients with localized (M0) or metastatic (M+) disease during the study period led to two distinct cohorts: C1 and C0 according to M1 or M0 period considered. A bootstrap internal validation was performed on 1000 samples, followed by an external validation using Kaplan–Meier curves for risks groups.
Results: 1279 pts entered the program, 662 had at least 1 assessment of fatigue. Excluded pts (617) due to lack of survival status did not differ (log-Rank=0.98). Median age=64.9 y, sex-ratio=1.1, more frequent localization (%): lung: 25, breast: 21, urogenital: 21, gynecological: 13, ENT: 12. OS (m, 95% CI) was 27.8 (26.2–29.4). Median follow-up was 26.7m (25.5–27.9). F score was still strongly associated with prognosis after updating data. Model obtained from the initial dataset was internally validated (C-index=0.733, shrinkage=0.957). To evaluate prognostic value, 197 patients among 617 previously excluded were used for external validation. Concordance was very good (Kendall t=0.816, $p < 0.0001$). Predicted F score HR (95% CI): 0.17 (0.09–0.35) and 0.34 (0.21–0.56) for the "Good" and "Intermediate" prognosis groups, respectively; actual HR for the same groups (validation cohort): 0.19 (0.11–0.37) and 0.31 (0.19–0.52).
Conclusion: This study confirmed through internal and external validation the prognostic value of our fatigue score based on patients reported outcomes.
No conflict of interest.

1352 POSTER

Quality of life improves after placement of percutaneous tunneled drainage catheter for refractory ascites in prospective study of patients with end stage cancer

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Background: Refractory ascites in the terminal cancer patient causes debilitating symptoms often managed by serial paracenteses. Percutaneous tunneled drainage catheters (PTD) offer the advantage of home management but the impact on quality of life (QoL) has not been described.
Materials and Methods: Adult patients with stage IV or end-stage cancer undergoing PTD placement for refractory ascites were eligible for this prospective study. Subjects completed the EORTC QLQ-30 (EORTC) and McGill Quality of Life (MQoL) instruments prior to the procedure, immediately post procedure (PP) (2−7 days), and 3 weeks PP (+/− 7 days). Patients were interviewed for catheter function at the time of the instrument assessments as well as 2, 4, 6, 8 weeks (wks) and 4 and 6 months PP. Completion rates were defined as total number of completed instruments out of number of subjects surviving. QoL data were scored according to instrument manuals and analyzed using a pattern-mixture model to adjust for informative drop-out.
Results: 50 patients enrolled, 48 were evaluable of which 3 withdrew during follow up. All evaluable patients had a Tenckhoff catheter placed (Cook Inc., Bloomington, IN). Median survival post catheter placement was 1.2 months (95% CI: 1−1.8 months). For all time points, median completion rate among survivors was 88% (range: 65%-100%). Three PTD were removed for infection (26, 101, 170 days PP). Analysis of EORTC demonstrated an improvement in global QoL ($p = 0.04$), functional role ($p = 0.01$), emotional ($p < 0.01$), and cognitive ($p = 0.02$) scales at 1 wk PP. At the same time point significant symptom improvement was seen in reported fatigue ($p = 0.005$), nausea/vomiting ($p = 0.002$), pain ($p = 0.005$), dyspnea ($p = 0.001$), insomnia ($p = 0.001$) and appetite loss ($p = 0.009$). This improvement was sustained at 3 wks for dyspnea ($p = 0.006$), insomnia ($p = 0.002$), and appetite loss ($p = 0.03$). Baseline scores did not effect survival. The MQoL offered similar results with a significant overall QoL improvement at 1 wk ($p < 0.001$) and 3 wks ($p = 0.016$).
Conclusions: QoL and symptoms improved for end-stage patients after placement of a tunneled catheter to relieve refractory ascites. The benefits of placement diminish over time, likely due to progression of disease. This study supports the use of a PTD to palliate the debilitating symptoms associated with refractory ascites.
No conflict of interest.

1353 POSTER

What do patients really mean when they complain of fatigue after treatment? Reliable identification of post cancer fatigue

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Introduction: Fatigue is a ubiquitous symptom. Self-reported fatigue symptoms following cancer diagnosis and treatment are common. A definitive diagnosis of post cancer-related fatigue (PCF) is challenging due to lack of consensus on diagnostic criteria and the diversity of measurement tools currently used to identify the syndrome(predominantly self-report). A semi-structured clinical interview to reliably identify PCF and differentiate co-morbid symptoms (like insomnia or mood disturbance) has been developed.
Methods: Using both qualitative and quantitative methods, a semi-structured clinical interview to identify PCF was developed. Analogous to clinical interview schedules used in sleep medicine or psychiatry, it incorporates published diagnostic criteria for the syndromes of cancer related fatigue (CRF); chronic fatigue syndrome (CFS) and major depression. For validation, the interview was trialled in patients with clinician identified fatigue syndromes: multiple sclerosis ($n = 9$), post infectious and chronic fatigue ($n = 108$) and post cancer fatigue ($n = 30$).
Results: In the interview seven symptom domains were assessed: fatigue; fatigability; neurocognitive difficulties; mood disturbance; sleep problems; pain and other symptoms (e.g. night sweats). Symptom severity − both frequency and intensity − were identified. A diagnostic algorithm was developed to classify the symptom complexes. Sensitivity (sens) and specificity (spec) was determined against specialist-clinician diagnosis and syndrome diagnostic criteria ($n = 128$): CFS (sens 100, spec 83); major depression (100, 72) and PCF (72, 58).
Conclusion: While the interview schedule facilitates the diagnosis of clinically significant fatigue and co-morbid symptoms the lower sensitivity and specificity in those patients reporting fatigue post cancer, in comparison to those in groups diagnosed with CFS or major depression, suggests need for the further refinement of the diagnostic criteria for post cancer fatigue. Potential uses of the interview are in aetiopathological studies (identification of homogenous cases), for clinical management, and monitoring of patients participating in clinical intervention trials.
No conflict of interest.

1354 POSTER

A prospective investigation of nutritional status of ambulatory Irish oncology patients undergoing chemotherapy: prevalence of malnutrition, cachexia, sarcopenia and impact on quality of life

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Background: Malnutrition is a significant factor in predicting quality of life (QoL) in oncology patients. Our study describes the general health of Irish cancer patients (pts), including QoL, and determines the prevalence of cachexia, malnutrition, and sarcopenia in ambulatory pts undergoing chemotherapy in a regional cancer centre.
Methods: A prospective cross sectional study of ambulatory adult cancer pts, undergoing chemotherapy at a university teaching hospital was conducted. The risk of malnutrition was examined using the Malnutrition Universal Screening Tool (MUST). QoL was measured using the European Organisation for Research and Treatment of Cancer QoL Questionnaire (EORTC QLQ-C30). In addition, CRP (C-reactive protein) levels were recorded. Cancer cachexia was defined as weight loss (WL) >5% over the

past 6 months or WL >2% in combination with a Body Mass Index (BMI) <20 kg/m^2 or sarcopenia. Skeletal muscle cross-sectional area at L3 was measured on baseline CT scan. Sarcopenia was defined using published cut offs.
Results: 150 pts (96 male) with solid tumours, mean age 64 yrs, were included. 52.7% were overweight/obese (BMI>25 kg/m^2). Frequency of cancer subtypes was recorded: colorectal cancer(35%), upper gastro-intestinal cancer (GI, 31%), and lung cancer (15%) were the most common. Sarcopenia was present in 54% (38% of normal BMI, 40% of overweight groups) with fatigue significantly associated with sarcopenia in males ($p < 0.05$). Sarcopenia and reduced adipose tissue index were significantly associated with adverse QoL ($p < 0.05$) in females but not in males. Overall 73% met the criteria for cachexia, with the highest prevalence of cachexia observed in hepatobillary (86%) and upper GI cancers (79%). Using MUST, 42% of pts were classified as at risk of malnutrition (n = 63) and appetite loss scores were worse in malnourished patients than in non malnourished ($p < 0.05$). WL ($\geqslant$5%) in the previous 6 months was reported by 34%, 45% and 50% of pts with colorectal, lung and upper GI tumours, respectively. Furthermore, WL ($\geqslant$5%) in the previous 6 months was significantly associated with loss of appetite ($p < 0.05$), low fat free mass ($p < 0.05$) and advancing age (65 yrs vs. 61 yrs $p < 0.05$). 55% had a CRP >10 mg/L which was significantly associated with adverse QoL ($p < 0.05$). There was a significant association between cancer type and poor QoL ($p < 0.05$) with upper GI cancers reporting the worst global QoL scores.
Conclusion: Cancer patients undergoing chemotherapy experience weight loss, sarcopenia and a high percentage are cachectic in an inflammatory milieu. Site of primary tumour appears to be associated, at preliminary analysis, with significant weight loss, nutritional risk and QoL. Early nutritional screening is warranted in cancer patients.
No conflict of interest.

1355 POSTER

A prospective analysis of the association between skeletal-related events and quality of life in patients with advanced lung cancer (CSP-HOR13)

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Background: Bone metastasis (BM) is a frequent complication in patients with advanced lung cancer. We had reported incidence of BM and **skeletal-related events** (SREs) in patients with advanced lung cancer as a prospective study in the previous meeting, while there have still been few reports on the association between SREs and quality of life (QOL). The aim of this study was to investigate prospectively how QOL of patients with advanced lung cancer was affected by SREs.
Material and Methods: The eligibility criteria are newly-diagnosed patients with stage III B or IV lung cancer, whose ages were over 20-years old, and those who had a written informed consent. The patients were closely followed up in every four weeks to see if they developed SREs. QOL questionnaires were conducted at the time of the enrollment, three- and twelve-months later, and one month after the onset of SREs, using QOL scores including EQ-5D, FACT-G and Barthel Index. Then each QOL score was analyzed. Treatment for lung cancer and use of zoledronate were done at the discretion of the investigator. We evaluated QOL of the patients who developed SREs. SREs are defined as pathologic fracture, radiation or surgery to bone lesion, spinal cord compression or hypercalcemia.
Results: 274 patients were enrolled in this study from April 2007 through December 2009 (median age was 68-years old). Small/non small cell = 77/197. Stage IIIB/IV = 73/124, Male/female = 193/81. The median follow-up period was 13.8 months. 78 patients already had BM at the enrollment. Among them, 24 had accompanying SREs and another 12 developed SREs during the follow-up. Among 196 patients without initial BM, 34 developed BM. 16 patients of these 34 developed SREs during the follow-up.
A chronological analysis did not show statistically significant difference in QOL of all patients in whom the QOL evaluation was performed. QOL data were collected in nine patients out of 28 who had SRE during the follow-up. For those nine patients, QOL scores fell by 0.05 in EQ5D, by 9.4 in FACT-G, and by 6.9 in Barthel Index. Statistically, these declines in QOL scores subsequent to SREs were not significant. Analysis on FACT-G by four factors (physical, social/family, emotional, functional), however, showed that the emotional factor decreased by 4.76, which was statistically significant.
Conclusion: QOL of the patients with advanced lung cancer was not proven to have been affected by SREs when measured by EQ5D, FACT-G and Barthel Index. However, the evaluation by each four factor of FACT-G revealed that the statistically-significant decline in the emotional factor after SREs.
Conflict of interest: *Ownership: Yuko Saito is Clinical Trial Head at Novartis pharma K.K.*

1356 POSTER

Be positive, it can help you! The role of positivity on quality of life of cancer patients

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Background: Positive beliefs and emotions among people experiencing adversities are crucial to manage the emotional costs associated with negative events. Self-esteem, life satisfaction, and optimism to well-being, all traced to the common factor of Positivity, correspond to pervasive views of experience, highly correlated to each other and commonly associated with various domains of functioning and across the life-span.
The Authors examined the function of positivity and proper management of positive emotions in buffering the progress of illness, the recovery and the quality of life (QoL) in cancer patients.
Material and Methods: 110 patients with pulmonary, colorectal and breast cancer, aged 40−70, have been prospectively enrolled between 2012 and 2013, at the S. Andrea Hospital in Rome. Patients with previous diagnosis of other malignancies and psychiatric disorders were excluded from the analysis. Positivity was assessed by the Positivity scale (Caprara et al., 2012), EORTC QLQ-C30 was used for the QoL and physical functioning evaluation and the Mini-mental adjustment to cancer scale for the patients coping style assessment.
Results: Level of positivity is significantly associated to better QoL ($r=-.26$, $p < 0.01$) and less reported symptoms of worse physical ($r=-.26$, $p < 0.01$), cognitive ($r=-.30$, $p < 0.01$) and emotional functioning ($r=-.25$, $p < 0.01$). Moreover, positivity is related to the implementation of coping strategies focused on good illness management. In particular, patients with medium-high level of positivity tend to cope actively the illness($r=-.32$, $p < 0.01$) and to report less feelings of hopelessness($r=-.36$, $p < 0.01$). Furthermore, hierarchical regression analysis showed the role of positivity in predicting the impairment in physical functioning, after controlling for sex, type of diagnosis and coping strategies. Finally, a significant interaction between sex and positivity was found, showing that males tend to report less impairment in physical functioning than females.
Conclusions: According to previous studies, our results support the hypothesis that psychological characteristics may influence the QoL of cancer patients. In particular, in our sample, the level of positivity is associated to better QoL, less impairment in physical, cognitive and emotional functioning.
Positivity can predict QoL in cancer patients, and can support physicians to promptly identify patients that could need psychological support.
No conflict of interest.

1357 POSTER

Ocular disorders in long-term survivors

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Background: To describe the frequency of ocular disorders in long-term cancer survivors ($\geqslant$3 years) observed in Interdisciplinary Units and evaluate the relationship with comorbidities.
Patients and Methods: In 118 consecutive long-term survivors with different cancer type we identified 18 patients, surviving $\geqslant$3 years after primary diagnosis, who reported ocular sequelae. All patients received multimodality treatments, including surgery (n = 17, 14%), conventional chemotherapy (n = 12, 10%), radiotherapy (n = 6, 5%), hormonal therapy (n = 9, 7.6%) and biological treatment (n = 2, 1.69%).
Results: Of 18 patients, 22% (n = 4) were males and 77% (n = 14) females, median age 62.5 (range 35−84 years); of them, 11 were affected of breast cancer, 3 of colorectal cancer, 1 of prostate cancer, 1 of kidney cancer, 1 of testicular cancer, 1 of GIST. 16.6% (n = 3) patients reported diabetes non-insulin-dependent, 33.3% (n = 6) hypertension in medical treatment. In particular, we have seen that 6 patients (33.3%) reported cataract, 7 (38.8%) visual deficit, 2 (11%) myopia, 1 (5.5%) keratoconjunctivitis, 1 (5.5%) retinal detachment and 1 (5.5%) periorbital edema.

Conclusion: The ocular complications may affect the quality of life of these patients and need more attention in clinical practice, especially in consideration of the use of new biological drugs.
No conflict of interest.

1358 POSTER

Efficacy of tapentadol for managing severe pruritus related biological cancer treatments: Multicentric experience

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Background: Severe pruritis affects a large proportion of the cancer patients treated with anti-EGFR antibodies and tyrosine-kinase inhibitors. Tapentadol is a centrally acting analgesic with 2 mechanisms of action, μ-opioid receptor agonism and norepinephrine reuptake inhibition. We designed a multicentric study to asses of Tapentadol for the management pruritis induced by biological treatments.
Material and Methods: In this multicentric study we enrolled 30 patients with metastatic solid tumours treated with biological drugs between November 2012 at February 2013. Intensity of itch was evaluated by Visual Analogue Scale (VAS) score. The primary endpoint was change in median VAS score during treatment with biological drugs. All patients were enrolled in the failure of standard therapies for itch. All patients received tapentadol 50 mg cpr bid.
Results: Median VAS was 9.00 at baseline and 1.00 after 3 days of treatment. 25 patients responded to Tapentadol. the only side event was experienced nausea G1 resolved in a week.
Conclusions: Tapentadol showed excellent efficacy in the control of pruritus associated with the use of biological drugs. is not a minor reduction on the quality of life of pain associated with hand–foot syndrome typical of TKI inhibitors.
No conflict of interest.

1359 POSTER

To assess the effect of regular exercise, involvement with art (origami) and group therapy on quality of life, anxiety, depression, patient satisfaction and hope levels in patients with remission who had a variety of cancer diagnoses "quality of life support program (QoLSP)" was developed

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Informed consents and demographic information was compiled prior to the onset of study, HOPE, HADS (Hospital anxiety and depression) and EORTC QLQ-C30 (30th question assessing the quality of life) quality of life scales were used at the beginning and at the end of the study. Apart from these scales, program satisfaction and scales evaluating the arm use in breast cancer patients were also used. QoLSP consisted of excercise on Mondays, art therapy (origami) or group therapy on Wednesdays (rotating once a week) and home excercise on Fridays.
A total of 26 patients took part in this study, 23 of whom were female and the remaining 3 were male patients. Twenty patients were diagnosed as breast cancer, 2 patients had cancer of the overy and the remaining four had endometrium, colon, larynx cancer and soft tissue sarcoma.
When the analyses were completed, average hope scores of the patients were 25.6±3.9 and EORTC QLQ-C30 scale 30th question average score was found as 5.1±1.5 before QoLSP. After the QoLSP, average score for the HOPE scale was raised to 29.7±1.9 and EORTC QLQ-C30 scale's 30th question score average was increased to 6.6±0.82. Before QoLSP, HADS anxiety scale score was 8.2±4.7 on the average and HADS depression scale average score was found as 6.4±4.4. After QoLSP HADS anxiety scale score average was decreased to 3.5±3.3 and HADS depression scale score average was down to 2.5±3.2. All differences in scale scores between before and after QoLSP program were considered as statistically significant ($P < 0.001$).
After QoLSP, factors which might have been involved with quality of life were also evaluated. In multivariate analysis, hope score differences were statistically significant when compared with preliminary hope scale ($\beta = -0.89$, $t = 11.21$, $p < 0.001$), which is also true for anxiety score differences when compared with HADS preliminary anxiety scores; and global QoI preliminary scores ($\beta = -0.55$, $t = -3.65$, $p = 0.001$ and $\beta = 0.33$, $t = 2.2$, $p = 0.038$ respectively), depression score differences according to HADS depression scale preliminary results ($\beta = -0.74$, $t = -5.39$, $p < 0.001$), as well as Global QoI score differences according to Global QoI preliminary results ($\beta = -0.88$, $t = -9.22$, $p < 0.001$) were also statistically significant.
In the study population 6 patients had breast sparing surgery + lymph node dissection out of 20 patients who were operated for breast cancer. When assessed arm movement of 3 patients (out of the 6) have been defined as 'much beter', 2 patients' arm movements were 'better' and 1 patient reported 'no change'. Out of 14 patients who had modified radical mastectomy 13 had rated their arm movements as 'much beter' and 1 reported arm movement as 'beter'.
When program satisfaction was assessed via a questionnaire, all of the 26 participants rated themselves as 'highly satisfied'.
QoLSP a multidisciplinary activity, if established in other centers, can have very positive influence on cancer patients' quality of life, anxiety, depression, hope and patient satisfaction by having an active part in diagnosis and treatment.
No conflict of interest.

1360 POSTER

The experience of partners of cancer patients' participation in a phase I study after the patients' death: A retrospective study

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Background: Research data on the impact of patients (pts)' participation in a phase I study on the well-being of their partners after death is scarce. Yet, partners' well-being is essential as it can affect their mental and physical health. This study aimed to explore the experience of partners of deceased pts who participated in a phase I study and investigate their well-being after pts' death.
Patient and Methods: 63/74 (85%) eligible partners of deceased pts participating in a phase I study between 2007 and 2010 agreed to participate. Between 0.5 and 2 years after bereavement, they completed 5 self-assessment questionnaires, the RAND-36 Health Survey (RAND-36), Shortened Fatigue Questionnaire (SFQ), Beck Depression Inventory for Primary Care (BPI-PC), Inventory of Traumatic Grief (ITG) and the Hospital Anxiety and Depression Scale (HADS). Furthermore, they completed a general questionnaire (GQ) about their experience on the participation in a phase I study.
Results: Participants had a mean age of 58 years (range 37−82), 67% was female. 58/63 partners returned the questionnaires. Retrospectively partners reported negative effects on the pts' QoL (14/58), burdensome side effects (21/58) and burdensome increase of visits to the outpatient clinic (16/58). In contrast, 55/58 partners did not regret participation of the pts in a phase I study, where 24/58 partners even reported a positive effect on the pts' QoL. Regarding the impact that the disease and it's treatment have on partners after pts' bereavement, the GQ reports that 8/58 partners experienced a decline in their general health after bereavement compared to the time before the diagnosis. In addition, the RAND-36 showed significantly lower average scores on 2 subscales compared to normative data, namely limitations in social functioning ($p < 0.011$) and mental functioning ($p < 0.004$). Assessment of severe fatigue, depression, complicated grief and distress showed no abnormalities on the SFQ, BPI-PC, ITG and HADS respectively.
Conclusion: Even though one third of the partners reported burdensome consequences and negative effects on the QoL of pts during participation in a phase I study, retrospectively most of the partners did not regret pts' participation in phase I studies. Assessment of the well-being of the partners after pts' death shows, aside from significant differences compared to normative data on social and mental functioning, no abnormalities.
No conflict of interest.

1361 POSTER

Chemobrain in patients participating in clinical trials

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Background: The observation that cytotoxic drugs given systemically for non-CNS tumors might have neurotoxic effects on cognitive functioning was made decades ago.The term chemobrain or chemotherapy-induced cognitive impairment is recognized as a common adverse effect of chemotherapy. In the past years, the number of clinical trials has increased rapidly in Croatia and the actual degree of understanding or perceptions of

clinical trial participating is unknown. Aim of this study is to evaluate does patients which signed informed consent to participate in clinical trials (both, academic and sponsored) have different chemobrain status than other.
Methods: Adult cancer patients receiving chemotherapy in General Hospital Pula between January 2010 and December 2012 were included. In experimental arm were 32 adult patients with advanced cancer, ECOG PS 0−3, without CNS involvement which signed clinical trial ICF. In control arm were 92 patients matched for same conditions as experimental arm patients (matched for location, age, stage, gender, ECOG PS, fatigue, anemia, and chemotherapy line.Cognitive impairment was detected using cognitive tests HVLT-R, TMT, and COWA after signed Informed consent form (ICF). After approval of sponsors and conductors of clinical trials, for using some data from trials, patients in both arms were evaluated.
Results: Median age was 63.5 years, 39% were female, and 11% had poor ECOG PS ($\geqslant$2). Patients had advanced solid tumors (Lung: 32%; colorectal: 27%; breast: 15%; other solid tumors: 26%). Average time of follow up and chemotherapy were 14.5 and 6.7 months, respectively. Patients were well balanced between arm in age, gender, overall survival (8.7 months), performance status, locations of tumors, stage, anemia, number of chemotherapy lines, and fatigue (FACIT-F test result). There were less cognitive impairment in term of chemobrain (detected with HVLT-R, TMT, and COWA tests) in experimental arm than in control arm 21.9% and 39.1% of patients, respectively ($p < 0.05$). Also, patients in control arm had trend to be more anemic (21.9% vs 31.5%) but not statistically significant ($p = 0.07$).
Conclusion: This is, to our knowledge, the first evaluation of chemobrain in patients inside and outside of clinical trials. Cognitive impairment could significantlly influence willing to participate in clinical trials independently of clinical trial eligibility criteria. This data provides more light on importance of psycho-oncological estimation of patients affected by cancer.
No conflict of interest.

1362 POSTER

Alternative and complementary treatments in cancer patients

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Background: Alternative and Complementaries therapies (CT) are used widely, especially among cancer patients. Insufficient clinical research data exist to indicate whether CT is safe and efficacious. The purpose of this study was to determine the prevalence and the impact of sociodemographic and clinical factors on CT use among cancer patients.
Methods: A cross-sectional survey was conducted in a sample of adults with cancer seeking care at Instituto Oncologico Nacional within a 4-month period. Univariate and multivariate analyses were performed to detect differences between CT users and nonusers.
Results: 421 pts were interviewed. Median age was 57 years. 69% female, 31% male. Breast (34%) and gastrointestinal cancer (14%) were the most frequent tumors. 47% of pts were within the first year of diagnosis. 128 pts (30%) used CT. The most common was herbal remedies (38%). Median use time was 4 months. Factors associated with CT use were female gender ($p = 0.04$), recent diagnosis ($p = 0.001$), higher education level ($p = 0.001$) and income ($p = 0.08$). The main reason for CT use was to assist conventional treatments (45%). 50% of CT users did not informed to their physician about its use. In 43% of cases the use of CT was recommend by friends and family. Multivariate analysis showed that higher education (OR 2.01 95% CI 1.18–3.43) and recent diagnosis (OR 2.03 95% CI 1.26–3.27) were predictive for CT use.
Conclusion: Educational level and recent diagnosis are associated with CT use. Patient and physician communication regarding potential risk and benefit is highly recommended.
No conflict of interest.

1363 POSTER

Decreasing anxiety with welcoming workshops in a radiation oncology unit

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Background: In recent years the treatment of cancer has changed as more and more people are treated and the greater number survive the disease. The main goal of cancer treatment is survival, but also the treatment of symptoms and quality of life of patients and their family members also become important. Cancer treatment by radiotherapy is an opportunity to control, improvement or cure of the disease, but also involves facing major challenges that can affect their quality of life and emotional state. In order to improve the emotional care, we have begun work on workshops within the welcoming plan of our unit, where through group techniques and information received as well as the opportunity to resolve doubts and feel heard, we improve the management of anxiety in patients and their families, and therefore, dealing with the treatment and disease.
Material and Method: We choose patients who will receive radiation treatment in our unit as long as they are not palliative, and invite their main caregiver too. After signing the informed consent of the study, are given a first HADS questionnaire (Hospital Anxiety and Depression Scale) and then they assist to the workshop. The first day of radiotherapy answer a second test and the third is answered at the end of radiation therapy. The three test results are compared.
Results: Data shows that at baseline levels of anxiety and depression are very high, and decrease at the beginning and as the treatment goes on. This study demonstrated that the welcoming workshop decreased symptoms of anxiety and depression during radiation therapy, In addition there was a high prevalence of anxiety and depressive symptoms in family caregivers groups, and also was improved.
Conclusions: The emotional state, in particular anxiety, is a variable that should be assessed throughout the entire radiotherapy process as it affects the welfare status of patients and caregivers. The welcoming workshops, as support groups, are affective in treatment of the oncological disease.
No conflict of interest.

1364 POSTER

Symptom clusters and demographic characteristics in advanced cancer

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Background: Little is known about demographic variations in cancer symptom clusters (SC). Our objective was to determine whether SC are associated with age, gender, race, performance status (PS), or primary cancer site.
Material and Methods: Symptoms from 1000 advanced cancer patients referred to a palliative medicine program were recorded prospectively. Among 922 patients with complete symptom data, hierarchical cluster analysis identified 7 SC. A SC was considered present if the patient had $\geqslant$50% of the symptoms in the cluster. Comparisons were made between patients with and without each cluster using the chi-square test (age <65 vs. $\geqslant$65 years; gender female (F) vs. male (M); race Caucasian (C) vs. African American (AA); 10 primary site groups (PSG), or Wilcoxon rank sum test (ECOG PS 0−4). A p value <0.05 indicated statistical significance.
Results: 83% of patients were C, 52% $\geqslant$65 years, 56% M, and 55% ECOG PS 3−4 Most common PSG were lung (25%), genitourinary (18%), and gastrointestinal (GI) (11%). Fatigue/anorexia-cachexia cluster was associated with race (58% AA vs. 68% C, $p = 0.032$) and PSG (range 47% melanoma to 83% pancreas, $p = 0.012$); Neuropsychological cluster was associated with older age (29% $\geqslant$65 vs. 39% <65, $p < 0.001$) and race (22% AA vs. 36% C, $p = 0.001$). Upper GI cluster was associated with female gender (16% M vs. 22% F, $p = 0.035$) and PSG (range 8% Head & Neck to 32% pancreas, $p = 0.035$). Nausea/vomiting cluster was associated with younger age (35% $\geqslant$65 vs. 43% <65, $p = 0.010$) and female gender (33% M vs. 47% F, $p < 0.001$). Aerodigestive cluster was associated with male gender (36% F vs. 44% M, $p = 0.010$) and PSG (range 24% pancreas to 58% Head & Neck, $p < 0.001$). Debility cluster was associated with race (33% AA vs. 44% C, $p = 0.016$) and poor PS (range 17% PS0 to 54% PS4, $p < 0.001$). Pain cluster was associated with younger age (88% $\geqslant$65 vs. 92% <65, $p = 0.028$).
The table briefly summarizes the associations that are significant at P<0.05.

Cluster	Age	Gender	Race	Performance status	Primary Site
Fatigue/anorexia-Cachexia					+
Neuropsychological	+		+		
Upper GI		+			+
Nausea/vomiting	+	+			
Aerodigestive		+			+
Debility			+	+	
Pain	+				

Conclusions: We identified 7 SC whose prevalence were influenced by age, gender, race, PS, or primary cancer site. This supports the clinical relevance of the cluster concept in palliative and supportive care. Demographic characteristics may warrant different clinical approaches to patient care. Identification of these differences may help develop more effective cancer treatment and management strategies.
No conflict of interest.

1365 POSTER

Denosumab treatment of hypercalcemia of malignancy (HCM) in patients not responding to bisphosphonate therapy

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Background: HCM, resulting primarily from tumor-induced bone resorption, is commonly treated with intravenous (IV) bisphosphonate therapy but patients may relapse or not respond. We present results evaluating denosumab for treatment of HCM in patients who remained hypercalcemic despite IV bisphosphonate by bone metastases (BM) or PTHrP status at study baseline (ClinicalTrials.gov NCT00896454; May, 2009; sponsor Amgen Inc.).
Material and Methods: In this single-arm, open-label study, patients with HCM (corrected serum calcium [CSC] >12.5 mg/dL; CTCAE grade $\geqslant$3) despite IV bisphosphonate treatment $\geqslant$7 and $\leqslant$30 days before screening, received subcutaneous denosumab 120 mg on days 1, 8, 15, and 28, then every 4 weeks. The primary endpoint was the proportion of patients with CSC $\leqslant$11.5 mg/dL (CTCAE grade $\leqslant$1) within 10 days of denosumab initiation.
Results: The study enrolled 33 patients (64% men; mean age 60 years; 39% with BM; median PTHrP 4.2 pmol/L). Median baseline CSC was 13.7 mg/dL and median time from last bisphosphonate treatment to enrollment was 17 days. By day 10, 21 patients (64%) reached CSC $\leqslant$11.5 mg/dL, with a total of 23 patients (70%) over the course of the study; estimated median response duration was 104 days. Of patients without BM, 14 of 20 (70%) reached CSC $\leqslant$11.5 mg/dL by day 10 compared with 7 of 13 (54%) with BM. The estimated median time to reach CSC $\leqslant$11.5 mg/dL was 8 days for patients without BM and 11 days for patients with BM. Of patients with PTHrP $\leqslant$4 pmol/L, 10 of 12 (83%) achieved CSC $\leqslant$11.5 mg/dL by day 10 compared with 6 of 12 (50%) with PTHrP >4 pmol/L. The estimated median time to CSC $\leqslant$11.5 mg/dL was 8 days for both the $\leqslant$4 pmol/L and the >4 pmol/L PTHrP groups. The most frequently reported serious adverse event was hypercalcemia (5 patients, 15%). Two patients had isolated episodes of CSC levels $\leqslant$8.0 mg/dL and no patients had CSC <7.0 mg/dL.
Conclusions: Denosumab lowered CSC to CTCAE grade $\leqslant$1 in 64% of patients within 10 days and induced durable responses in patients with HCM not responding to IV bisphosphonate treatment. Denosumab decreased CSC levels in patients independent of BM or PTHrP status. These results suggest that denosumab may offer a new treatment option for HCM in this challenging patient population.
Conflict of interest: *Ownership: none. Advisory board: none. Board of directors: none. Corporate-sponsored research: Amgen Inc. Other substantive relationships: W.Ying, A.Braun, and R.Jain are employed by and own Amgen Inc. stock.*

1366 POSTER

Palliative effect of MR guided focused ultrasound (MRgFUS) on patients with bone metastases previously receiving sham treatment

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Background: Radiation therapy (RT) is the primary treatment for most patients with painful bone metastases. Many patients have persistent or recurrent pain after RT or are not candidates for RT. Magnetic resonance guided focused ultrasound (MRgFUS) combines non-invasive focused ultrasound with MR guidance. We showed in a multi-center phase III trial significantly greater pain relief for patients treated with MRgFUS (67% response) compared to controls receiving sham treatment (21% response). Non responders on the placebo arm were unblinded and offered MRgFUS. We analyse here the response to MRgFUS in these patients who acted as self-control.
Materials and Methods: Patients with a painful bone metastasis amenable to MRgFUS treatment and NRS pain score >4 for whom RT was not considered appropriate (e.g. prior RT to target site) were randomized 3:1 to MRgFUS or sham. Subjects were followed for 3 months. Sham subjects without pain relief after 2 weeks were offered crossover to MRgFUS treatment. Significant pain response was defined as decrease in worst pain NRS score >2 from baseline without increase in pain medication. Quality of life (QOL) including BPI-QOL, and safety were also evaluated.
Results: Blinding of sham subjects was excellent; 94% of MRgFUS and 88% of sham subjects believed they had received MRgFUS treatment. 18 of 28 non-responders on the placebo arm elected to receive MRgFUS therapy. One patient did not complete MRgFUS therapy due to transient pain exacerbation during treatment. There were no other side effects. 13 of 17 treated patients (76%) had significant pain reduction. 15 patients were followed for the 3 month study period, follow up was discontinued for 2 patients after 2 months. One died of disease progression at other sites and one received additional RT. Mean NRS pain score of all 17 patients improved from 7.6 after sham treatment and before MRgFUS treatment to 3.1 at 2 months after treatment and 2.7 three months after treatment. BPI-QOL score improved from a mean of 5.8 before MRgFUS to 3.4 at 2 months and remained stable.
Conclusions: MRgFUS is well tolerated and results in significant durable pain relief, improvement in QOL, and function for patients with metastatic bone pain who are not candidates for RT. This analysis of patients who did not respond to prior sham treatment confirms that pain relief after MRgFUS is not due to placebo effect. MRgFUS should be considered for patients with painful bone metastases when RT is contraindicated.
Conflict of interest: *Corporate-sponsored research: This phase III study was sponsored by Insightec Ltd.*

1367 POSTER

Weight loss in solid tumors: Clinical features and prognostic importance

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Background: Large cancer databases provide valuable information on weight change and its impact on different clinical parameters. Body weight change in adults with solid tumors examined in outpatients. Objective was to determine if demographics, clinical and biochemical indices predicted weight loss (WL). Examine if WL and related parameters were prognostic for survival.
Material and Methods: Electronic medical records (EMR) for outpatient visits from a tertiary cancer center retrospectively reviewed. Body weight and other clinical parameters on first visit (V1) − within a year post diagnosis − last visit (V2) $\geqslant$3 weeks after V1. WL at V2 from V1 categorized as: $\leqslant$5%, 5.01−10%, >10%. Logistic regression and Cox proportional hazards analysis identified risk factors for WL and prognosis.
Results: N = 5901; Mean age ($\pm$SD): 61$\pm$12 years; 82% were Caucasians; 16% African Americans. Common cancers were genitourinary (GU) 31%; gastrointestinal (GI) 16%; breast 15%; lung 15%; head and neck 6%; brain 5% and others 12%. Metastatic disease in 18%. Bone, brain, lymph nodes − common. 45% had radiotherapy and

41% chemotherapy. Median (min, max) weight, kgs: V1 = 81 (32.0, 223), V2 = 79 (34, 221). Median duration (min, max), days V1→V2: 195 (22, 1080).
Weight loss V1→V2: ⩽5% (73%), 5.01−10% (13%) and >10% (14%). Median change in BMI V1→V2: −0.2 (−19, 13). Median change systolic/diastolic blood pressure (BP) V1→V2: −3 (−99, 80)/−1 (−57, 47). Change in REE V1→V2: −13 (−890, 365). Median survival for 5.01–10.0% WL = 9.4 months, >10.0% = 5.3 months and not observed for ⩽5%.
Conclusions:
1. Majority lost ⩽5% of body weight by V2
2. Head & Neck and GI cancers (primary) − the greatest risk of WL; breast − lowest
3. High BMI predicted greater WL compared to normal or underweight
4. ⩽5% WL had a survival advantage 5.01−10% and >10%
5. WL remained prognostic for survival after adjusting for other prognostic factors

No conflict of interest.

1368 POSTER

Malignancy-related hypercalcemia in the bisphosphonate era

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Background: Malignancy-related hypercalcemia (MRH) is associated with a poor prognosis. With advances in supportive care and cancer treatment, the impact of such occurrence might have diminished. Bisphosphonates (BP) play a role in symptom control but survival gain is unknown. In order to assess the prognostic implication of MRH in a present population, this retrospective analysis was performed.
Methods: Charts of 310 consecutive patients (pts) hospitalized due to symptomatic hypercalcemia in a single tertiary institution were retrospectively reviewed, from 2009 to 2012. All patients had solid tumors and serum ionized calcium (iCa) >5.5 mg/dL or total Ca >10.5 mg/dL. The Kaplan–Meier survival curves, long-rank test and the Cox regression model were used for analysis.
Results: 310 pts were included with a median age 58 y.o., most with diagnosed squamous cell carcinoma (61%) and ECOG-PS >1 (96%). 141 pts (45%) had no previous chemotherapy (no CT) and mean iCa 6.8±0.9 mg/dL. Most frequent primary sites were head and neck (27%), lung (15%), esophagus (10%) and breast (10%). At presentation, 171 pts (55%) had altered mental status (AMS); median Hb 9.7 g/dL (3.9–15.4), C-reactive protein (CRP) 129 mg/L (3–448, NV <5), albumin (alb) 2.9 g/dL (1.6−4.5) and creatinine clearance 66 mL/min (9.7–199). Hypercalcemia episodes ranged from 1−5 (median 1). 245 pts (79%) were treated with pamidronate and 11 (4%) with zoledronic acid. No difference in overall survival was seen between those pts treated or not treated with BP (HR 0.65, p 0.7). Subsequent CT was administered to 99 pts (32%). Median OS was 40 d (95% CI 33−47 d). Pts with ECOG-PS >1, AMS, CRP >30, alb <2.5 or body mass index <18 kg/m^2 had significantly poorer survival. Longer OS was related to treatment-naive pts, subsequent CT and breast primary. On multivariate analysis, subsequent CT led to a survival improvement (HR 0.23, 95% CI 0.14–0.38, p < 0.0001).
Conclusions: MRH implicates a dismal prognosis in pts with solid tumors, despite administration of BP. Even so, pts treated with CT had a better survival, suggesting that appropriate treatment of selected pts can alter the course of this syndrome.
No conflict of interest.

1369 POSTER

Should patients with advanced colorectal cancer and ECOG 3/4 be treated with chemotherapy?

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Background: Patients (pts) with metastatic colorectal cancer (mCRC) and ECOG 0/1 benefit from chemotherapy (CT). However, the impact of CT on the overall survival (OS) of ECOG 3/4 pts remains uncertain, since they are generally excluded from clinical trials.
Material and Methods: We retrospectively analyzed all consecutive mCRC pts who started first line CT at our institution in a 4-year period. The objectives were to compare the OS of pts with ECOG 3/4 who underwent CT with those receiving best supportive care (BSC) only and to compare the outcomes of these pts with those with ECOG ⩽2. Multivariable Cox regression model was used to verify prognostic factors and logistic regression, to identify predictive factors for grade 3/4 toxicity.
Results: From Jun/2008 to Jun/2012, 240 consecutive pts were included: 72 pts had ECOG 2, 54 ECOG 3 and 11 ECOG 4. Among pts treated with CT, the median OS was: 18.4 months for ECOG 0/1, 10.8 months for ECOG 2 and 6.8 months for 3/4. For pts with ECOG 3/4, CT led to a non-significant OS gain (median: 6.8 vs 2.3 months for BSC; p = 0.13). Factors significantly associated with worse OS were right-sided tumors (HR: 2.97; p = 0.005), ECOG 2 (vs ECOG 0/1, HR: 1.67; p = 0.025) and ECOG 3/4 (HR: 2.67; p < 0.0001). The rate of grade ⩾3 toxicities during first cycle did not differ significantly whether ECOG 3/4 pts received or not CT; likely because 40% of them received upfront dose-reduced CT. This was confirmed by multivariable analyses. While 70% of ECOG 3/4 pts were hospitalized during the first cycle, only 19% were admitted due to CT toxicity. This rate was similar across other ECOG groups.
Conclusions: Despite the small sample size, it seems that palliative CT may benefit selected pts with mCRC and poor performance status, without resulting in an increase in the risk of major adverse events when a reduced CT dose is used and pts are closely followed for toxicity. Further research may help to better identify the best candidates for CT.
No conflict of interest.

1370 POSTER

Impact of race on cancer symptom profiles and survival in advanced cancer

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Background: Racial differences have not been investigated in detail in advanced cancer. In this study, we first examined whether race had an influence on cancer symptom prevalence and severity. Secondly, we investigated whether survival differed by race.
Material and Methods: 38 symptoms were assessed in 1000 consecutive advanced cancer patients referred to a palliative medicine program. Moderate/severe symptoms may be more clinically relevant than overall prevalence; hence, they were grouped together and referred to as 'clinically important'. Race was unknown in 30 patients. Age was compared between 167 African-Americans (AA) and 803 Caucasians (C) with the t-test. Gender and primary site groups (PSG) were compared with the Chi-square test. Performance status (PS) and symptom severity was compared with the Wilcoxon rank sum test. Survival after referral was estimated using the Kaplan–Meier method and compared with the log-rank test. A p value ⩽0.05 indicated statistical significance.
Results: Age, gender, PS, and PSG did not differ between AA and C (p⩾0.36). AA had less edema (21% vs. 30%, p = 0.02), depression (27% vs. 44%, p < 0.001), anxiety (14% vs. 26%, p = 0.001), tremors (1% vs. 6%, p = 0.018), anorexia (57% vs. 67%, p = 0.022), and dry mouth (48% vs. 59%, p = 0.01) than C, but more headache (17% vs. 11%, p = 0.035). Severity of 5 symptoms was lower in AA relative to C: edema (p = 0.038), depression (p < 0.001), anxiety (p < 0.001), tremors (p = 0.048), and dry mouth (p = 0.021). AA had more clinically important weight loss (24% vs. 16%, p = 0.024), but less depression (12% vs. 23%, p = 0.002) and anxiety (3% vs. 13%, p = 0.001) than C. AA had longer survival than C (median 2.4 vs. 1.6 months, p = 0.006).
Conclusions: We identified 7 symptoms whose prevalence and/or severity was associated with race. Caucasians had more common and severe edema, depression, depression, anxiety, tremors, and dry mouth. AA had less moderate/severe weight loss. Survival after referral was better among AA than C. Our study demonstrated that it is important and clinically relevant to examine race as a variable of cancer symptom research. This may stimulate research to evaluate racial variability in the provision of supportive and palliative care services for individuals with advanced cancer.
No conflict of interest.

1371 POSTER

The use of catumaxomab for treatment of malignant ascites in clinical practice: Results of an observational trial

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Background: The trifunctional antibody catumaxomab (anti-EpCAM x anti-CD3) is approved in the EU for intraperitoneal (IP) treatment of

malignant ascites (MA) in patients (pts) with EpCAM positive carcinomas. Catumaxomab (CATU) has been investigated in two randomized phase III and several phase I/II trials but there are no data on routine use of CATU. Therefore, a prospective observational study (CARMA, DRKS00000458) started in 2010 investigating the administration of CATU in a total of 160 pts with MA under routine conditions. Participating centers were hospitals and oncologic practices in Germany and Austria. Results of the pre-planned 2nd interim CARMA analysis are reported here.

Patients and Methods: This analysis included 103 pts with MA due to EpCAM positive carcinomas: ovarian, n = 37; gastric, n = 13; breast, n = 13; pancreatic, n = 10; colorectal, n = 6, other, n = 24. Pts were treated with CATU according to the approved posology schedule with 4 increasing IP dosages over up to 20 days. Primary endpoint was puncture-free interval (PFI). Secondary endpoints included safety and overall survival (OS).

Results: The study population was more advanced compared to the phase III studies with regard to distant metastases, performance status, time since first diagnosis of tumor and of MA. Patients were treated in 24 hospitals (73%) and in 9 outpatient facilities (27%). Before treatment, pts suffered from typical MA-related symptoms such as abdominal swelling (77%), pain (56%), dyspnea (27%), anorexia (31%), constipation (14%). 67 pts (65%), received the planned CATU schedule, 36 pts (35%) received <4 infusions. Median PFI was 57 days (d), median OS was 100 d. For the subgroups ovar/non-ovar, a median PFI of 93/41 d and a median OS of 115/72 d was observed. Preliminary results show improved quality of life after CATU therapy. Most frequent adverse events related to CATU were fever (20%), abdominal pain (17%), nausea (14%), vomiting (9%) and diarrhea (6%).

Conclusions: CARMA represents the first systematic evaluation of CATU therapy given for MA under routine conditions. Despite the fact that pts were more advanced than in prior interventional trials, the data demonstrate a clinically relevant benefit of CATU which was particularly pronounced in ovarian cancer pts. Overall, the data confirm the position of CATU treatment in clinical practice including outpatient setting for adequately selected pts with MA. The final CARMA analysis will be performed after including 160 pts.

Conflict of interest: *Advisory board: Fresenius Biotech GmbH. Corporate-sponsored research: Fresenius Biotech GmbH. Other substantive relationships: Employee Fresenius Biotech GmbH*

1372 POSTER

A phase II study of cediranib as palliative treatment in patients with symptomatic malignant ascites or pleural effusion

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Background: Malignant ascites and pleural effusion are challenging clinical problems with a major impact on quality of life. Because malignant effusions are associated with high levels of VEGF we wanted to determine the palliative effect of the oral VEGF TKI cediranib.

Materials and Methods: We conducted an open label, randomized phase II trial (ClinicalTrials.gov nr. NCT01262612). After a baseline paracentesis or thoracentesis (day 0), pts with symptomatic malignant ascites and/or pleural effusion were randomized between immediate treatment with cediranib (ITC) or delayed treatment with cediranib (DTC) on day 29, or after a new puncture was needed. The starting dose of cediranib was 30 mg orally once daily. The primary objective of the study was the puncture free survival (PuncFS), defined as the time from study start (day 1) to the first need for paracentesis or thoracentesis, or time to death, which event occurred first. Secondary objectives of the study were the change in puncture free interval (PuncFI) (defined as the difference between the PuncFS and the PuncFI before start of the study in days) and the tolerability of cediranib. Cediranib was provided by AstraZeneca for this investigator-initiated study.

Results: Twelve pts were enrolled. The median PuncFS was 45 days (range 10–368 days) in the ITC pts and 7 days (range 4−13) in the DTC pts ($P = 0.011$). The PuncFI increased with a median of 31 days in the ITC pts and shortened with a median of 3 days in the DTC pts ($P = 0.015$). Cediranib was well tolerated; the most common observed AEs were fatigue and anorexia. Dose reductions took place in 25% of pts. No bowel perforations were observed, contrary to other studies with intravenous anti-VEGF treatments for ascites. We planned to enroll 32 pts but the study was prematurely discontinued, due to slow accrual and the withdrawal of cediranib for further clinical development by AstraZeneca.

Conclusions: Cediranib increased the PuncFS and PuncFI in pts with malignant ascites or pleural effusion with an acceptable toxicity. This is the first study in which an oral VEGFR TKI showed beneficial palliative effects in pts with malignant ascites or pleural effusion. Although confirmation of these results by a larger prospective placebo-controlled trial would be preferred, the feasibility in terms of patient accrual rate appears low. Our data suggest that an oral anti-VEGFR treatment may be considered as palliative treatment in pts with malignant effusions.

No conflict of interest.

1373 POSTER

Can megesterol acetate induce thrombosis in oncology patients?

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Background: Megestrol acetate (MA) is a white, crystalline solid steroid origin medicine often use for cachexia in oncologic palliative care. Thrombosis is a common problem in oncology patients. There is a question can MA induce thrombosis in oncologic care setting? So, this trial is a retrospective, registry-based analysis to assess the thrombotic process in oncology patients using MA.

Materials and Methods: Data on oncology patients at metastatic stage using MA were obtained from the archives of our center. Outcomes of patients were evaluated if they developed any thrombotic process during the treatment.

Results: Fifty five oncology patients with metastatic disease using MA were analyzed if they developed any venous thrombosis. The median age of the patients was 64 (40−84) years. Most of the patient's diagnostic histopathology consists of lung cancer, gastric cancer, colorectal cancer, and pancreatic cancer. During the mean follow-up of 31.80 months, 34 (61.81%) patients died and 21 (38.18%) patients are still alive. The median time of overall survival (OS) was 19 months (6–180). All patients had been treated with chemotherapy. Cisplatin, taxanes, gemcitabine and 5-fluorouracil had been commonly used agent. Three patients received bevacizumab, one received cetuximab and one patients received everolismus as targeted therapy. Twenty six patients (47.27%) received radiotherapy. MA had been initiated if patient's weight loss was more than 10% on palliative care settings. The mean time of MA use was 8.69 months ($\pm$3.53). Seven thrombotic process have detected after MA use. Three of seven patient's diagnosis were pancreatic cancer. The other four patient's diagnosis were gastric cancer (2), lung cancer and endometrial cancer. Five of seven patients had received platin based chemotherapy. The patients with thrombosis non-significantly had worse OS, comparing without thrombosis ($P = 0.106$).

Conclusion: As a conclusion, in this trial it is revealed that the patients on MA treatment have rarely developed thrombosis. As a general rule, cisplatin based chemotherapy and pancreatic cancer seems to be more related with thrombosis than MS use. More detailed and prospective randomized studies should be planned on MA use in oncologic care.

No conflict of interest.

1374 POSTER

Symptomatic palliation of musculoskeletal metastasis: Efficacy and safety of intra-arterial chemoembolization

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Background: Metastasis to musculoskeletal tissues is commonly associated with severe or sometimes intractable pain. If it is not sufficiently controlled with standard therapies including chemotherapy, radiotherapy, and opioid analgesics, patients' quality of life (QoL) might be seriously compromised. This study evaluated the efficacy and safety of intraarterial chemoembolization in the palliation of the musculoskeletal metastasis resistant to standard therapies.

Materials and Methods: From 2008 June to 2012 December, intraarterial chemoembolization was tried in total 51 patients with musculoskeletal metastasis. All patients had intractable pain or discomfort unresponsive to medication and/or radiotherapy, compromising patients with serious deterioration of QoL. Correlating clinical symptoms with findings on CT or PET-CT, arterial suppliers to problematic lesions were selected. Cocktail of chemoagents (gemcitabine 200 mg, oxaliplatine 50 mg, adriamycin 10 mg mixed in glycirrhyzinic acid 40 ml) was infused, followed by 15 mg pamidronate in bone metastasis. Embolization with imipenem-induced micro-particles (40−50um) was performed when the lesions were highly vascular and safe for embolotherapy. This treatment was repeated per 4 to

8 weeks according to the patients' response and clinical condition. Changes of bone pain, analgesics consumption, and quality of life were evaluated after treatment.
Results: Technical success was achieved in 45 patients. Six patients underwent just angiography, showing no definite tumour staining in them. In 45 patients, improvement of pain (reduction of numerical pain rating scales, reduction of analgesics consumption) was demonstrated in 31 patients (clinical success 68.9%). Neurological improvement was demonstrated in 2 patients. The pain was not changed in 9 patients, and aggravated in 5 patients. Improvement of quality of life occurred in 28 patients. The time reaching maximum clinical improvement ranged from 1 day to 8 days. Clinical improvement maintained for 2 to 8 weeks. The procedure was well tolerated without significant complications.
Conclusion: Intraarterial chemoembolization is a useful, sometimes like a saviour, modality for the symptomatic palliation of musculoskeletal metastasis uncontrolled with standard therapies. However, personal difference exists in the commencement of palliation and duration of effectiveness. To maintain therapeutic effectiveness, decision for interval of procedure repetition is important.
No conflict of interest.

1375 POSTER

Initial symptom management of cancer patients, as an outcome of care, in a home palliative care unit in Greece

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Background: 'Galilee' palliative care service provides home care for adult cancer patients, in a large suburban area of Athens since March 2010. The purpose of the study was to explore symptom management of patients for the first two months of home palliative care.
Material and Methods: A total number of 162 cancer patients received home palliative care from March 2010 to December 2012. Retrospective data collection included: demographic and clinical characteristics and patients' ESAS-r (Edmond Symptom Assessment System Revised) self evaluation of symptoms (Likert type 0−10 scale) at the time of referral to the service (T_0), one month (T_1) and two months later (T_2).
Results: Most of patients were female (53.1%). Their mean age was 67.1 years and ECOG performance status 2.7. The most frequent diagnosis was lung cancer (18.5%) followed by breast (17.3%) and gastrointestinal cancer (17.3%). Most of the patients (46.9%) did not receive any antineoplasmatic treatment and 56.2% were not hospitalized during home care. Health status deterioration (27.5%), unrelieved breathlessness (19.6%) and persisted infection/ fever (15.7%) were the most prevalent reasons for hospital admission. Patients' median length of care was 54.5 days. The majority of patients (70.8%) died and 36.8% and 20.2% of them within the first and the second month respectively after referral to service. Anxiety (T_0 6.2$\pm$3.6, T_1 4.9$\pm$3.8, T_2 5.3$\pm$3.8), depression (T_0 5.9$\pm$3.3, T_1 5.2 $\pm$3.4, T_2 5.3$\pm$3.5), tiredness (T_0 5.1$\pm$3.6, T_1 4.7$\pm$3.3, T_2 4.5$\pm$3.8), and pain (T_0 4.8$\pm$3.4, T_0 4.1$\pm$3.2, T_2 4.3$\pm$3.7) were the most self reported symptoms at referral to the service and the two subsequent months. On the contrary nausea (T_0 1.1$\pm$1.0, T_1 0.8$\pm$0.6, T_2 0.4$\pm$0.1), breathlessness (T_0 1.5$\pm$1.0, T_1 1.0$\pm$0.2, T_2 1.2$\pm$0.5) and drowsiness (T_0 1.8$\pm$1.0, T_1 1.9$\pm$0.3, T_2 2.4$\pm$0.6) were less frequently reported. Overall during the study period, patients' well being improved. Moreover all of their symptoms were alleviated except for drowsiness, but only anxiety and depression at a statistical significant level ($p < 0.050$).
Conclusions: Study results highlight that regardless of the deterioration of patients' health and high rates of death among them, they reported improved well being in a home palliative care program. Further research is needed to specify the relevant involved factors.
No conflict of interest.

1376 POSTER

Four years experience of treatment painful bone metastases with magnetic resonance guided focused ultrasound

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Background: Magnetic Resonance guided Focused Ultrasound Surgery (MRgFUS) is an innovative technology combining non-invasive deposition of high intensity focused ultrasound energy into a specified target inside the body, with high resolution Magnetic Resonance Imaging (MRI) guidance and real-time thermal feedback. Starting from 2009 up to 2012 our Institute participated in the clinical randomized multi-site study to evaluate safety and efficacy of MRgFUS for palliative treatment of Bone Metastasis. This study was approved by FDA at 18 October 2012.
Material and Methods: 37 patients with painful bone metastases were treated with the ExAblate® system (*InSightec*, Haifa, Israel) at Petrov Research Institute of Oncology, St. Petersburg, Russia. Immediately after procedure patients were examined for any adverse events and after a brief recovery discharged. Patients were followed up on 1 and 3 days, 1 and 2 weeks, 1, 2 and 3 months post treatment. During each visit, treatment safety was evaluated by recording and assessment of device or procedure related adverse events. Effectiveness of palliation was evaluated using the standard pain scale (0-no pain/10-worst pain imaginable) and by monitoring changes in the intake of pain-relieving medications. A reduction of 2 points or more on pain scale was considered a significant response to treatment. 8 patients were male and 29 female. Mean age was 58 years old (19−76). The primary cancers were: 25 breast, 4 stomach, 2 bronchus, 2 bladder, 4 other. Targeted lesions were 14 osteolytic, 8 osteoblastic and 15 mixed. 27 were pelvis metastases, 4 were located in the humerus bone and 6 were located in the ribs.
Results: No significant device or procedure related adverse events were recorded. 4 patients died during the follow-up period due to disease progression, thus 3 months follow-up data includes only results of 33 patients. All patients reported significant improvement in pain with no change in their medication intake. Mean worst pain score at baseline, 1 day, 3 days, 1 week, 2 weeks, 1, 2 and 3 months post-treatment was 6.9, 6.1, 5.1, 3.5, 2.6, 1.8, 1.2 and 0.9.
Conclusions: MRgFUS can provide effective, safe and noninvasive palliative therapy for patients suffering from painful bone metastases. The ability to achieve rapid pain relief after only one treatment session, combined with the high safety profile of the procedure implies that MRgFUS has a significant potential for patients suffering from painful bone metastases.
No conflict of interest.

1377 POSTER

Attitudes and referral patterns of lung cancer specialists in europe to specialized palliative care (SPC) and the practice of early palliative care (EPC)

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Purpose: To examine availability of Palliative Care (PC) services as well as referral patterns of European Lung cancer specialists to PC and in particular the timing of this referral.
Methods: All members of the EORTC Lung Cancer Group (LCG) were asked via email to participate in an on-line survey. Three (3) emails were sent.
Results: 50 out of 170 (29.4%) EORTC LCG members replied. Among the respondents there were 24 (48%) medical oncologists, 14 (28%) radiation/clinical oncologists, 11 (22%) pulmonologists and 1 (2%) thoracic surgeon. All but one of respondents (98%) reported that either most of their practice (30%) or a substantial proportion of their practice (68%) involved the care of patients with metastatic/incurable cancer. All but two (2) of respondents (96%) had access to at least one component of PC services. Twenty seven (54%) had access to comprehensive PC services, including hospital based teams and outpatient/community based PC teams and inpatient Hospice services. In terms of referral of metastatic lung cancer patients to PC almost 75% of participants would refer almost all or most of their patients when they were close to death, while 22% or less would refer their patients at earlier stages of disease. Regarding barriers for referral to PC, negative attitudes of patients to PC was cited by 26% of participants, lack of availability of PC services by 20%, lack of expertise of PC physicians by 18%, and only 8% of participants felt that referral to PC signifies abandoning their patients, and that PC specialists interfere or discourage active oncological therapy. Although most of the respondents expressed positive attitudes towards PC, 12−22% had overtly negative attitudes towards PC. Seventy-eight (78%) of participants expressed an interest to participate in a trial of early PC (EPC).
Conclusion: There is good availability of PC services at institutions of members of the EORTC LCG. Most respondents expressed positive attitudes towards PC, however the majority of them referred patients to PC late in the disease trajectory, hence lung cancer specialists in Europe have not adopted the practice of EPC concurrent with active oncological care. Negative attitudes of patients to PC and lack of expertise of PC physicians remain the major barriers, according to Lung Cancer specialists, for referral to PC. The majority of EORTC LCG members would like to participate in a trial of EPC.
No conflict of interest.

1378 POSTER

Availability of informal caregivers for palliative care patients with cancer: Is there a difference between higher- and lower-income settings?

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Background: The modern palliative care movement started in higher-income countries where palliative care models were developed to meet the needs of patients and their families. Although the principles of palliative care are the same, the ideal palliative care models in lower-income countries may be different from that in higher-income ones due to many variables related to culture and resources. Among the factors that need to be considered when developing suitable palliative care models in lower-income settings are the availability of informal caregivers and the degree to which they are involved in the care of palliative care patients. This study was conducted to compare the availability of informal caregivers between a higher-income setting and a lower-income one.
Patients and Methods: We investigated the availability of informal caregivers for 190 palliative care patients with advanced cancer from a higher-income setting in the United Kingdom (UK) and 115 patients from a lower-income setting in Egypt.
Results: Patients in Egypt were significantly younger than patients in UK (mean age 52 vs. 71, respectively; $p < 0.001$) and were more likely to be married (84% vs. 48%, respectively; $p < 0.001$). An informal caregiver was available in 92% of the cases from Egypt compared to 76% of the cases from the UK ($p < 0.001$). While 100% of Egyptian informal caregivers were family caregivers, 10% of those from the UK were non-family caregivers. In the Egyptian setting, 100% of informal caregivers were living with the patient compared to 63% in the UK setting ($p < 0.001$). In total, 92% of Egyptian palliative care patients with cancer had an informal caregiver living with them. In comparison, 48% of palliative care patients with cancer from the UK had an informal caregiver living with them ($p < 0.001$).
Conclusions: The results of this study suggest that there are significant differences between higher-income and lower-income settings regarding the availability and characteristics of informal caregivers for palliative care patients with cancer. The palliative care models developed in higher-income countries may not be 'universally' suitable for lower-income countries. Future research is essential to develop palliative care delivery models suitable for the culture and resources in Egypt and other lower-income settings.
No conflict of interest.

1379 POSTER

Hyponatremia severity among cancer patients and its association with type of cancer and mortality

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Background: Hyponatremia is common in patients with cancer, and results in clinical symptoms that might increase the burden of the disease. It has been associated with increased mortality and length of hospital stay. The objectives of this study are to investigate the severity distribution of hyponatremia among different malignancies and study its association with mortality at a tertiary cancer center in Qatar.
Material and Methods: This is a retrospective study of all cancer patients admitted or seen at the National Center for Cancer Care and Research in Doha, Qatar between 2008 and 2012. We reviewed electronic medical records for patients and analyzed demographics and clinicopathological reports. Descriptive statistical analysis was used to determine hyponatremia severity distribution among malignancy groups. A model was built through multivariate analyses to investigate the role of hyponatremia in mortality.
Results: A total of 2048 patients were included in this study. Prostate (57.1%), pancreatic (50%), liver (49%), and lung (40.2%) cancers showed the highest frequency of severe hyponatremia, while breast cancer showed the lowest frequency at 23.5%. In the multivariate analyses, patients with moderate-severe hyponatremia (Na <130 mmol/L) were 4.28 times more likely to die than those with normal sodium levels ($p < 0.05$).
Conclusion: The present study shows that hyponatremia is a common electrolyte disturbance among hospitalized patients with cancer diagnosis. The severity of hyponatremia was a statistically significant independent factor associated with higher in-hospital mortality. This is in accordance with the reported literature and emphasizes the importance of early diagnosis and correction of hyponatremia.
No conflict of interest.

1380 POSTER

Palliative care in the last days of cancer patients admitted to Torrecardenas Hospital

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Introduction: The cancer is still an incurable disease, and in the last moments of life aims primarily to avoid the pain and consequently suffering of cancer patients. The objective of this study is to describe the characteristics of patients who died in the ward of Medical Oncology during 2012.
Material and Methods: We retrospectively reviewed all patients who died in our service between January and December 2012, and performed a descriptive analysis of the following variables: sex, age, primary tumor, symptoms that led to the hospitalization, length of hospital stay, presence of refractory symptoms, and if received palliative sedation.
Results: We analyzed 90 patients: 52 were male (57.7%) and 38 women (42.2%) with a median age of 59 years (range 23−89). According to the primary tumor: lung cancer 38.8%, non-colorectal gastrointestinal cancer 21.1%, breast cancer 10%, colorectal cancer and cervical cancer 8.8%, genitourinary 6.6% and soft tissue sarcoma and 5.5%. All patients were in an advanced or terminal stage of their condition, and 49.5% in an agonal phase. The most common symptoms that prompted admission were dyspnea (22.6%), followed by fatigue (18.6%) and uncontrolled pain (15.4%). The median stay was 11 days, but 19 patients (21.1%) died in the first day of admission. Symptoms leading to sedation were: dyspnea (42.7%), pain (26.6%) and delirium (21.8%). Informed consent (IC) was explicit in 9% of the cases, and given prior to the appearance of refractory symptoms and/or agonal phase. In 82% of sedation cases, the IC was given by a representative. Midazolam was the most used drug of choice in 91% of the cases. Up to 75% of sedations required drug changes or combinations.
Conclusions: The tumor with increased mortality was lung cancer followed by gastrointestinal cancer (esophagus, gastric and pancreas). Dyspnea as a symptom and liver failure secondary to tumor progression were the main reasons for admission. The most common refractory symptoms were: dyspnea, pain and dyspnea association with pain or delirium. The therapeutic approach to these patients is complex, since most suffer a variety of symptoms and any complications during hospitalization. In 100% of cases was agreed sedation, being in most cases the conformity with the patient.
No conflict of interest.

1381 POSTER

Exploring knowledge and experience of cancer patients in pain relief − a Greek study

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Background: The purpose of this study, funded by the University of Athens, was to explore Greek patients' knowledge and experience of cancer pain relief.
Material and Methods: A descriptive correlation research design was used. A sample of 100 cancer patients with pain was interviewed, in a central oncology hospital in Attica area. A demographic and clinical form and the Patient Pain Questionnaire (PPQ-Ferrell BR, 2000, City of Hope) were used for data collection. The PPQ consists of 16 items divided between two subscales. The 'Experience' subscale consists of seven items measuring current pain and pain relief, pain over the last week, expectation of future pain, sense of control over pain and distress related pain. The 'Knowledge' subscale consists of nine items to evaluate knowledge of, and attitudes to, cancer pain and medications. Patients rate their agreement or disagreement on 0−10 rating scales. Higher scores indicate poorer experience of pain, and poorer knowledge and attitudes.
Results: Most patients were female (55.5%), with a mean age 65.0 years. The prevalent diagnosis was lung cancer (20.0%). Median time since cancer diagnosis was 17.5 months and pain onset 6.5 months. More patients were prescribed with mild (45.0%), or strong (41.0%) opioids and only 14% non opioids analgesics. Patients reported a median knowledge about cancer pain management (5.3 ± 1.4) and a median experience of pain (5.3 ± 1.7). Although patients experienced almost severe pain over the past week (6.8 ± 2.3), they reported receiving a great deal of pain relief (3.1 ± 2.8). Patients' knowledge about cancer pain management was positively related with their pain experience (rho=0.22, $p = 0.028$). None of patients' demographic and clinical characteristics was related with patients knowledge and experience about cancer pain ($p > 0.050$). Patients'

analgesic treatment was associated with their pain experience ($z = -2.3$, $p = 0.021$). Patients prescribed with opioids described a poorer pain experience (6.4±2.0), than those prescribed with non-opioids (5.2±1.3). Additionally patients receiving opioids reported more pain over the past week (7.0±2.3 vs 5.5±2.2), present pain (4.0±2.8 vs 2.2±2.2) and more distress (7.6±2.6 vs 6.8±1.6), than those receiving non-opioids.
Conclusions: Although patients were undertreated they described a great deal of pain relief. Most patients held limited knowledge about pain and pain management, and those with poorer knowledge reported worse pain experience.
No conflict of interest.

1382 POSTER

Knowledge and experience in pain management of Greek cancer patients − the family caregivers perceptions

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Background: The aim of this study, funded by the University of Athens, was to investigate knowledge and experience of family caregivers in patient's cancer pain management.
Material and Methods: Patients with a cancer diagnosis who reported pain, in 'Ag. Anargyroi' Cancer Hospital, were approached for a three month period (January-March 2013) and accepted to name their primary family caregiver. A total of 100 caregivers consented to participate to the study. A demographic form and the Family Pain Questionnaire (FPQ-Ferrell BR, 2000, City of Hope) were administrated. The FPQ is a 16 item ordinal scale that measures the Knowledge and Experience of a family caregiver in managing chronic cancer pain. The FPQ includes 9 items that measure knowledge about pain and 7 items that measure the caregivers experience with patient's pain. Caregivers rate their agreement or disagreement on 0−10 rating scales (0= the most positive outcome, 10= the most negative outcome).
Results: Most caregivers (59.0%) were female with a mean age 52.9 years. The majority of them was patients' wife/ husband (48.0%) with no previous caregiving experience (66.0%), assisted by others (76.0%). Most of caregivers were married (76.0%) with two children (54.0%) having the same residence with the patient (66.0%). The median time of care provision was 13 months. Caregivers reported a median knowledge about cancer pain management (5.7±1.4) and a median patient's experience of pain (6.4±1.3), which were not correlated each other ($rho = -0.15$, $p = 0.146$). Caregivers reported almost severe patient's pain over the past week (6.7±2.4), mild current pain (4.2±2.9) and an inadequate pain relief (7.0±2.4). Caregivers' knowledge in pain management was associated only with patient's age ($r = 0.26$, $p = 0.006$). The caregivers of younger patients had higher score in knowledge subscale. Similarly, higher score in knowledge had those that did not receive assistance from others ($t=2.2$, $p = 0.030$). Caregivers experience with patients' pain was worse for patients receiving opioids analgesic ($z = -2.3$, $p = 0.019$) particularly strong opioids ($z = -2.7$, $p = 0.006$), than those receiving non opioids. Moreover, caregivers reported that patients receiving strong opioids had worse pain experience over the past week ($p < 0.006$) and current pain ($p < 0.018$), than those receiving non opioids or mild opioids.
Conclusions: Family caregivers had a moderate knowledge about cancer pain management and experienced undertreated their patient's pain.
No conflict of interest.

1383 POSTER

Optimal timing of influenza virus vaccination during chemotherapy treatment in adult patients with solid tumours

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Background: Higher rates of hospitalisation and mortality are described in oncology patients with influenza virus infection compared to the general population. Yearly influenza vaccination is strongly recommended for patients treated with chemotherapy or other immunosuppressive drugs. The optimal moment to administer the vaccine during a treatment cycle has not been studied extensively.
Patients and Methods: During the influenza season 2011–2012 we conducted a multicenter randomised controlled trial (OFLUVAC, NTR2858, no sponsoring) in the Netherlands. Patients receiving adjuvant chemotherapy for breast or colorectal cancer were randomized between early (day 5 after chemotherapy) and late (day 16 after chemotherapy) vaccination with the influenza virus vaccine (Influvac® 2011/2012, Abbott Biologicals B.V, Weesp, the Netherlands and Vaxigrip® 2011/2012, Sanofi Pasteur MSD, Brussels, Belgium). Influenza virus-specific antibody titres were determined before and 3 and 12 weeks after vaccination by haemagglutination inhibition.
Results: Thirty-eight breast cancer patients (early = 21; late = 17) and 18 colorectal cancer patients (early =8; late = 10) were analysed. In breast cancer patients overall serologic responses were adequate. A statistically significant higher response in patients who received early compared to late vaccination in the chemotherapy cycle was observed. Geometric mean titres post vaccination day 5 versus day 16 were 69.3 versus 27.4 (H3N2), 76.4 versus 17.5 (H1N1) and 34.4 versus 26.0 (B/Brisbane), respectively. In colorectal cancer patients overall serologic responses were adequate, no significant difference was found between early and late vaccination with the influenza virus vaccine. Geometric mean titres post vaccination day 5 versus day 16 were 170.1 versus 192.4 (H3N2), 233.0 versus 280.8 (H1N1) and 62.6 versus 75.9 (B/Brisbane), respectively.
Conclusion: The overall serologic response to the influenza vaccine in patients treated with chemotherapy for breast or colorectal cancer patients is adequate. The optimal timing of vaccination in breast cancer patients is early after receiving chemotherapy ($\leqslant$ day 5). No difference was found between early and late vaccination in colorectal cancer patients.
No conflict of interest.

1384 POSTER

Impact of chemotherapy on activated protein C-dependent thrombin generation − association with venous thromboembolism occurrence

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Background: Cancer patients have an increased risk of venous thromboembolism (VTE), which differs among patients, or even in the same patient over the course of cancer natural history. The high VTE rates observed during the first year after diagnosis have been possibly related to the administration of combined anti-cancer therapies. However, the prevalence of coagulation abnormalities or VTE occurrence as a result of different anticancer agents or treatment schemes is largely uncharacterized. Thus, we aimed at analyzing the impact of different anticancer drugs on the pro-thrombotic status of cancer out-patients scheduled for chemotherapy.
Material and Methods: Activated protein C (APC) function (by HemosIL ThromboPath) was prospectively analyzed in 505 cancer out-patients with primary or relapsing solid cancer at the start of a new chemotherapy regimen (6% neoadjuvant, 31% adjuvant and 63% metastatic treatments). Blood was withdrawn in all 505 patients prior to chemotherapy start and before the second cycle. Additional samples were obtained from 51 patients before the start of the third and sixth cycle (elapsed time between cycles: 28d).
Results: APC function was impaired in roughly 27% of all cases at baseline and significantly decreased after one cycle of chemotherapy (mean ThromboPath value: 78.0±11.8 PICI%, $p = 0.0001$). Subgroup analysis of the 51 patients who consented to repeated blood withdrawal showed that APC functionality was progressively impaired during the first 3 months of chemotherapy (82.3±8.9 PICI% at T0 vs. 78.4±12.2 PICI% at T1 vs. 78.7±11.5 PICI% at T3), but reverted to baseline levels by the sixth month (84.9±8.6 PICI% at T6; Friedman's ANOVA among the four study points: $p = 0.008$). Advanced age (>65 y, $p = 0.01$), ECOG-PS ($p = 0.01$), platinum-based ($p = 0.035$) and fluoropyrimidine-based regimens ($p = 0.008$) were independent predictors of impaired APC function during chemotherapy. Multivariate Cox proportional hazards analysis demonstrated that a decline in APC function ($HR = 2.4$; $p = 0.013$) and platinum-based regimens ($HR = 2.2$; $p = 0.042$) were both capable of predicting the occurrence of a first VTE episode during chemotherapy. Indeed, 14% of patients with platinum-associated APC impairment had VTE over a 1 yr follow-up, compared to 3% of patients treated with other regimens and in whom APC function remained stable ($HR = 1.5$; $p = 0.003$).
Conclusions: Use of platinum-based regimens is responsible for induction of an acquired thrombophilic condition in the first three months of therapy and represents a predictor for VTE even after adjustment for other risk

Table 1 (abstract 1386). Congruence scores

	All Pts	Oncology Pts	Haematology Pts	*p**
Pt Risk Score 0−11 (mean±SD)	2.82±1.94	2.81±1.88	2.87±2.15	0.6544
Correct type of prophylaxis given	48.8%	49.0%	47.8%	0.7501
Biosimilar filgrastim initiated 24−72 hrs after chemo	52.9%	58.1%	33.1%	<0.0001
Biosimilar filgrastim persisted as recommended	91.6%	92.5%	87.8%	0.4304
Overall Congruence Score 0−3 (mean±SD)	2.26±0.61	2.31±0.61	2.09±0.59	<0.0001

*Significance of difference between oncology and haematology pts.

factors. Monitoring coagulation changes during the first cycle, more than the determination of a single point measurement at baseline, could provide a valid estimate of the associated pro-thrombotic risk and might help to identify patients susceptible of developing VTE during treatment.
This work has been performed within the PhD Programs XXVI and XXVII Ciclo and was partially supported by the Italian Ministry of Health Grant MERIT RBNE08NKH7.
No conflict of interest.

1385 POSTER

Complications and mortality associated with febrile neutropenia in a Spanish multicenter cohort of patients with cancer

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Background: Febrile Neutropenia (FN) is associated with complications, mortality, severe infections and long hospital stays, in a significant number of adult cancer patients. Nevertheless, FN is a heterogeneous disease, and patients are not exposed to the same risk factors.
Patients and Method: An ambispective registry of adult cancer patients with FN from 15 Spanish hospitals was carried out from 2006 to 2013. Cases were clustered according to the primary tumor and the source of infection. Primary outcomes included mortality, complications and hospital stays. Univariate and multivariate analyses were performed to fit these variables to other well-known risk factors.

Table 1. Multivariate Logistic regression analysis: severe complications

Category	OR	95% CI	p-value
Pneumonia	3.4	1.92−6.2	<0.0001
Lower respiratory infection	2	1.21–3.58	0.007
Stomatitis ⩾2	1.9	1.25–3.05	0.003
ECOG PS ⩾2	2.3	1.31–3.56	<0.0001
Cardiovascular disease	2.08	1.22–3.56	0.007
Palliative chemotherapy	1.5	1.03–2.41	0.036
Bacteremia	2	1.23–3.36	0.005
MASCC <21	4.8	2.81–8.31	<0.0001

Results: 734 events were included with 28.5% complications, 3.8% deaths and a mean hospital stay of 7.1±5.8 days. The most frequent tumors were breast (30.3%) and lung (25.2%) cancers, while other tumors occurred at a frequency below 10%. Complications were significantly higher in patients with pancreatobiliar (68.8%) and lung (40.4%) tumors*, while breast cancer had the lowest rate (17.9%)*. Mortality was higher in patients with lung (6.6%), colorectal (10.8%) and ovarian cancer (11.1%)*. Otherwise, the most common infections were fever of unknown origin (FUO) (28.7%), stomatitis (15.2%), enteritis (11.9%) and pneumonia (10.3%). A higher rate of complications was associated with pneumonia (61.8%) and bronchitis (42%)*, whereas coughs and FUO had the lowest rates. Mortality showed a similar trend, highlighting the role of lower respiratory infections, specially pneumonia. These disparities persisted even after adjustment for comorbidities and other risk factors, as shown on Table 1. Otherwise, the rate of bloodstream infections was significantly higher in patients with catheter-related infections (42.9%), urinary infections (31.4%) and cellulitis (25%)*.
*$p < 0.05$ (z-test of proportions with Bonferroni method for multiple comparisons).

Conclusions: This study revealed several risk factors for complications, mortality and longer hospital stay, with potential implications for prevention and treatment, especially in lung cancer and respiratory pneumonia.
No conflict of interest.

1386 POSTER

Congruence to EORTC guidelines of biosimilar filgrastim treatment in patients enrolled in MONITOR-GCSF

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Background: The MONITOR-GCSF study is a prospective observational study of practice patterns and outcomes of biosimilar filgrastim (Zarzio®, Sandoz) for prophylaxis of chemo-induced febrile neutropenia (CIN/FN). One study objective is to describe the congruence of individual patients' (pts) biosimilar filgrastim treatment with the 2010 EORTC GCSF guidelines. The goal of this interim analysis is to assess the internal validity of a proposed congruence scoring methodology.
Methods: A methodology for scoring pt-level congruence of actual biosimilar filgrastim treatment with EORTC guidelines was developed (possible range 0−3). Scoring focuses on 4 aspects of therapy: 1) pt risks; 2) primary vs. secondary prophylaxis, 3) day of treatment initiation, 4) persistence. We conducted this interim analysis on 1168 pts enrolled to date (target 1500) from 139 centers in 12 European countries.
Results: In this mainly female (61%) and older (61.6±11.7 y) sample with predominately (79%) solid tumours, 11% of pts were on chemo regimens with <10%, 54% on regimens with 10−20%, and 35% on regimens with >20% FN risk. Table 1 summarizes biosimilar filgrastim congruence scores by tumour type. About half of pts were treated with biosimilar filgrastim (either primary or secondary prophylaxis) as recommended by the guidelines; just over a quarter of pts on chemo with FN risk >20%, or 10−20% FN risk in combination with other pt-related risk factors, did not receive primary prophylaxis as recommended. Half were initiated 24−72 hours after chemo and with few exceptions pts persisted as recommended.
Conclusions: Variability in biosimilar filgrstim (Zarzio®) treatment is captured in the congruence scoring indicating internal validity. Proportionately more oncology pts were initiated within the 24−72 hr time window, explaining also the higher overall congruence scores in these pts. Initiation time for haematology pts may need to be reconsidered. The relationship between EORTC guideline congruence and clinical outcomes will be evaluated at study end.
Conflict of interest: *Advisory board: HL, MB, MA, PG, CB are part of the Monitor GCSF advisory board for Sandoz. Corporate-sponsored research: HL, MB, MA, PG, CB, KD, IA, KM are all involved in Sandoz-sponsored research (Monitor GCSF study). Other substantive relationships: MT and MM are employees of Sandoz Biopharmaceuticals*

1387 POSTER

The use of probiotics in people with cancer: A systematic review

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Background: Probiotics are living microorganisms that are generally thought of as being beneficial to the recipient. They may be consumed

as dairy drinks and have been shown to be effective in people with acute infectious diarrhoea. Probiotics may have a role in people with cancer, as various cancer treatments often lead to diarrhoea; however, guidance for their use is yet to be determined. People with cancer are often immunocompromised, so it is important to assess for adverse events such as infection, which could potentially be a consequence of deliberate ingestion of living microorganisms.
Materials and Methods: A systematic review was performed to collect, analyse and synthesise all available data on the efficacy and safety of probiotics in people with cancer (PROSPERO registration: CRD42012003454). Randomised control trials (RCTs), identified through screening multiple databases and grey literature, were included. Primary outcomes were the reduction in duration, severity and incidence of antibiotic-associated diarrhoea and chemotherapy-associated diarrhoea, and adverse events, especially probiotic-associated infection. All included studies and data extraction forms were independently reviewed. Where possible, data was combined for meta-analysis by a random effects model, assessing causes of heterogeneity, including differences in strains, dosage and patient characteristics.
Results: Data was extracted from 10 RCTs totalling 1431 participants. There was little strong evidence of difference in mean number of average daily bowel movements between probiotic and control groups of −3.98 stools per day [95% confidence interval (CI)-14.99 to 7.04; p = 0.48]. Liquid stools tended to be less common in the probiotic group [odds ratio (OR)=0.37; 95% CI 0.06 to 2.43; p = 0.30], whereas soft/semi-solid stools possibly occurred more often (OR=2.12; 95% CI 0.49 to 9.18; p = 0.31). The change in enterobacteriaceae count was lower in the probiotic group; mean difference of −1.98 (log10 CFU/g of faeces) (95% CI −2.56 to −1.39; p < 0.00001) compared to the control group. Probiotics seemed to decrease the use of rescue (anti-diarrhoeal) medication (OR=0.63; 95% CI 0.27 to 1.45; p = 0.28). No probiotic-associated infection was identified in any of 1311 patients assessed for adverse events.
Conclusions: There is a potential that probiotics may reduce the severity and frequency of diarrhoea in patients with cancer and may reduce the requirement for anti-diarrhoeal medication, though there is currently insufficient evidence with which to draw conclusions. More studies are needed to assess the true efficacy and safety of probiotics in people with cancer.
No conflict of interest.

1388 POSTER

Neutropenia score as an overall survival (OS) prognosis factor

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Background: Chemotherapy (CT) is a common cause of neutropenia (N). N is a prognostic factor in several studies. Prognostic value of N can be evaluated with global scores calculated over the whole CT period.
Methods: Patients included in the PROCHE program between 2008 and 2011 at the HEGP hospital (Paris, France). PNN levels were assessed at least once before each CT and graded using the CTC-NCI scale: 0: >2000, 1: [2000–1500[, 2: [1500–1000[, 3: [1000–500[, 4: <500. Scores were calculated as weighted mean of grades from 1st cycle to end CT (mean grade per cycle when multiple values). OS was calculated from CT initiation to death or censured at last contact. Cox regression covariates: age, tumor localization, disease setting, neutropenia after 1st cycle, and continuous or categorized PNN score. Patients with localized (M0) or metastatic (M+) disease during the study period led to two distinct cohorts: C1 and C0 according to M1 or M0 period considered. Bootstrap validation was performed using 1000 samples.
Results: Among the 1279 pts who entered the program, data were available for 657 who had at least 1 assessment of PNN. Excluded pts (622) due to lacking or dubious PNN results did not differ (log-Rank=0.98). Median age=63 y, sex-ratio=1, more frequent localization: lung (25%), breast (21%), urogenital (21%), ovary (13%), ENT (12%). 269/388 and 191/466 pts had localized/metastatic disease respectively for C0 and C+. Median cycles received: 4 (IQR=5). Median follow-up time=26.9m. Median PNN (/μl) was 4400 at baseline and 3820 thereafter. Score: 308 pts (47%) and 349 had a score>0 (S+: at least 1 neutropenia) and a score=0 (S0), respectively. 148 (22%) were S+ as soon as the 1st cycle. OS (m, 95% CI) was S+=35.2 (28.5-NR) and S0=17.0 (14.5–21.5). PNN continuous score was an independent predictor of OS: HR(C0)=0.70 (0.56–0.88), HR(C1)=0.72 (0.56–0.91). Categorical PNN score (S+/S0): HR(C0)=0.58 (0.45–0.73), HR(C1)=0.55 (0.43–0.69). The deeper the neutropenia after 1st cycle, the longer the OS. Other independent factors were age, disease setting, ENT and lung tumors. The model was internally validated (C-index=0.732, shrinkage=0.956).
Conclusion: Neutropenia scored over the whole CT period is a strong prognostic factor of OS.
No conflict of interest.

1389 POSTER

Epidemiology, resistance profile and origin of bacteremia in non-neutropenic patients with solid tumor

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Background: In oncology, and especially for solid tumors, the principal studies describe bacteriema in patients with neutropenia, Few microbiological data are available without neutropenia. Furthermore, bacteria resistance in immucompromised patients is increasingly reported.
The aim of this study is to describe the bacteremia occurring in solid tumors and to identify a potential association with other sites of infection.
Materials and Methods: This retrospective study was conducted in patients visiting an emergency oncology department for acute onset symptoms. Urinary, skin and/or sputum samples were analyzed according to clinical symptoms. Central venous catheter infection (CVC) was defined with the differential time to positivity between hub-blood and peripheral-blood cultures.
Results: We reported 290 bacteremia, Gram-positive represented 58%: coagulase-negative staphylococci (CNS) (n = 105), *Staphylococcus aureus* (SA) (n = 38) (one methicillin-resistant), *Streptococcus* sp (n = 36). The majority of gram-negative were Enterobacteria (E) (n = 97) and most of them were *E coli* (n = 62). Only 2 (*E coli*) developed extended spectrum beta-lactamases resistance. Two ore more microorganisms were found in 41 bacteremia.
When CNS, SA and *Candida* sp were isolated it was most often related to CVC, and, 25/98 of E bacteremia were also attributed to a catheter infection.
It is important to highlight that all the bacteremia were associated with another site of infection.
Conclusion: In patients with solid tumors without the context of neutropenia, all the bacteremias are associated with documented sites of infection. Bacteria resistance is the exception (1%), 58% of the bacteremia are Gram-positive microorganisms and catheter infection could be with Enterobacteria microorganisms.
No conflict of interest.

1390 POSTER

Real-world hypertension (HTN) adverse events (AEs), interventions and outcomes in bevacizumab (BV) − treated patients

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Background: HTN is one of the most common AE associated with BV. In clinical trials, the incidence of NCI CTCAE Grade 3 or 4 HTN ranged from 5−18%. Utilizing US clinical practice data, this study aimed to understand the occurrence of HTN AE, interventions and outcomes in cancer patients receiving BV.
Methods: Adult patients with select cancer types including mCRC, NSCLC, mBC, OC and other indications who initiated BV between 2007 and 2011 were identified from the IMS US Oncology Electronic Medical Record database. Patients were followed for 12 months post initial administration of BV for the occurrence of HTN events, defined as either elevated/suboptimal blood pressure (BP) readings, HTN related diagnosis, or use of antihypertensive medications. Post AE interventions, including BV treatment modification and/or HTN treatments, as well as HTN outcomes were evaluated.
Results: Final sample consisted of 3,850 adult cancer patients; median age was 61 years and 62.9% were female. The top four cancer types–mCRC (43.8%), non-squamous NSCLC (26.4%), mBC (23.6%), OC (4.6%)-- accounted for almost all study patients, and most were stage III or IV. Baseline HTN were observed in 37.7% (n = 1,453) of patients; most of them (90.3%, n = 1312) did not have an exacerbation during the 12-month follow-up. Overall, 21.1% (n = 811) of patients had either newly developed HTN (n = 670; 28.0% of patients without baseline HTN) or exacerbated HTN (n = 141; 9.7% of patients with baseline HTN). 54.4% (365/670) of patients with newly developed HTN and 34.8% (n = 49/141) of patients with exacerbated HTN were grade 3 or 4. The majority continued BV post AE; only 9.6% had a BV dose reduction, 3.3% had a dose withheld and 18.9% discontinued BV. HTN medications (new or addition to existing) were prescribed for 58.8% of the AE patients (n = 477); diuretics or ACEI were most commonly prescribed. BV modification and HTN treatments mostly occurred within 2 weeks of each other (92.5%). Among approximately half

of the HTN AE patients (n = 406) with known HTN status before the end of follow-up, 92.3% (n = 375) had HTN resolved within 45 days; only 7.6% (31 patients) were confirmed to have persistent HTN.
Conclusions: Results of this real-world study suggest that after BV treatment, HTN AE occurred in 9.7% of patients with baseline HTN and 28.0% of patients with normal baseline blood pressure. In most cases, the AE is manageable without causing significant interruptions to BV treatment in patients.
Conflict of interest: *Ownership: E.Yu owns stock/options of Roche. Corporate-sponsored research: Genentech Inc. sponsored this research. Other substantive relationships: E.Yu, A.Ravelo, and K.Look are employees of Genentech Inc.*

1391 POSTER

Osteonecrosis of the jaw (ONJ) in patients with renal cell cancer (RCC) treated with bisphosphonates and sunitinib or other biological agents: Characteristics of 39 cases in a multicenter survey

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Background: Up to 35% of advanced renal cell cancer (RCC) develop bone metasteses and are often treated with Bisphosphonates (BPs), mainly Zoledronic Acid. Osteonecrosis of Jaw (ONJ) is a complication of BP treatment, but it was rarely reported in RCC patients in first years of ONJ observation (2003–2006). Recent studies reported that angiogenesis suppression may play a role in increasing risk of BP-related ONJ. On the other hand, treatment and prognosis of most metastatic RCC patients have improved thanks to availability of 7 novel agents: one anti-VEGF monoclonal antibody (Bevacizumab), 4 Tyrosine Kinase Inhibitors (TKIs), i.e.Sorafenib, Sunitinib, Pazopanib and Axitinib, and 2 mTOR inhibitors, i.e.Temsirolimus and Everolimus. Recently sporadic ONJ cases have been reported in RCC patients receiving both BPs and biological agents, and even Sunitinb alone. An interaction between BPs and biological agents towards an increased ONJ risk has been suggested, underlined by EMA (European Medical Agency) alerts.
Materials and Methods: Three Medical Oncology units and 5 referral Oral Medicine and Surgery centres in Italy were asked to look for cases of ONJ in RCC patients in their database. Collected characteristics: age; sex; BP treatment (type and duration at ONJ diagnosis time); biological agent treatment ongoing at ONJ diagnosis time, its duration, and eventual other targeted therapy administered in the past; basic data about ONJ (site, ONJ risk factors or triggers).
Results: Charts of 39 ONJ patients have been found, treated with BPs (34 receiving Zoledronic Acid only, 1 Ibandronate, 2 Pamidronate, 2 switching from Pamidronate to Zoledronic Acid) and biological agents (27 Sunitinib, 3 Sorafenib, 1 Bevacizumab, 1 Deforolimus, 7 two or more of these agents in sequence) at time of ONJ diagnosis. Patients' characteristics: 32 males/7 females; median age 62 years (range 45−85). BP treatment duration at ONJ onset: median 12 months (range 1−48). Latest biological treatement was Sunitinib on 34/39 cases (87%). Treatment duration of latest biological agent at ONJ onset: median 8 months (range 1−26). Site of ONJ: 20 in mandible, 14 in maxilla, 4 in both (1 unspecified). Possible risk factors or precipitating events (teeth extraction, oral surgery, dental implants, ill-fitting denture, infections, etc.) have been reported on 28/39 cases (72%).
Conclusions: At our best knowledge, only 16 similar ONJ cases in RCC patients have been reported in recent medical literature as case reports worldwide. Furtherly, 5 ONJ cases among 21 patients were recorded by Bozas et al (ASCO 2011) and 5 out of 49 patients by Beuselinck et al (BJC 2012), with high ONJ cumulative hazard after 24 months of treatment with BPs and TKIs. The unexpectedly high number of cases collected in our survey (39 ONJ cases in 8 Italian centers) suggests that ONJ incidence in RCC patients could be largely underestimated in literature and seems to confirm a potential role of antiangiogenic agents and other biological agents in increasing ONJ risk in RCC patients treated with Bisphosphonates.
Conflict of interest: *Ownership: NO. Advisory board: C. Porta (GSK, Pfizer, Bayer-Schering, Novartis, Astellas, Aveo, Boehringer-Ingelheim). Board of directors: NO. Corporate-sponsored research: C. Porta (GSK, Pfizer, Bayer-Schering, Novartis, Astellas, Aveo). Other substantive relationships: C. Porta (GSK, Pfizer, Bayer-Schering, Novartis, Astellas)*

1392 POSTER

First comparison of biosimilar epoetin alfa and darbepoetin alfa for the treatment of chemotherapy-induced anaemia

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Background: A biosimilar epoetin alfa (Binocrit®) was approved in 2007 for the treatment of chemotherapy-induced anaemia (CIA). There is currently little, if any, comparative data on the relative effectiveness of this biosimilar epoetin alfa and darbepoetin alfa in this setting.
Patients and Methods: This was a retrospective, matched-cohort analysis of patients from a single centre with solid tumours and CIA. Patients were treated with biosimilar epoetin alfa 40,000 IU once weekly (n = 95) or darbepoetin alfa 500 μg once every 3 weeks (n = 50), with the aim of achieving a haemoglobin (Hb) level of 12 g/dL. For this analysis, both treatments were assessed against several parameters, including Hb outcomes and red blood cell (RBC) transfusion requirements.
Results: The two cohorts were well matched in terms of tumour type (85% and 81% in the biosimilar epoetin alfa and darbepoetin group, respectively, were patients with breast cancer) and chemotherapy received (>50% in each group received one of the following regimens; docetaxel/adriamycin/cyclophosphamide [TAC] and 5-fluorouracil/doxorubicin/cyclophosphamide [FEC] with or without docetaxel). All patients received concomitant oral iron. Mean (SD) Hb level before erythropoiesis-stimulating agent (ESA) treatment was 9.85 (0.57) g/dL in the biosimilar epoetin alfa group and 9.92 (0.62) g/dL in the darbepoetin group. The mean maximum Hb achieved was 11.91 and 11.93 g/dL in the biosimilar epoetin alfa and darbepoetin group, respectively. The median time to achieve a Hb increase >1 g/dL was 2 weeks in both groups, and median time to achieve an increase >2 g/dL was 4 weeks in both groups. Four patients (4.2%) in the biosimilar epoetin alfa group and 3 (6%) in the darbepoetin group underwent RBC transfusion during their period of ESA therapy. No adverse events were recorded in either group.
Conclusions: The ability of biosimilar ESAs to effectively and safely treat CIA is the subject of debate. These data indicate the real-life clinical effectiveness and safety of managing CIA with biosimilar epoetin alfa (Binocrit®). Once-weekly treatment with this agent appears to be as effective as darbepoetin once every 3 weeks for raising Hb levels and transfusion avoidance in patients with solid tumours and CIA.
No conflict of interest.

1393 POSTER

Utility of 2D-speckle tracking echocardiography in diagnosis of left ventricular dysfunction in anti-ErbB2 therapy

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Background: ErbB2 is overexpressed in about 25% of breast cancers; in the heart, it modulates myocardial development and function. Trastuzumab (T), an anti-ErbB2 inhibitor, has improved the prognosis of patients with breast cancer, but is related to an increased risk of asymptomatic left ventricular (LV) dysfunction (3−34%) and heart failure (2−4%). Conventional measures of ventricular function, such as fractional shortening (FS) and ejection fraction (FE) are insensitive in detecting early cardiomyopathy induced by antineoplastic therapy.
Here, we aim at assessing whether myocardial strain by 2D-speckle tracking (ST) is able to identify early LV dysfunction in mice treated with doxorubicin (D) and T, alone or in combination (D+T) and to relate data of cardiac function with tissue alterations.
Material and Methods: Cardiac function was measured with FS, by M-mode echocardiography, and with radial myocardial strain with ST in sedated C57BL/6 mice (8−10 wk old) at time 0, 2 and 6 days of daily administration of D (2.17 mg/kg/day), T (2.25 mg/kg/day), D+T (2.17 mg/kg/day + 2.25 mg/kg/day, respectively) and in a control group. In excised hearts, we evaluated TNFα and CD68 by immunohistochemistry; interstizial fibrosis was analyzed with picrosirius red staining.
Results: FS was reduced in group D and D+T at 2 days (52±0.2% and 49±2% respectively), both $p < 0.001$ vs 60±0.4% (sham), while in group T it decreased only at 6 days (49±1.5% vs 60±0.5%, $p = 0.002$). In contrast, after 2 days, myocardial strain was already reduced not only in D and D+T, but also in T alone: 43±3%, 49±1%, and 44±7%, respectively, all $p < 0.05$ vs sham (66±0.6%). Cardiotoxicity was associated with significant alterations in extracellular matrix remodeling as confirmed by an increase of interstizial collagen with D (4.56%), T (2.17%) and D+T (3.77%) at 6

days $p < 0.05$ vs sham (1.17%) and by increased cardiac inflammation, in fact the myocytes were positive for TNFα and CD68 cells/mm^2 at 6 days in group D (16.46% and 155 respectively), in group T+D (12.35% and 74.16) and in group T (5.65% and 72.32) $p < 0.01$ vs sham (0.56% and 2.3).
Conclusions: Myocardial strain identifies LV systolic dysfunction earlier than conventional echocardiography and can be a useful tool to predict cardiotoxicity in this setting.
No conflict of interest.

1394 POSTER

Is there any role of intravenous iron for the treatment of anemia in patients with cancer?

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Background: Anemia is a major cause of morbidity in cancer patients resulting in poor physical performance, prognosis and therapy outcome. Anemia causing clinical symptoms is characterized as a decline of haemoglobin (Hb) below 12 g/dL. The incidence of anemia in initial diagnosis of cancer is about 50% or more, depending on the type and stage of disease. Iron deficiency as a cause of anemia in oncology can be considered under two main headings, those of reduced iron intake and those of increased iron loss. The aim of this study is to evaluate the effect of intravenous (IV) iron treatment on anemia, blood transfusion rates and survival.
Material and Methods: Anemia is defined by World Health Organization criteria; Hb <12 g/dL in women and <13 g/dL in men, and Iron deficiency was defined as serum ferritin <20 μg/dL. The medical records of 34 patients who had IV iron treatment between January 2008 and October 2012 were reviewed. Of these patients, 11 had metastatic disease receiving palliative treatment while 23 had localized disease receiving adjuvant treatment. Patients with haemoglobin levels between 9 and 10 mg/dL, without anemia symptoms undergoing treatment either with chemotherapy, radiotherapy or both were administered IV iron infusion (100 mg IV iron sucrose in 100 mL of saline solution, in 30 minutes, 5 times in 10 days). All patients were followed regularly by physical examination, complete blood count, serum ferritin and serum iron levels one month after the end of IV iron administration and at every 3 months subsequently. The profile of anemia over 24 months of follow-up was analyzed.
Results: Median age was 57 (range 24−81), 58.8% were female and 25.6% had gastrointestinal cancers. Median follow-up period was 19.5 months. Initial median serum hemoglobin, serum ferritin and serum iron levels were 9.2 g/dL, 63 μg/ml and 30 ng/dL respectively. All patients received IV iron as described above during their planned treatment. Median serum hemoglobin, serum ferritin and serum iron levels 1 to 3 months after intravenous iron treatment were 10.7 g/dL, 259 μg/mL and 63 ng/dL, respectively. During 6 to 12 months of follow up, median serum hemoglobin was 11.4 g/dL, serum ferritin was 138 μg/ml and serum iron was 52 ng/dL. At the end of the follow-up period, only 9 patients needed blood transfusion. In this study, IV iron increased serum hemoglobin, serum ferritin and serum iron levels with decreased necessity of blood transfusion.
Conclusions: IV iron is efficacious and effective for the treatment of anemia in cancer patients under treatment either with chemotherapy, radiotherapy or both. Increase of hemoglobin by IV iron administration is cheap and safe and it may prevent blood transfusion and associated complications.
No conflict of interest.

1395 POSTER

Comparison of the effect of filgrastim vs. lenograstim started during febrile neutropenia attack in patients with solid tumors

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Background: Chemotherapy induced Febrile neutropenia (FN) in solid tumors causes mortality and morbidity at a significant rate. In this study, we aimed to compare the effects of filgrastim or lenograstim started with the first dose of antibiotics in patients diagnosed with FN.
Patients and Methods: Between february 2009 and May 2012, one hundred and fifty one patients diagnosed with FN were evaluated retrospectively. Patient's characteristics and other data were collected from patient files. Febrile neutropenia was defined as the number of a single body temperature equal or greater to 38.3ºC measured from mouth or a constant body temperature with equal or greater to 38.0ºC in one hour period in patient with neutropenia which has an absolute neutrofil count less than 500/mm^3. Whenever febrile neutropenia was defined antibiotics to gether with granocyte colony stimulating factors(GCSF) either filgrastim or lenograstim started in 30 minutes.
Results: In this study 175 febrile neutropenia attacks in 151 patients were examined. Seventy three of the patients were male and 78 of them were women. The median age was 53.6 and 53.6 in male and females respectively. The most common solid tumor was breast carcinoma in 38 (25%) patients. One hundres and five FN patients (58%) were patients who received GCSF as primary propylaxis. Demographic characteristics and laboratory findings of patients given Filgrastim and Lenogastrim are represented in Table 1.

Table 1. The characteristics of cases according to the type of GSCF given during febrile neutropenia attack

	Filgrastim use (n = 131)	Lenogastrim use n = 44	P value
Number of cases (M/F)	65/66	21/23	0.82
Age	52.45±15.54	53.13± 17.05	0.76
Days with fever (Mean±SD)	2.27±1.63	2.73±2.40	0.44
Comorbid illness (Y/V)	75/56	23/21	0.56
Number of days in hospital (Mean)	7.79±5.93	7.75±4.63	0.42
Recovery day from neutropenia (Mean)	3.31±1.55	4.00 ±1.79	**0.02**
Number of days given GSCF in hospitalization (Mean)	4.31±2.02	5.46±2.36	**0.002**
Duration of antibiotic treatment (Mean)	7.36 ±5.10	7.66±4.85	0.45

Conclusion: Compared to lenograstim filgrastim shortens the duration of hospitalization time during FN attack by correcting neutropenia faster in solid tumors.
No conflict of interest.

1396 POSTER

Evaluation of sleep disorders in cancer patients with Pittsburgh Sleep Quality Index

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Background: The estimated prevalence of insomnia in cancer patients varies between 23% and 61%. Insomnia, poor sleep quality, short sleep durations are the most common problems seen in cancer patients. In Turkey, there are not enough studies about sleep disorders of cancer patients and more studies are needed. In our study we aimed to investigate the frequency of sleep disorders and the effects of these problems to the quality of life in cancer patients.
Material and Methods: 314 patients receiving chemotherapy for cancer are involved in our study. After getting informed consent from the patients Pittsburgh Sleep Quality Index (PSQI) was administered as a self-report instrument.
Results: The median age for women was 54.8 while for men the median age was 61.8. 53.2% of patients were female, and 46.8% were male. 33.8% of patients had gastrointestinal system malignancies 22.6% had breast cancer, 21.7% had lung cancer, 8.3% had gynecological and 13.7% had other type of malignancies. From the Psychometric evaluation of the Turkish version of the Pittsburgh Sleep Quality Index (PSQI) in cancer patients, 127 (40.4%) had patients had global PSQI scores >5, indicating poor sleep quality. There were no statistically significant difference in PSQI scores between patients according to sexuality, marital status, stage and chemotherapy type ($p > 0.05$). when PSQI was evaluated according to metastatasis regions the patients with bone and visseral metastasis had more lower PSQI scores (p:0.006). In patients with ECOG scores 3 or more had lower PSQI scores (p: 0.02).
Conclusion: PSQI is short,easy to administer, and has well established validity and reliability. This questionnaire may be used to evaluate the sleep disorders in cancer patients. It is important to determine the sleep disorders in cancer patients and the effect of insomnia to patients'quality of life.
No conflict of interest.

1397 POSTER

Epidemiological characteristics of febrile neutropenia in medical oncology unit: Torrecardenas Hospital experience

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Background: Febrile neutropenia (FN) in cancer patients is among the most serious complications related to chemotherapy. In patients with febrile neutropenia are treated with empirical antibiotics until the absolute neutrophil count (ANC) has recovered and the fever has abated. The aim of this study was to analyze the characteristics and infectious complications of neutropenic patients in a referral hospital.
Material and Methods: We retrospectively reviewed 51 patients (pts) diagnosed with febrile neutropenia of Torrecardenas Hospital between January and December 2012. We analyzed: age, sex, neutrophil count, daily living abilities of patients with ECOG performance status (Eastern Cooperative Oncology Group), type of neoplasic, chemotherapy and evolution. We also analyzed the microbiological variables.
Results: The following variables were studied: age 58±13 years, sex 19 males (34%) and 36 females (66%). ECOG performance status: 0 (24 patients: 43.6%), 1 (17 patients: 30.9%), 2 (8 patients: 14.5%), 3 (6 patients: 10.9%). We analyzed the neoplasia type: breast in 25 patients (45.5%), lung in 13 patients (23.6%), gastric in 6 patients (10.9%) and other (ovarian, prostate and pancreas cancer) in 9 patients (16%). Nine (17.5%) had an ANC less 100 cells/mm(3), 12 (23%) one between 100–300 cells/mm(3) and 30 (58%) an ANC greater than 300 cells/mm(3). Thirty five (70%) patients showed ANC recovery in 1−3 days, and 16 (30%) within 4−7 days. The overall mortality was 2 (3.6%) patients. 69.1% (38 patients) received adjuvant chemotherapy. 90% received granulocyte colony stimulating factors (GCSF). Blood cultures were performed in all patients. Only two blood cultures were postive (with methicillin-susceptible staphylococcus aureus). The source of the feber were found in 8 patients: urinary in 2 patients, lung in 3 and abdominal in 3. The most used antimicrobial agents were cefepime and amikacine (65%). 47.3% of patients received antibiotics at discharge (combinations with: fluoroquinolones + amoxicillin clavulanate).
Conclusions: The use of intravenous antibiotics, in addition to GCSF, in treatment of patients with chemotherapy induced febrile neutropenia accelerates neutrophil recovery, and shortens antibiotic therapy and hospitalization.
No conflict of interest.

1398 POSTER

Dutch multidisciplinary evidence-based guideline 'Malnutrition in patients with cancer'

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Background: Malnutrition is highly prevalent in patients with cancer, however, a multidisciplinary evidence-based guideline was not available in the Netherlands. Therefore, the aim of this project was to formulate evidence based recommendations for daily practice to support optimal nutritional care.
Material and Methods: With an inventory among patients and professional care givers, the most important bottlenecks concerning malnutrition and cancer were selected. A multidisciplinary expert group was initiated consisting of an oncologist, surgeon, radiation oncologist, general practitioner, nursing home physician, patient, oncology nurses, oncology dieticians, epidemiologist and with process management of IKNL (Cancer Center the Netherlands). Seven research questions were formulated using the PICO method (P=population; I=intervention; C=control group; O=outcome). Thereafter, a systematic literature search was performed in Pubmed, Embase and Cinahl for the period 1995 till 2010. All articles were evaluated on methodological quality and summarized in evidence tables. The recommendations where formulated using the EBGD method.
Results: From the 5250 articles found in the literature search, 320 were used to answer the research questions. For the following topics the multidisciplinairy guideline describes recommendations for daily practice based on the conclusions from the literature and considerations of the expert group.
1. The definition of malnutrition in patients with cancer and the determination of malnutrition.
2. The consequences of malnutrition.
3. The value of early screening of malnutrition and the preferential screeninginstrument.
4. The increase of requirements for energy, protein and other nutrients in cancer?
5. The effect of nutritional counseling and oral nutritional supplements on malnutrition.
6. The effect of enteral and parenteral nutrition on malnutrition during surgery, radiotherapy, chemotherapy and in the palliative stage of disease.
7. The effect of pharmacological interventions on malnutrition in patients with cancer.

Conclusion: The Dutch multidisciplinary evidence-based guideline 'Malnutrition in patients with cancer' describes the definition, prevalence and consequences of malnutrition in patients with cancer and provides recommendations for the diagnosis, early detection (nutritional screening) and interventions which can be used to treat malnutrition. This guideline is being implemented in clinical practice of all professionals dealing with malnutrition in cancer patients.
No conflict of interest.

1399 POSTER

Safe omission of blood test prior to day 8 dose of oral vinorelbine

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Background: Vinorelbine is a standard treatment for non small cell lung cancer (NSCLC) and advanced breast cancer (ABC). The main dose limiting toxicity is neutropenia and a blood test is recommended prior to each administration. However the incidence of neutropenia detected following a blood test is not known. In addition, the test requires resource on the day ward and incurs laboratory and transport costs, as well as putting pressure on peripheral veins. As most of the patients receiving vinorelbine are being treated in the palliative setting, it is important to minimise any impact on quality of life. We perceived a low incidence of dose delays and haematological toxicity with vinorelbine so initiated an audit of day 8 blood tests and their consequences, with a view to omission.
Methods: Retrospective review of chemotherapy charts/laboratory results of all patients receiving vinorelbine at the hospital between January 2012 to February 2013. Further patients number until August 2013 will be evaluated and included at the time of presentation.
Results: Twenty-five were identified who received vinorelbine in the selected time frame. Seven patients were male and 18 were female with an age range 39 to 82 years. Thirteen patients were receiving vinorelbine for NSCLC and 12 for advanced breast cancer; 13 received vinorelbine as a 1st line treatment, 5 as 2nd line and 7 as 3rd line. 16 patients received vinorelbine in the oral form and 9 as iv.
Vinorelbine was scheduled 121 times and was deferred on 10 (8.3%) occasions, with only 3 delays due to neutropenia. The absolute neutrophil count was found to be below 1 000/mm (grade 3)on five occasions; however vinorelbine was given on time for two of these following careful clinical assessment.
Conclusion: Our data shows that in 121 cycles of treatment, deferment due to neutropenia was only required on three occasions. On the basis of a low incidence of dose delays and haematological toxicity we plan to initiate a local policy of omitting the day 8 blood test in selected patients. There are five published audits looking at the value of a day 8 blood test with vinorelbine. They have generally concluded that the blood test can be omitted provided that patients are reviewed by an oncologist before a day 1 dose, and undergo a telephone assessment by the Oncology nurse specialist before a day 8 dose. We believe our results will support this recommendation.
No conflict of interest.

Proffered Papers Session (Sun, 29 Sep)
Public Health and Epidemiology

1400 ORAL

Discrepancies in cancer incidence and mortality and its relation to health expenditure among the 27 European Union member states

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Background: The European Union (EU) is a political and economic confederation composed by 27 member states (EU-27). EU-27 has established a common market by standardized systems of laws, common policies on trade and legislation in justice and home affairs. The EU-27 is not in charge of promoting health care, this is responsibility of the national governments nevertheless, the Charter of Fundamental Rights of the EU states in article 35, that 'A high level of human health protection shall be ensured.' We aim to evaluate the EU-27 health expenditure and its relation to cancer incidence and mortality.
Material and Methods: This is a descriptive study based on data extracted from the World Health Organization, the International Monetary Fund and the World Bank databanks. To visualize the potential links between cancer indicators and the health expenditure descriptive scatter plots were made. For approximate health expenditures, we have examined countries' population, total and per capita gross domestic product (GDP), percentage and per capita GDP allocated to health and percentage of government health reimbursement.
Results: Health expenditure is higher in Western Europe. The 'cutoff' west-east is around 2600 dollars per capita/year. Higher GDP per capita is related to higher allocation of GDP in health. In both blocks the national governments reimbursed most health expenses. West Europe has higher cancer incidence and lower mortality than East Europe. This discrepancy is more marked in breast cancer.
Conclusion: The 27 EU member states seem to be compliant with article 35 as most of the health costs are reimbursed by the national governments. Higher health expenditure is related to increased cancer incidence and reduced cancer mortality. Although cause-effect cannot be established through this data this is a rational association. We are conducting further studies exploring the relationship of national drug usage with cancer indicators.
No conflict of interest.

1401 ORAL

State of oncology 2013

P. Boyle[1], R. Sullivan[2], C. Zielinski[3], O.W. Brawley[4]. [1]*International Prevention Research Institute, Lyon, France;* [2]*Kings Health Partners Integrated Cancer Centre, London, United Kingdom;* [3]*Medical University Vienna, Department of Medicine I and Comprehensive Cancer Center, Vienna, Austria;* [4]*American Cancer Society, Atlanta, USA*

Background: The world is facing a developing epidemic of cancer due to the growth and ageing of the world's population coupled with a rapidly increasing incidence and prevalence in many countries which are in formerly lower income regions of the world. This presents serious challenges to provide therapy for patients in countries where income is very modest and spending on health is low. It is also timely since science is starting out in a new era where personalised medicine offers great hope of improving cancer outcome.
Methods: We invited experts to provide brief descriptions of the state-of-the-art of Oncology, from the Clinical, Scientific and patient perspective, as background. We invoked the assistance of experts from many parts of the world to describe the current state of oncology in their region (David Khayat (Europe), Murat Tuncer (North Africa and Middle East), Clement Adebamowo (sub-saharan Africa), Yi-Xin Zeng (South-east Asia), Nise Yamaguchi (Latin America), Fadlo Khuri (North America) and Robert Thomas (Australasia).
Results: Cancer is important from many perspectives particularly for patients and their families. The economic importance cannot be under-estimated. In high-resource countries, while more of the global health budget is spent on vascular disease, one case of cancer costs, on average, more than one case of vascular disease or any other disease. There has been great progress made in treating and curing cancer patients in recent decades. There have been magnificent success stories such as in the treatment of Testicular Cancer, Breast Cancer, GIST tumours and chronic myeloid leukaemia where cure has been established for many patients. Importantly, due to advances in treating and improving survival in advanced disease, there are more and more people with advanced cancer who are living longer and longer with a good quality of life. Unfortunately, many of these advances have not been transferred to cancer patients in many parts of the world.
Conclusions: Not every patient with treatable and curable disease has been able to benefit from such successful treatments as indicated above. These disparities in cancer care, and hence cancer outcome, are increasingly apparent and increasingly unacceptable in modern society. Providing rapid diagnosis and effective treatment at affordable costs for all cancer patients in the world is a major challenge for everyone involved in Oncology.
No conflict of interest.

1402 ORAL

A meta-analysis on breast and colorectal cancer in diabetic patients: Higher incidences and mortality rates

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Background: Obesity and subsequent diabetes mellitus (DM) are major public health challenges. There is increasing evidence of an association between diabetes and cancer incidence and mortality. Several mechanisms involved in obesity and diabetes, such as those promoting cell proliferation and decreasing apoptosis, may foster carcinogenesis. This meta-analysis provides up-to-date information on cancer incidence and cancer-specific mortality of breast cancer and colorectal carcinoma in relation to DM.
Material and Methods: We conducted a meta-analysis of Level I and II studies published after 2007. Studies were identified searching Embase, Pubmed and the Cochrane Library. We identified twenty studies from which we could extract or calculate hazard ratios (HRs) for the relation between DM and breast and colorectal cancer incidence and cancer-specific mortality.
Summary HRs were calculated using a random-effects model. Sensitivity and subgroup analyses were performed on adjustment for confounders, mode of DM assessment and follow-up time.
Results: A total of twenty studies concerning 1.930.309 patients were included. Analysis of all studies showed an overall HR of 1.23 (95% CI 1.12–1.34) for breast cancer incidence and an overall HR of 1.26 (95% CI 1.14–1.40) for colorectal cancer incidence. Regarding cancer-specific mortality the overall HR was 1.38 (95% CI 1.20–1.58) for breast cancer and 1.30 (95% CI 1.15–1.47) for colorectal cancer. Moreover, there was no evidence of publication bias and no or moderate heterogeneity among studies.
Conclusions: This up-to-date meta-analysis indicates that DM-status increases breast and colorectal cancer incidence and cancer-specific mortality. With the expected rise in numbers of obese and DM patients, awareness and prevention should be incremented. Otherwise, incidences and mortality rates of two of the most common cancers will only tend to increase.
No conflict of interest.

1403 ORAL

The effect of metformin and sulfonylurea derivatives use after colorectal cancer diagnosis on survival

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Background: This observational population-based study aims to assess whether, and to which extent, the use of metformin *after* the diagnosis of colorectal cancer (CRC) is associated with an increased overall survival compared with use of sulfonylurea derivatives.
Methods: Patients with primary CRC stage I−IV diagnosed between 1998 and 2010 in the South-Eastern Netherlands were included from the Eindhoven Cancer Registry (ECR). The included patients were linked to

data on drug dispensing from the PHARMO Record Linkage system. The association between the use of metformin and overall survival in CRC patients, compared with the use of sulfonylurea derivatives, was analysed using Cox proportional hazard models, with cumulative duration of drug use as a time-varying determinant. Patients were censored at the time of start of another diabetes drug than the drug of the first prescription.
Results: In this study, 162 patients started with metformin monotherapy and 105 patients started with sulfonylurea derivatives monotherapy *after* CRC diagnosis. The use of metformin after CRC diagnosis was associated with a lower overall mortality (HR 0.39, 95% CI 0.19–0.79), compared with the use of sulfonylurea derivatives, when adjusting for patient-, tumour-, and co-medication-related variables. In CRC patients who received chemotherapy (n = 71), the use of metformin was associated with a lower overall mortality, compared with the use of sulfonylurea derivatives (HR 0.06, 95% CI 0.01–0.39). When including patients who used a first dose which was higher than the median, again a protective effect of metformin compared to sulfonylurea derivatives was seen (HR 0.14, 95% CI 0.04–0.53) and this effect was not significant in patients with a first dose which was lower-than-the-median dose (HR 0.59, 95% CI 0.22–1.57). The effect of metformin on survival was not significantly different between colon and rectal cancer patients.
Conclusions: The first results of our study showed that cumulative exposure to metformin *after* CRC diagnosis was associated with a lower overall mortality, compared with cumulative exposure to sulfonylurea derivatives *after* CRC diagnosis. This association was strongest in CRC patients who received chemotherapy as initial treatment. However, whether this association could indeed be seen as a direct effect of metformin on survival, or as an effect of confounding by indication, remains to be clarified in a larger study population.
No conflict of interest.

1404 ORAL

KBP-2010-CPHG: Characteristics of 201 new cases of non-small-cell-lung-cancer (NSCLC) with EGFR mutation

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Background: In 2010, the French College of General Hospital Respiratory Physicians (CPHG) performed KBP-2010-CPHG, a prospective, national, epidemiological study aimed to analyze all new cases of primary lung cancer.
Material and Methods: Data were collected on a standardized form for all patients ⩾18 years with primary lung cancer, histologically or cytologically diagnosed between January 1 and December 31, 2010 and managed in a general hospital.
Results: 7610 patients were enrolled in 119 centers. 7051 from 104 centers were included in the analysis. 6083 included patients had a non small cell lung cancer (NSCLC). Epidermal growth factor receptor (EGFR) mutation was explored in 2105 NSCLC patients. 201 of these patients had an activating EGFR mutation. The main characteristics of included, explored, and mutated patients are compared in the following table.

	Overall population (N = 7051)	EGFR mutation explored (N = 2105)	EGFR mutated (N = 201)
Age (years): mean±SD	65.5±11.3	63.7±11.4*	67.5±12.2**
Female: %	24.3	33.7*	67.7**
Non-smoker: %	10.9	18.4*	64.7**
Performance status 0 or 1: %	68.9	74.2*	76.4
Adenocarcinoma: %	45.4	84.6*	92.0**
Stage IV: %	60.0	70.0*	76.1
1-year mortality rate: %	56.4	53.9	33.3**

*Statistically significant as compared with non-explored patients; **Statistically significant as compared with explored and non-mutated patients.

Conclusions: In France, in 2010, an EGFR mutation was explored in about 1 of 3 patients with NSCLC and found in about 10% of explored patients. The French physicians follow the current French recommendations, exploring mainly patients with advanced adenocarcinoma. Mutated patients were mainly non-smoker women with adenocarcinoma. One-year mortality rate was significantly lower in mutated patients than in the whole population. One-year survival improvement in EGFR mutated patients needs to be further analyzed to evaluate the role of targeted therapy.
No conflict of interest.

1405 ORAL

Trends in colorectal cancer mortality and screening activities in European countries

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Background: Randomised trials have shown that fecal-occult-blood-test (FOBT) and endoscopic examinations of the large bowel were able to decrease the risk of CRC death. We examined whether changes in CRC mortality in Europe were associated with a history of screening.
Methods: We used data collected as part of the Survey of Health, Aging, and Retirement in Europe (SHARE) project to extract information on exposure to CRC screening in subjects 50 years old or more living in 11 European countries. Distinct data were collected for endoscopy (colonoscopy or sigmoidoscopy) and FOBT. Using the WHO mortality database on causes of deaths, we fitted linear regressions from 1989 to 2010 and calculated changes in mortality for men and women living in each of the 11 countries. We used least square regression and computed R-square statistics (expressed in %) to provide estimates of the association between screening history and changes in CRC mortality.
Results: Over the 22-year period, changes in age-adjusted CRC mortality rates among males/females were −39/−47% in Austria, −34/-32% in France, −30/-44% in Germany, −26/-35% in Switzerland, −17/-23% in Italy, −14/-18% in Denmark, −10/-8% in Sweden, −4/-10% in the Netherlands, +29/-6% in Spain, and +30/+2% in Greece. In males, reports of ever having had an endoscopic examination of the large bowel ranged from 8% in Greece to 35% in Austria. For females, proportions of ever endoscopic examinations ranged from 8% in Greece to 36% in Austria. FOBT screening over the last 10 years, ranged from 4% in the Netherlands to 61% in Austria for both sexes. In males, a history of one or more endoscopic examination of the large bowel explained 73% of the decrease in CRC mortality. At least one endoscopy or FOBT over the past 10 years explained 54 and 53% of the observed decrease in CRC mortality, respectively. In females, a history of one or more endoscopic examination of the large bowel explained 82% of the decrease in CRC mortality. At least one endoscopic or FOBT over the past 10 years explained 89 and 72% of the decrease, respectively. All R-squares had an associated p value <0.001.
Conclusions: Changes in CRC mortality are correlated with the level of screening uptake. This provides evidence of the effectiveness of screening to prevent CRC mortality in the general population and a strong rationale for current national CRC screening programmes.
No conflict of interest.

Poster Session (Mon, 30 Sep)
Epidemiology and Prevention

1406 POSTER

Spanish familial pancreatic cancer registry: genomic analysis of affected individuals and screening of high-risk individuals

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Background: The prognosis of patients diagnosed with Pancreatic Cancer (PC) is dismal with a 5 year survival rate of around 5%. Familial Pancreatic Cancer (FPC) is an autosomal dominant rare syndrome defined as families with two or more first-degree rela-tives with pancreatic cancer that do not fulfill the cri-teria of any other inherited tumor syndrome. Approximately, 15−20% of families carry germline mutations in BRCA2, PALB2 and ATM, for the majority of families the major underlying genetic defect(s) are unknown. The Spanish familial pancreatic cancer registry, Pan-Gen-FAM

was established in 2008 in order to identify and manage families at high risk of developing PC.
Materials and Methods: The phenotype of families is studied using family history information to determine whether they present PC alone or in combination with other cancer syndromes and this data is combined with genetic testing of known FPC associated genes. The main objectives of this project include the identification of novel mutations or variants that predispose to an increased risk of PC by DNA exome ultrasequencing of both tumor and germline DNA. Furthermore, we offer a clinical follow-up program of high risk individuals with a screening program for the detection of early PC lesions consisting of periodic monitoring by imaging techniques (EUS, CT and MRI) and the evaluation of minimally-invasive tumor biomarkers approaches Circulating Tumor Cells (CTC) and micro RNAs.
Results: To date the registry includes over 100 individuals representing some 33 families presenting with pancreatic cancer aggregation. BRCA2 germline mutations were detected in 4 families and BRCA1 mutations in 1 family. More pancreatic abnormalities were found by EUS (41%) than by CT (12%) or RMI (33%). The most frequent abnormal findings were parenchymal changes associated with chronic pancreatitis (hyperechoic foci, echogenic strands, lobularity, cysts, pancreatic heterogeneity). Overall 14 (39%) patients showed at least 1 of these changes. In total six cystic lesions were identified. One lesion was compatible with a mucinous tumor and another patient underwent EUS-FNA which showed benign cytology. Subsequent EUS one year later identified a well differentiated neuroendocrine tumor in one patient and a mucinous tumor in another. All patients with cystic lesions are undergoing close clinical observation. One CTC was detected is one patient, although this was consistent with the false negative detection rate of the system.
Conclusions: Since this study involves both clinical and basic scientists this means that participating individuals can benefit from a medical screening program as well as the individualized analysis of their genome for the detection of as yet undiscovered genetic determinants. Preliminary data suggest that EUS is the most sensitive method to detect small tumors and premalignant lesions.
No conflict of interest.

1407 POSTER

The difference in mortality between cancer patients with and without venous thromboembolism: A systematic review and meta-analysis

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Background: The risk of developing a venous thromboembolism (VTE) is 4.7 times as high in cancer patients compared to those without cancer. Studies suggest this risk of VTE renders poorer survival in affected patients, but it is still necessary to quantitatively synthesize all available evidence on this association, of which no previous attempts have been made. This would help determine at-risk groups for whom primary prophylaxis would be of value. Thus this review will aim to establish if the mortality risk is higher in cancer patients with VTE than those without, by conducting a systematic review and meta-analysis.
Material and Methods: MEDLINE was searched to identify all relevant cohort studies which presented survival data for cancer patients with and without VTE. We included studies which presented data on all cancers together and then specifically with cancers of the breast, lung, prostate or bowel. Data were extracted using available hazard ratios if available and if not these were estimated from Kaplan–Meier plots. Random-effects meta-analyses were used to estimate pooled hazard ratios and 95% confidence intervals for the mentioned groups and a subgroup of studies where VTE was diagnosed simultaneously or after cancer diagnosis, to see how these results affected heterogeneity.

Table 1. Summary of results

	Hazard Ratio	95% Confidence Interval	I^2(%)
All Cancers	1.60	1.17, 2.17	99.8
Colorectal	1.41	1.15, 1.73	91.0
Breast	1.54	1.06, 2.24	91.9
Lung	1.58	1.23, 2.04	98.7
Prostate	1.75	1.21, 2.54	96.4
VTE after cancer	1.87	1.39, 2.51	98.6

Results: Of 1838 papers retrieved from the search strategy, 21 papers from 18 different cohorts were included in the final analysis. Twelve of these were used to generate results on the meta-analysis of 'all cancers'. Eleven of the papers were conducted in the USA, 3 in Korea, 3 in the UK, 3 in the remainder of Europe, and 1 in South America. All papers had participants with a mean age over 18, and all but three of the papers had participants exclusively over 18. Risk of death was significantly higher in 'all cancer' patients with VTE than those without (HR: 1.60; 95% CI: 1.17, 2.17; I^2: 99.8%). Significant increases in mortality risk associated with a VTE were also found for all the assessed cancer types: colorectal (HR: 1.41; 95% CI: 1.15, 1.73; I^2: 91.0%); breast (HR:1.54; 95% CI: 1.06, 2.24; I^2: 91.9%); lung (HR: 1.58; 95% CI: 1.23, 2.04; I^2: 98.7%); prostate (HR: 1.75; 95% CI: 1.21, 2.54; I^2: 96.4%). In the analysis using papers where VTE was diagnosed simultaneously or after cancer, the hazard ratio was higher than in 'all cancer' patients (HR: 1.87; 95% CI: 1.39, 2.51; I^2: 98.6%). These results are summarised in Table 1.
Conclusions: Patients diagnosed with both VTE and malignancy have a significantly increased risk of death compared to those with malignancy alone. However, high heterogeneity between included studies accompanies these results, the reasons for which offer important information about at-risk groups. This provides a basis for further research clinically relevant to primary targeted prophylaxis.
No conflict of interest.

1408 POSTER

Population-based incidence, treatment and survival of patients with peritoneal metastases of unknown origin

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Background: Until recently, peritoneal metastases (PM) were regarded as an untreatable condition, however promising treatment options are now available for patients presenting with PM from colorectal, ovarian or gastric carcinoma. Therefore, it is of increasing importance to diagnose patients presenting with PM as accurately as possible. The aim of this study was to investigate the incidence, treatment and survival of patients presenting with PM of unknown origin.
Materials and Methods: Data from patients diagnosed with PM of unknown origin during 1984–2010 were extracted from the Eindhoven Cancer Registry. European age-standardized incidence rates were calculated and data on treatment and survival were analyzed.
Results: In total 1,051 patients were diagnosed with PM of unknown origin. In 606 patients (58%) the peritoneum was the only site of metastasis, and 445 patients also had other metastases. Chemotherapy usage has increased from 8% in the earliest period to 16% in most recent years ($p = 0.016$). Median survival was extremely poor with only 42 days (95% CI 39−47 days) and did not change over time. Median survival of patients not receiving chemotherapy (36 days) was significantly worse than of those receiving chemotherapy (218 days, $p < 0.0001$).
Conclusions: The prognosis of PM of unknown origin is extremely poor, and no sign of improvement is observed over time. Given the recent progress that has been achieved in patients presenting with PM from various origins, more efforts should be undertaken in order to diagnose the origin of PM more accurately and to explore potentially effective treatment strategies in this specific category of patients.
No conflict of interest.

1409 POSTER

Alcohol drinking, smoking, and risk of melanoma

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Background: Several reports suggest that risk of melanoma may be increased in alcohol drinkers and decreased in smokers.
Methods: We explored the role of alcohol drinking and smoking in a cohort of 129,917 persons. From baseline data collection in 1978−85 through 2008 melanoma was diagnosed in 1,042 persons. We utilised Cox proportional hazard models that included age, sex, race/ethnicity, marital status, education, and body mass index. Alcohol and smoking were studied categorically, with lifelong abstainers as referent.
Results: In multivariate models the hazard ratios (HR) and 95% confidence intervals (CI) for persons in the alcohol categories were: exdrinkers = 1.2 (0.8−1.8), <1 drink per day = 1.3 (1.1−1.5, $p = 0.005$), 1−2 drinks per day = 1.5 (1.2−1.8, $p < 0.001$), and $\geqslant$3 drinks per day = 1.7 (1.3−2.2, $p < 0.001$). The higher risk of drinkers was generally similar for men, women, invasive and non-invasive tumours, and persons in various baseline smoking categories (never, ex-, current), but was greater for tumours diagnosed

after 10 years (HR = 1.9, p < 0.001) than for those diagnosed within 10 years of baseline (HR = 1.3, ns) and also stronger for drinking wine than for drinking liquor or beer. The HRs (CIs) for persons in smoking categories were: exsmokers = 0.9 (0.8−1.0), <1 pack per day = 0.9 (0.7−1.1), and ⩾1 pack per day = 0.6 (0.5−0.8, p < 0.001). The inverse HR for ⩾1ppd smokers was stronger for men (HR = 0.5, p < 0.001) than for women (HR = 0.8, ns) and also for tumours diagnosed after 10 years (HR = 0.6, p < 0.001) than for those diagnosed within 10 years of baseline (HR = 0.9, ns). Among covariates the risk was higher (p < 0.001) for men vs women, whites (vs each other race), and college graduates (vs no college).
Conclusions: These data about risk of melanoma in a large population show that alcohol drinkers, especially wine drinkers, are at increased risk, while smokers, especially male smokers, are at lower risk.
No conflict of interest.

1410 POSTER

Cancer incidence in the families of children with bone and soft tissue sarcomas

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Background: The aims of the study were to investigate the incidence of cancers in the relatives of children with sarcoma.
Materials and Methods: Families of children aged 0 to 14 diagnosed between 1954 and 2008 with Ewing sarcoma (EWS), osteosarcoma/chondrosarcoma or soft tissue sarcoma (STS) from the population-based Manchester Children's Tumour registry were traced. Interviews were conducted and the medical histories taken and, where possible, verified from hospital records for the grandparents of the case and their descendants. The parents and siblings were flagged for continuous notification of cancers and deaths. Expected numbers of cancers aged 0−84 years were calculated using English national cancer registration data.
Results: There were a total of 10,841 relatives among the 629 families in the study. Information was available on 95% of mothers, 91% of fathers and 76% of grandparents. There were significant excesses of cancer in the relatives of STS (observed 280, expected 248, P = 0.03) and osteosarcoma/chondrosarcoma (observed 188, expected 158, P = 0.01) but not EWS (observed 123, expected 137, P = 0.89). The excesses were confined to relatives under 60 with greater relative risk at younger ages (P<0.0001). The Osteosarcoma/Chondrosarcoma families had significant excesses of embryonal tumours (observed 6, expected 0.5, P<0.001), Central Nervous System (CNS) tumours (observed 11, expected 5.0, P = 0.01), STS (Observed 9, expected 4.2, P<0.001) and melanoma (observed 10, expected 4.0, P = 0.01). Overall, the age distribution of the cancers was younger than that expected from national cancer rates (Table 7, P<0.0001) with the embryonal (P = 0.02) and, possibly breast cancer cases (P = 0.07) and leukaemias (P = 0.06) occurring at younger ages than predicted. The STS families had excesses of STS (Observed 12, expected 3.7, P<0.001), embryonal tumours (Observed 5, expected 1.0, P = 0.003), bone tumours (Observed 4, expected 1.1, P = 0.005), stomach (observed 20, expected 10.9, P = 0.01), breast (Observed 56, expected 40.6, P = 0.01) and cervical (Observed 17, expected 7.3, P = 0.001) cancers. The breast cancers (P = 0.03) and possibly STS (P = 0.06) occurred at younger ages than expected. Families of younger STS index cases had higher relative risks of cancer than those of older index cases (P = 0.005). For the relatives of the EWS cases there was an excess of CNS tumours under the age of 60 (observed 7, expected 2.9, P = 0.03), which appeared more concentrated in children (ages 0 to 14, observed 3, expected 0.5, P = 0.02).
Conclusion: The wide range of cancers in excess in relatives of sarcoma cases imply that there may be a variety of either inherited or environmental factors involved. This has implications for both counselling, surveillance and aetiology.
No conflict of interest.

1411 POSTER

Risk of multiple primary malignancies following treatment of Hodgkin's lymphoma

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Background: Patients treated for Hodgkin's lymphoma (HL) have a strongly increased risk to develop a 2nd primary malignancy, causing significant morbidity and mortality. The burden of multiple primary malignancies has, however, rarely been studied. We assessed the risk of 2nd, 3rd and subsequent malignancies in a Dutch cohort comprising 2,814 5-year HL survivors, treated before the age of 51 years between 1965–1995.
Methods: Cumulative incidence of a 3rd malignancy was estimated with death as competing event. Using recurrent event analyses, we assessed risk factors for the development of a 3rd malignancy and examined whether the risk of a 3rd malignancy is increased after a second.
Results: After a median follow-up of 22.1 years, 740 (26.3%) patients developed a 2nd primary malignancy. Median follow-up of 1-year survivors of a 2nd malignancy was 5.0 years (interquartile range 2.2–10.4). Ninety-eight patients developed a 3rd malignancy. In women, breast cancer was the most frequently observed malignancy both as a 2nd (n = 148) and as a 3rd (n = 31) malignancy. In men, lung cancer was the most frequent 2nd malignancy (n = 110), and cancer of the gastrointestinal tract the most frequent 3rd malignancy (n = 9). The 10-year cumulative incidence of any 3rd malignancy after a 2nd malignancy was 15.6% (95% Confidence Interval (CI) 11.6–20.1%) in women and 9.0% (95% CI 6.1–12.6) in men.
Only patients who developed a 2nd malignancy after HL treatment before age 25 had an increased risk to develop subsequent malignancies (HR 1.6, 95% CI 1.2−2.3), compared to those who did not develop a 2nd malignancy. Risk of a second solid non-breast tumor was higher for males compared to females (p = 0.007), older patients (>35 years vs. >25 years at HL diagnosis) (p < 0.001), patients who received radiotherapy (p < 0.001) and patients treated with chemotherapy (p = 0.035). Risk factors for 2nd and 3rd malignancies were similar with the exception of radiotherapy ($p_{interaction}$=0.013). While radiotherapy was associated with an almost 3-fold increased risk (95% CI 1.2−3.5) of a 2nd primary malignancy, a stronger association was seen for a 3rd primary malignancy (HR 6.0, 95% CI 1.4–24.9).
Conclusion: Female survivors of a 2nd malignancy have an almost 16% risk to develop a 3rd malignancy within 10 years after the 2nd malignancy. Patients treated before age 25 who develop a 2nd malignancy have a higher risk of developing subsequent malignancies compared with HL survivors who do not develop a 2nd malignancy.
No conflict of interest.

1412 POSTER

Increased risk of urinary tract neoplasm among patients who had ever urolithiasis: A population-based cohort study in Taiwan

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Background: There were estimated 386,300 new cases and 150,200 deaths from bladder cancer worldwide in 2008. In Taiwan, the crude incidence rate of urinary tract cancer increased from 11.74 to 14.8 during 2000–2009. Though cigarette smoke and occupational exposure are the most documented etiologies, hereditary factor may also play a pivotal role in recent studies. Urolithiasis contributing to neoplasm, especially in upper urinary tract, is controversial till now. Seldom population-based evidences had studied the relationship between urinary stone which can cause chronic inflammation and urinary tract neoplasm.
Materials and Methods: We conduct a national population-based cohort study by applying the Database of National Health Insurance in Taiwan. Patients who were diagnosed as urinary tract stone in admission or in out-patient department above their age of thirty were enrolled in our study

during 2000 to 2011. The compared group was chosen by comparable age, sex and diagnosis time by the ratio of 1:5. All of the patients in this cohort were followed to the event of urinary tract cancer, death or the end of 2011. Cox proportional regression models were used to estimate the hazard ratios and 95% confidence interval for the association between urolithiasis and urinary tract cancer.
Results: In this cohort, the number of patients who had urinary tract cancer followed by urolithiasis is 488, composed of 309 men and 179 women. The adjusted HR in total patients with urinary tract neoplasm is 2.32 (95% CI: 2.10–2.58). In our study, the association between urinary stone and cancer in women (adjusted HR: 2.87, 95% CI: 2.39–3.44) is stronger than in men (adjusted HR: 2.06, 95%: 1.80–2.35). After stratification by age, we discovered that men who had urolithiasis in their forties have higher risk to get urinary tract neoplasm (adjusted HR: 2.82, 95% CI: 1.76–4.49), while women in their fifties (adjusted HR: 3.62, 95% CI: 2.32–5.63).
Conclusions: Our study proved that urinary stone disease is indeed a precipitating factor of urinary tract neoplasm. Among these various factors, urinary tract stone play a role in contributing to malignancy, especially in women and in their middle age (30−49).
No conflict of interest.

1413 POSTER

Effect of chronic comorbidities on risk of chemotherapy-induced febrile neutropenia

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Background: Chemotherapy-induced febrile neutropenia (FN) is a clinically important complication that impacts a cancer patient's outcome, in part by delaying chemotherapy doses or reducing dose intensity. Risk of FN is known to depend on the chemotherapy regimen and patient-specific factors. In this study, we determined the effects of chronic comorbidities on risk of FN.
Methods: We conducted a cohort study to examine the association between a wide variety of chronic comorbidities and risk of FN in patients diagnosed with cancer (non-Hodgkin lymphoma or cancers of the breast, colon/rectum, lung, ovary or stomach) and treated with chemotherapy from 2000–2009 at Kaiser Permanente Southern California, an integrated healthcare delivery system in United States. We excluded patients receiving primary prophylactic granulocyte colony-stimulating factor (G-CSF), as this alters the risk of FN. History of comorbidities and FN events (based on the juxtaposition of neutropenia with fever and/or infection) were identified using electronic medical records. To assess the association between each comorbidity and FN, a Cox model adjusting for cancer type and the propensity score for the specific comorbidity was used to estimate the summary hazard ratio and 95% CI.
Results: A total of 19,160 patients (mean age of 60 years) were included; 963 (5.0%) patients developed FN in the first chemotherapy cycle. The most common comorbidities were hypertension (39.4%) and diabetes (18.5%). Anemia [HR = 1.24, 95% CI, 1.03–1.49], HIV infection [HR = 3.44 (1.93–5.70)], chronic obstructive pulmonary disease [HR = 1. 30 (1.08–1.57)], congestive heart failure [HR = 1.43 (1.00–1.98)], peptic ulcer disease [HR = 1.57 (1.04–2.26)], renal disease [HR = 1.60 (1.21–2.09)], and thyroid disorder [HR = 1.33 (1.06–1.64)] were all associated with a significantly increased FN risk. FN risk increased with number of comorbidities: HR = 1.21 (1.00–1.46), 1.37 (1.09–1.73) and 1.56 (1.21–2.00) for those who had 1, 2 or 3+ comorbidities compared with those who did not have any of the comorbidities examined.
Conclusion: Our findings suggest that several chronic comorbidities are associated with increased FN risk in the first chemotherapy cycle among patients not already receiving prophylactic G-CSFs. This information may aid clinical decision making with respect to use of prophylactic G-CSF during the chemotherapy course.
Conflict of interest: *Ownership: John Page and Vicky Chia are employees of Amgen and are Amgen stock holders. Corporate-sponsored research: Chun Chao, Roberto Rodriguez and Su-Jau Yang received research funding from Amgen to conduct this study.*

1414 POSTER

Anaemia and iron status management in patients with chemotherapy-induced anemia (CIA) − clinical practice in Eastern Europe

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Background: Anaemia and iron deficiency (ID) are frequent in cancer patients, particularly during chemotherapy. This study evaluated current practice in diagnosis and treatment of chemotherapy-induced anaemia (CIA) in Eastern Europe.
Material and Methods: Onco-haematologists from Bulgaria, Czech Republic, Poland, Romania, Russia, Slovakia, and Slovenia were surveyed about diagnostic parameters and therapies used for the last five cancer patients that have been treated for CIA in the six months before the survey (Jan-Feb 2012). Data were checked for plausibility; in 15% of cases also by phone calls. Results are shown as total or median of all patients and range across countries.
Results: 176 oncologists reported data of 920 CIA patients (solid tumours 89% [71−97%], metastatic 47% [29−61%], female 54% [46−66%], mean age 57 y [47−63 y]). Hospital-based oncologists provided data from 738 patients (80.2%). At anaemia diagnosis, 98% [91–100%] of patients were tested for haemoglobin (Hb). Serum ferritin and transferrin saturation (TSAT) were tested in 29% (11−64%) and 11% (1−23%), respectively. Median Hb level was 9.0 g/dL (8.8−9.3 g/dL). Among tested patients, median ferritin level was 98ng/mL (32–226ng/mL) and TSAT 20% (6−22%). Moderate-to-severe anaemia (Hb $\leqslant$10 g/dL) was diagnosed in 81% (67−89%) of patients; 16% (7−26%) had Hb $\leqslant$8 g/dL. Insufficient iron for erythropoiesis (TSAT $\leqslant$20%) was seen in 65% of patients and depleted iron stores (serum ferritin $\leqslant$100ng/mL) in 54%. Iron was given to 69% (31−95%) within 12 months before the survey. However, only 15% (2−34%) received intravenous (i.v.) iron whereas 60% (30−75%) received oral iron despite erythropoiesis-stimulating agent (ESA) treatment in 40% (16−70%). Notably, 40% (7−73%) had received blood transfusions (most of them [70%] as regular treatment) and 8% (0−27%) intramuscular iron.
Conclusion: Cancer patients' anaemia and iron status management is far from optimal in some Eastern European countries. In contrast to guidelines, blood transfusions are often used as regular treatment. Despite i.v. iron can reduce transfusion and ESA needs, whereas oral iron is not effective in cancer patients with functional iron deficiency, only a minority of patients had received i.v. iron. The high frequency of ID at anaemia diagnosis suggests insufficient monitoring or repletion of iron status. Broader awareness and implementation of evidence-based recommendations for anaemia and iron status management in cancer patients is needed in Eastern Europe.
Conflict of interest: *Advisory board: Vifor Pharma, Amgen. Corporate-sponsored research: Vifor Pharma, Amgen. Other substantive relationships: Vifor Pharma (employment J. Lange, D. Mitchell)*

1415 POSTER

Prevalence of hypercalcemia of malignancy in the United States: Projection methods using oncology electronic health records (EHR)

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Background: Hypercalcemia of malignancy (HCM; CTCAE grade $\geqslant$1, CSC >10.7 mg/dL) is a serious metabolic complication with unknown prevalence. Rates of HCM differ by tumor type, with highest rates reported in multiple myeloma (MM) and lowest among prostate cancer patients (pts). This analysis estimates the prevalence of HCM utilizing projection methodology developed for oncology EHR from clinics in the US.
Materials and Methods: This retrospective study used the Oncology Services Comprehensive Electronic Records (OSCER) warehouse of EHR including lab values from >640,000 pts treated at 525 oncology outpatient sites. The projection methodology developed to estimate prevalence simultaneously estimates relationships between key data elements and projects these estimates to the entire US population utilizing pt EHR linked to prescription (Rx) and medical office claims data. Rx and medical office claims are projected by tumor type. The claims totals are then used to create factors to project the EHR sample to the US population. These factors are used to project pts by tumor type with lab values that are nationally representative of treated cancer pts. Pts included were $\geqslant$18

years, and had serum calcium (Ca) and albumin (for corrected serum Ca [CSC]) records. Period prevalence was estimated by HCM CTCAE grade, tumor type, and year (2007–2012). Estimates were adjusted to capture pts with HCM outside oncology practices using a subset of pts linkable to office/hospital data.
Results: The analysis included 50912 (2007) to 100449 pts (2012), projected to 3.3 to 3.6 million cancer pts. In 2012, pts with HCM had a median of 5 Ca tests, 54% had chemotherapy, and 35% had bone modifying agents. HCM rates were highest for MM (7.6–10.7%), lowest for prostate (1.4−1.8%). Estimated annual 2007–2012 (adjusted) prevalence of HCM was 72382, 86213, 103746, 105119, 98058, and 98997, respectively. HCM is estimated to affect 2.7% of cancer pts in 2012 (table).
Conclusions: Approximately 100000 pts are affected by HCM in the US each year. The OSCER projection method used has the potential to improve and expedite similar estimates in pharmacoepidemiology studies.
Conflict of interest: *Ownership: Amgen. Other substantive relationships: Amgen*

Table: Prevalence of HCM in 2012 (adjusted estimates)

Tumor type	Cancer pts		HCM (%) by CTCAE Grade (CSC mg/dL)			
	OSCER	US	⩾1 (>10.7)	⩾2 (>11.5)	⩾3 (>12.5)	⩾4 (>13.5)
Lung	6613	325018	4.9	2.1	0.8	0.3
Breast	39143	1124483	2.3	1.1	0.5	0.4
Colorectal	10869	329283	1.8	0.8	0.4	0.2
Prostate	3808	369852	1.5	0.8	0.2	0.2
MM	3178	103990	9.5	5.7	3.0	0.0
Other	36838	1393899	2.6	1.3	0.6	1.2
Total	100449	3646524	2.7	1.3	0.6	0.3

1416 POSTER

Development in self-reported arm-lymphedema in Danish women operated for breast cancer in 2005 and 2006 − a nationwide follow-up study

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Background: The population of women treated for breast cancer is steadily growing due to improved survival. One of the most feared complications is lymphedema. The majority of women developing lymphedema do so within the first years, but lymphedema can develop several years after end of treatment. The primary aim of the present nationwide follow-up study was to examine the development of self-reported lymphedema in the population of women operated on in Denmark for breast cancer in 2005–2006 and to assess the impact of axillary lymph node dissection (ALND) and sentinel lymph node dissection (SLND).
Methods: Two identical questionnaires were sent out in 2008 and 2012. All women between 18 and 70 years treated for unilateral primary breast cancer in Denmark in 2005 and 2006, and who participated in the 2008 study, were included. Exclusion criteria were death, recurrent-, new primary-, contralateral, or metastatic disease, other malignant disease, reconstructive/corrective breast surgery, and emigration.
Data regarding diagnosis and treatment was retrieved from The Danish Breast Cancer Cooperative Group, (DBCG), which covers 97% of all women operated on for breast cancer in Denmark.
Results: 2293 women reported on lymphedema in 2008 and 2012. In total, 31% reported lymphedema in 2012, a fall from 37% in 2008. Self perceived severity of lymphedema in 2008 and 2012 can be seen in table 1. 50% of women treated with SLND and reporting lymphedema in 2008 had recovered by 2012 in contrast to 30% treated with ALND. However, 19% of women treated with ALND and not reporting Lymphedema in 2008 had developed Lymphedema by 2012.
Overall, 10% of women who did not have lymphedema in 2008 reported so in 2012. The main risk factor showed to be ALND vs. SLND (adj. OR:4.07;95% CI:2.43–6.80,p < 0.001). In all, 34% of women reporting Lymphedema in 2008 did not report lymphedema in 2012. Recovery from lymphedema was negatively associated with ALND vs. SLND (adj. OR:0.38;95% CI:0.24–0.59,p < 0.001).
Conclusions: Half of women reporting lymphedema 1−3 years after surgery with SLND have spontaneously recovered 4 years later compared to 30% in women undergoing ALND. However, 19% of women undergoing ALND, but initially not reporting lymphedema have developed lymphedema 4 years later.
No conflict of interest.

Table 1. Development in severity of self-reported lymphedema from 2008 to 2012 in 2293 patients operated on for primary breast cancer in 2005–2006.

Intensity of lymphedema in 2008, N (%)	Intensity of lymphedema in 2012 N (%)					
	No lymphedema	Light lymphedema	Moderate lymphedema	Severe lymphedema	Missing	**Total**
No lymphedema	1295 (90)	77 (5)†	54 (4)†	14 (1)†	1 (0)	1441
Light lymphedema	196 (43)¶	178 (39)	59 (13)†	19 (4)†	4 (1)	456
Moderate lymphedema	70 (24)¶	81 (28)¶	108 (37)	33 (11)†	2 (1)	294
Severe lymphedema	16 (17)¶	10 (11)¶	35 (38)¶	30 (33)	1 (1)	92
Missing	4 (40)	3 (30)	1 (10)	1 (10)	1 (10)	10
Total	1581	349	257	97	9	2293

Light lymphedema: 1−3 on numerical rating scale (NRS); moderate lymphedema: 4−6 on NRS; severe lymphedema: 7−10 on NRS.
† Indicates increase in severity; ¶indicates decrease in severity.

1417 POSTER

Comorbidity in lung cancer patients: Trends and effect on prognosis

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Background: We evaluated the trends in prevalence of comorbidities in a cohort of unselected lung cancer patients. We also evaluated the influence of comorbidity on the prognosis of these patients.
Material and Methods: All patients (n = 21,535) diagnosed between 1995 and 2010 with lung cancer were included, identified from the population-based Eindhoven Cancer Registry, which also registers comorbidity.

Table: Hazard of death for lung cancer patients according to stage at diagnosis, 1995–2010 in the Southern Netherlands.

	HR					
	Non-small cell lung cancer				Small cell lung cancer	
	Stage I	Stage II	Stage III	Stage IV	Limited	Extensive
Comorbidities[#]						
None	1.00	1.00	1.00	1.00	1.00	1.00
1	1.05	0.96	0.98	1.00	1.09	1.01
2 or more	**1.25***	1.26	**1.11**	1.00	**1.22**	1.04
Unknown	1.10	1.44	1.14	1.12	**1.65**	0.87
Type of comorbidities[$]						
Diabetes	**1.15**	1.19	1.05	1.02	1.18	1.07
Other malignancy	**1.15**	0.95	1.06	0.93	1.00	1.01
Pulmonary diseases	1.03	0.96	0.98	0.97	**1.16**	1.02
Cardiac diseases	1.10	1.13	**1.10**	1.03	**1.20**	**1.18**
Vascular diseases	**1.17**	1.28	**1.12**	1.06	1.07	1.04
Hypertension	1.01	**1.40**	0.97	0.97	0.96	0.89
Cerebrovascular diseases	1.08	1.16	**1.20**	1.04	1.26	**1.29**
Digestive diseases	1.07	0.79	1.04	0.97	**0.71**	1.05

* Values in bold are significant (p < 0.05).
# All models are adjusted for sex, age, socioeconomic status, period of diagnosis and therapy.
$ A separate model was built for each comorbid condition with not having that specific comorbid condition as a reference.

Results: The prevalence of comorbidities increased with age from 59% in 1995 to 77% in 2010, and multimorbidity (i.e. 2 or more concomitant diseases) increased from 24% to 49%. Especially cardiac diseases (9% in ⩽59 to 37% in 80+) were more frequently seen. Among males, hypertension, cardiac and vascular diseases became much more common (11% to 29%, 17% to 33% and 11% to 25%, respectively). In females, rates of pulmonary diseases, hypertension, cardiac and vascular diseases also increased rapidly (19% to 28%, 15% to 28%, 11% to 18% and 6% to 15%, respectively). Patterns were similar in non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Presence of 2 or more comorbidities was associated with increased hazard of death in stage I−III NSCLC ($HR_{⩾2\_comorbidities\_vs\_no\_comorbidities}$ 1.11–1.26) and limited stage SCLC ($HR_{⩾2\_comorbidities\_vs\_no\_comorbidities}$ 1.22) (Table). The prognostic impact of specific comorbidities varied for different stages, with the strongest effect of hypertension in stage II NSCLC ($HR_{hypertension\_vs\_no\_hypertension}$ 1.40).
Conclusion: Comorbidity among lung cancer patients is very common and multimorbidity affects survival in non-metastatic disease. The increasing

burden of comorbidity in patients with lung cancer emphasizes the need for more focus on individualized medicine.
No conflict of interest.

1418 POSTER

Epidemiological studies of sweetened carbonated beverage consumption and cancer risk

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Background: There is speculation of possible links between sweetened carbonated beverage consumption and the risk of developing cancer. The aim of this study was to examine the association between sweetened, carbonated beverage consumption and cancer risk.
Methods: PRISMA guidelines of meta-analyses were followed as closely as possible. Over 50 independent estimates of risk were available, 11 for colas specifically. A random effects meta-analysis was performed with tests for publication bias (Begg, Egger, Macaskill) performed as well as Higgins and Thompson's I^2 measure of the percentage of heterogeneity between studies which could not be explained by chance.
Results: Overall the different sites of cancer, the summary relative risk (SRR) when all 56 independent estimates were considered together was SRR = 1.04 (95% CI (0.96, 1.13)). On this overall scale, there appears to be no association between consumption of soft-drinks and the risk of cancer. When individual cancer sites were considered, there was no significant increase, or decrease in the meta-analysis estimate of risk of cancer of the pancreas, bladder, kidney, oesophageal squamous cell or adenocarcinoma, colon, gastric cardia, gastric non-cardia, prostate, breast, larynx and ovary nor from the oral cavity, pharynx, glioma, leukaemia or non-Hodgkin's lymphoma where only one study was available. There was no evidence in a sensitivity analysis from those studies which reported results separately for coke, pepsi or other colas of an associated risk of pancreas cancer (SRR = 1.00, 95% CI (0.61; 1.65)) based on 3 studies. The results for all other forms of cancers were greatly hampered by poor methodology and small numbers of studies (mainly one report on each cancer site studied).
Conclusions: Overall, the findings are reassuring regarding the association between soft drinks, including colas, and cancer risk, although the quality of many of the studies is quite poor by acceptable, modern standards and no study has been conducted with use of carbonated beverages as a primary hypothesis.
No conflict of interest.

1419 POSTER

A history cohort mortality study in Jingchuan of China − the largest nickel population in world

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Background: Nickel is an essential trace metal used in the occupational setting and is naturally found in the general environment, resulting in both occupational and nonoccupational exposures to individuals at varying levels. Exposure to nickel has been associated with several toxicities and the International Agency for Research on Cancer has concluded that there is sufficient evidence in humans associating exposure to nickel or nickel compounds with risk of lung cancer. We evaluated overall and cause-specific mortality among Chinese workers involved in nickel production or utilisation in order to examine the long-term health effects of occupational exposure to nickel compounds.
Methods: The study design was a retrospective cohort mortality study including 432,526 workers who were involved with nickel mining or smelt between 2001 and 2010. We calculated standardised mortality ratios (SMR) using the death rates of Gansu Province in China, and estimated by the exact probabilities of the Poisson distribution.
Results: Overall, the all-cause mortality was decreased in all workers compared to the general population of Gansu province (SMR= 0.53, 95% CI: 0.51–0.55). Analyses examining cause-specific mortality revealed an increase in the mortality from bronchogenic carcinoma and lung cancer (SMR = 2.05, 95% CI = 1.84–2.29), cor pulmonale (SMR =4.08, 95% CI = 3.25–5.01), and silicosis (SMR = 13.59, 95% CI =11.90–15.52) in the workers exposed to nickel.
Conclusion: This study confirmed a significant excess of mortality from diseases of the lung including silicosis, lung cancer, and cor pulmonale among workers involved in nickel mining or smelt in China.
No conflict of interest.

1420 POSTER

A nickel workers cohort study in China (Jinchuan cohort) − the largest nickel population in world

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Nickel is one of the most widely distributed and used metals in the world and exposure to nickel compounds can result in a variety of adverse effects on human health. In order to evaluate the human health effects associated with joint occupational exposures to nickel and other metals, we are conducting a cohort study of workers in a large nickel plant in China which produces over 90% of the nickel compounds in China. It is estimated that more than 50 000 current or retired workers, who have had exposure to nickel as well as other contaminants and metals in the plant, will be included in The China Nickel Workers Cohort Study (Jinchuan Cohort) Since 2011, all staff and workers have been eligible for a medical examination every 2 years, and these workers who participated in the medical examination will be interviewed in-person with a standardized and structured questionnaire with trained interviewers and will be included in the Jinchuan Cohort study. The medical examination includes a comprehensive physical examination, biochemical examination, epidemiologic survey, and collection of biological samples. The Jinchuan Cohort has the largest data set from a cohort of nickel exposed workers with both questionnaire and laboratory-based information, and the exposure and disease information will be updated every 2 years through the biannual survey and medical examination. The comprehensive epidemiological and biological data will permit the evaluation of a number of hypotheses concerning the health effects in nickel workers resulting from joint exposure to nickel and other metals. The unique repository of blood samples including blood cell, plasma, and serum will provide a population-based platform to examine biological indicators that closely correlate with metal exposure and illness using molecular epidemiologic methods.
No conflict of interest.

1421 POSTER

Time trends in population-based breast cancer survival in Estonia: Analysis by age and stage

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Background: At the end of the 20th century, relative survival from breast cancer (BC) improved steadily in all European countries, although at different rates, with the gap between eastern and western European countries. Survival from BC in Estonia has been in previous comparative analyses among the lowest in Europe. The aim of this study was to examine most recent trends in BC survival in Estonia by age and stage, as considerable changes have occurred both in socioeconomic conditions and availability of diagnostic and treatment options.
Material and Methods: Estonian Cancer Registry data on all cases of BC, diagnosed in women in Estonia during 1995–2007 (n = 7424) and followed up for vital status through 2009 were used to estimate relative survival (RSR). Period hybrid approach was used to obtain the most recent estimates (2005–2009). Stage was classified as localized, local/regional spread or distant.
Results: The distribution of patients shifted towards older age and earlier stage at diagnosis. Overall age-standardized 5-year RSR increased from 63% in 1995−99 to 74% in 2005−09. Younger age groups experienced a more rapid improvement compared to women over 60. Significant survival increase was observed for both localized and locally/regionally spread BC with 5-year RSRs reaching 96% and 70% in 2005−09, respectively; the latest 5-year RSR for distant BC was 11%. Survival for T4 tumors was poor and very large age gradient was seen for locally/regionally spread BC.
Conclusions: Considerable improvement in BC survival was observed over the study period. Women under 60 benefited most from both earlier diagnosis and treatment advances of locally/regionally spread cancers. However, the survival gap with more developed European countries persists. Further increase in survival, but also decline in BC mortality in Estonia could be achieved by facilitating early diagnosis in all age groups,

but particularly among women over 60. Investigations should continue to clarify the underlying mechanisms of the stage-specific survival deficit between European countries.
No conflict of interest.

1422 POSTER

Missing data and survival analysis of central nervous system tumours amongst children and young people in Yorkshire, 1990–2009

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Background: Missing data is a common problem in many areas of research, including cancer registration. Severity of disease at diagnosis is often missing from medical records, and as a result this important prognostic variable is sometimes excluded from analysis. We investigated survival trends of central nervous system (CNS) tumours in children and young adults whilst using multiple imputation (MI) to impute missing values of disease severity (grade) and ethnicity.
Materials and Methods: Children and young people (<30 years) diagnosed with CNS tumours (1990–2009) were identified from a population based cancer register in Yorkshire. Logistic regression models were used to impute missing values of grade (WHO Classification, I−IV) and ethnicity (White, Asian and Other), this process was repeated 40 times. Age, sex, year of diagnosis, deprivation, diagnostic subgroup, relapse status and treatment data were all used as predictors of the missing data. Subsequently, a survival analysis was performed using Cox regression models for each set of imputed data, pooled hazard ratios (HR) were then obtained by averaging over all sets of results.
Results: There were 795 cases of CNS tumours diagnosed in Yorkshire between 1990 and 2009. Missing grade data occurred in 71 (8.9%) cases, and missing ethnicity occurred in 191 (24%) cases. Overall, missing data of one or both variables occurred in 242 (30%) cases. Kaplan–Meier survival curves were significantly lower for cases in which grade and ethnicity was missing, compared to those in which it was recorded (P<0.001). This implies that an analysis on only those with complete data (complete case analysis) would produce biased results towards improved survival over the whole cohort. The complete case survival analysis showed no difference in survival between ethnic groups or over time, however, it did show an increased risk of death for those with grade II, III and IV tumours compared to grade I (HR = 3.7, 7.02, 13.36 respectively). After MI, survival analysis showed an increased risk of death for 'other' compared to 'white' ethnicity (HR = 2.1; P = 0.034), and an increased risk of death for those with grade II, III and IV tumours compared to grade I (HR = 3.5, 6.4 and 10.4 respectively). Additionally, survival improved significantly by 4% over the study period (P=0.001). Age, sex and deprivation did not significantly affect survival in the complete case or MI analysis. MI reduced standard errors of coefficients by an average of 18% when compared to a complete case analysis.
Conclusion: MI was used to minimise bias and enhance the precision of analyses. This technique offers considerable advantages over other approaches such as performing a complete case analysis. Survival rates varied by grade and ethnicity, and showed a significant improvement over time.
No conflict of interest.

1423 POSTER

The risk of hepatocellular carcinoma associated with blood iron profile: Preliminary findings from a prospective cohort study

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Background: Iron is an essential nutrient but higher levels can catalyze free radical generation, leading to increased oxidative stress and possibly increased risk of cancer at various sites. This may particularly be the case for the liver, which is the main organ of iron storage and metabolism. It has been established that iron overload, for example in Haemochromatosis, is associated with increased risk of hepatocellular carcinoma (HCC). But, it is currently unclear to what extent mild or moderate excesses in body iron status contribute to HCC etiology. Furthermore, since iron is an essential nutrient, it can also be hypothesized that very low body status may be cancer promotive. These questions were explored within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.
Materials and Methods: EPIC is a large prospective cohort of over 520,000 subjects from 23 centers in 10 Western European countries. In a nested case-control setting, serum iron, ferritin and transferrin were measured in 121 (n men=82; n women=39) HCC cases and 242 control subjects matched by age, sex, study center and date of blood collection. Conditional logistic regression models were used to compute odds ratios based on quartiles of serum analyte levels.
Results: Compared to serum iron levels in the 2nd quartile, a significant increased risk of HCC was observed in subjects in the lowest (OR:2.10, 95% CI:1.03–4.28) and highest (OR:4.22, 95% CI:2.07–8.56) quartiles. For ferritin, subjects in the highest quartile had a significantly higher HCC risk (OR: 3.34, 95% CI:1.67–6.68) compared to those in the 2nd. For serum transferrin, a similar pattern of results was observed but was not statistically significant.
Conclusions: These findings indicate that serum iron parameters have a J-shaped relationship with HCC risk, and that higher iron status as indicated by serum iron and ferritin is significantly associated with higher HCC risk in this prospective European cohort.
No conflict of interest.

1424 POSTER

Dietary folate intake and risk of hormonal receptor defined breast cancer in the European prospective investigation into cancer and nutrition (EPIC) study

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Background: Dietary folate has been suggested to be related to Breast Cancer (BC) risk. However, the evidence on the association by menopausal status and hormonal receptor status is limited. We aimed at investigating the relationship between dietary folate and BC risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.
Material and Methods: A total of 367,993 women (aged 35−70 years) were recruited in 10 European countries. During a median follow-up of 11.5 years, 11,575 women with invasive BC were identified. Dietary folate was estimated from country-specific dietary questionnaires. Cox proportional hazards regression models were used to quantify the association between dietary variables and BC risk, controlling for energy intake with the residual method. Further analyses were performed by menopausal status, hormonal receptor status, and level of baseline alcohol intake.
Results: A borderline significant overall relationship was observed between dietary folate and risk of BC (HR_{Q5-Q1} = 0.92, 95% CI: 0.84–1.01, p_{trend} = 0.037). However, no significant associations were found according to menopausal status or hormonal receptor status. A 15% reduction of BC risk was found when comparing the highest to the lowest dietary folate intake tertiles in women having a high (>20 g/day) baseline alcohol intake (HR_{T3-T1} = 0.85, 0.75−0.97).
Conclusions: Diets rich in folate intake showed little association with BC risk, independently on menopausal status or hormone receptor expression in the tumors. The combined effect of high folate and high alcohol intake resulted in a 15% reduction in BC risk as compared to high alcohol and medium or low folate intakes, thus suggesting that large folate intake could reduce BC incidence in subjects with large baseline alcohol intakes.
No conflict of interest.

1425 POSTER

Breast cancer biology and risk of venous thromboembolism

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Background: Previous reports suggest a worse survival outcome for breast cancer patients with venous thromboembolism (VTE) compared to those without VTE. We determined whether breast cancer stage or biology influenced development of VTE independently of cancer treatment and quantified the impact of VTE on breast cancer survival.
Materials and Methods: Cohort study using the Clinical Practice Research Datalink, linked to Hospital Episode Statistics, Cancer Registry data and Office for National Statistics cause of death data. Our cohort comprised 13,206 patients with a first breast cancer diagnosis between 1997 and 2006 with follow-up for outcomes (VTE and all-cause mortality) continuing to the end of 2010. A multivariable cox regression analysis was performed to determine which demographic, treatment-related and biological factors independently affected VTE risk. Results were subsequently stratified by the 'first 6 months' and 'six months or more' following cancer diagnosis. Cox regression was also used to ascertain whether mortality was higher in patients who developed a VTE.

Results: The overall VTE rate in breast cancer patients was 8.5 per 1000 person years (95% CI, 7.9−9.2). In unavailable analysis, we found that VTE rates increased with increasing age, body mass index, pre-existing comorbidities, cancer stage and chemotherapy (although not radiotherapy and surgery). In the multivariate analysis, chemotherapy (HR 2.29, CI 1.88–2.80) was found to be a more important predictor of VTE risk than metastatic disease (HR 1.53, CI 0.97–2.42) when these variables were mutually adjusted. Estrogen receptor (ER) positive patients had almost half the risk of VTE (HR 0.57, CI 0.39–0.82) in the first six months after cancer diagnosis, but beyond six months from diagnosis, these patients had a higher risk of VTE (HR 1.38; 95% 1.01, 1.90) In the non-metastatic breast cancer subgroup, overall survival was significantly worse in patients with VTE compared to without VTE and this persisted for more than 5 years following breast cancer diagnosis.
Conclusions: Development of VTE in non-metastatic cancer is associated with reduced survival, even several years after diagnosis, and therefore unlikely to be VTE-related mortality. The association between poor prognosis breast cancer phenotypes (ER-ve), development of VTE, and reduced survival supports a symbiotic relationship between thrombosis and breast cancer progression.
No conflict of interest.

1426 POSTER

The association between sleep disorders and cancers: A nationwide population-based study

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Background: To investigate the risk of cancer among patients with non-apnea sleep disorders (SD).
Material and Methods: We recruited newly diagnosed SD patients aged 20 years or older without antecedent cancer from the National Health Institutes Research Database between 2000 and 2010. Standardized incidence ratios (SIRs) of cancers were calculated to compare the cancer incidence of patients with SD to the general population.
Results: During the 10-year study period, 2,062 cancers developed among 63,381 recruited SD patients with a follow-up of 382,826 person-years (median follow-up of 6.23 years). The SIR for all cancers was 1.19 [95% confidence interval (CI) 1.14–1.24]. The SIR was 1.20 (95% CI 1.12–1.28, $p < 0.001$) for men and 1.18 (95% CI 1.11–1.24, $p < 0.001$) for women. Subgroup analyses according to age at diagnosis revealed that patients aged $\geqslant$40 tended to have a greater risk ratio. In regards to specific types of cancer, SD patients had an increased SIR for liver (1.44, 95% CI 1.28–1.61), lung and mediastinum (1.34, 95% CI 1.18–1.51), breast (1.15, 95% CI 1.02–1.29), prostate (1.35, 95% CI 1.08–1.67) and kidney cancers (1.51, 95% CI 1.17–1.92).
Conclusions: The nationwide population-based cohort study found Taiwanese patients with SD have higher risk of overall cancer risk, especially the risk of liver, lung, breast, prostate and kidney cancers.
No conflict of interest.

1427 POSTER

Breast cancer in Niger: First results from the Niger Cancer Registry

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Background: Breast cancer is the most common cause of cancer death in women worldwide. The aim of this study is to determine the frequency and the epidemiological characteristics of breast cancer in Niger.
Material and Methods: This is a retrospective analysis of breast cancer cases, reported between 1992 and 2009 to the Niger Cancer Registry, established in 1992, in the Faculty of Health Sciences at the Abdou Moumouni University in Niamey.
Results: There were 1161 cases diagnosed with breast cancer in Niger, 96.8% in women and 3.2% in men, giving a female-male ratio of 31 and accounting for 16.5% of all new cancer cases reported during 1992–2009. During this period, breast cancer was the first most common cancer and the first leading cause of cancer death in women. About 40% of all breast cancers were invasive ductal carcinomas. The average age at diagnosis was 44±12 years. The risk of developing breast cancer is strongly related to age with 9.6% of new breast cancer cases diagnosed in people younger than 30 years, 82.5% in those aged 30−64 years and 7.9% in those aged 65 years and over. The rates of developing and dying from breast cancer varied among various ethnic groups. Djerma-Sonrai was more likely to get and die of breast cancer than any other ethnic groups, followed by Haoussa. Among all detected cases, 9% died during the study period.
Conclusions: Breast cancer was the leading cause of death from cancer in women. Early detection in order to improve breast cancer outcome and survival remains the cornerstone of breast cancer control.
No conflict of interest.

1428 POSTER

The age distribution and receptor status profile in Egyptian breast cancer patients

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Background: Breast cancer is the most common cancer of women in Egypt. The disease is often advanced at diagnosis. Since molecular profiling is not feasible in routine practice, we sought to characterize the hormone receptor profile in our patients in correlation with disease stage and outcome.

Table 1 (abstract 1426). Standardized incidence ratios (SIRs) for specific cancer types among patients with sleep disorders

Site of cancer	Total			Male			Female		
	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)
All cancers	2062	1738.77	1.19 (1.14−1.24)	906	755.06	1.20 (1.12−1.28)	1156	983.71	1.18 (1.11−1.24)
Head and neck	145	144.63	1.00 (0.85−1.18)	116	114.11	1.02 (0.84−1.22)	29	30.53	0.95 (0.64−1.36)
Digestive									
Esophagus	33	30.59	1.08 (0.74−1.51)	30	27.06	1.11 (0.75−1.58)	3	3.53	0.85 (0.18−2.48)
Stomach	75	83.28	0.90 (0.71−1.13)	39	44.08	0.88 (0.63−1.21)	36	39.21	0.92 (0.64−1.27)
Colon and rectum	268	242.17	1.11 (0.98−1.25)	115	108.92	1.06 (0.87−1.27)	153	133.25	1.15 (0.97−1.35)
Anus	0	1.79	0.00 (0.00−2.06)	0	0.61	0.00 (0.00−6.05)	0	1.18	0.00 (0.00−3.13)
Liver	306	213.21	1.44 (1.28−1.61)	176	128.41	1.37 (1.18−1.59)	130	84.80	1.53 (1.28−1.82)
Biliary tract	26	21.77	1.19 (0.78−1.75)	11	8.52	1.29 (0.64−2.31)	15	13.25	1.13 (0.63−1.87)
Pancreas	34	29.20	1.16 (0.81−1.63)	16	13.40	1.19 (0.68−1.94)	18	15.80	1.14 (0.68−1.80)
Lung and mediastinum	264	197.19	1.34 (1.18−1.51)	136	106.65	1.28 (1.07−1.51)	128	90.54	1.41 (1.18−1.68)
Bone and Soft tissue	19	14.20	1.34 (0.81−2.09)	11	6.49	1.70 (0.85−3.03)	8	7.71	1.04 (0.45−2.04)
Skin	39	31.95	1.22 (0.87−1.67)	18	13.50	1.33 (0.79−2.11)	21	18.45	1.14 (0.70−1.74)
Breast	284	247.16	1.15 (1.02−1.29)	2	0.82	2.44 (0.30−8.81)	282	246.34	1.14 (1.02−1.29)
Genitourinary									
Cervix	59	68.76	0.86 (0.65−1.11)	–	–	–	59	68.76	0.86 (0.65−1.11)
Uterus	36	35.55	1.01 (0.71−1.40)	–	–	–	36	35.55	1.01 (0.71−1.40)
Ovary	39	31.65	1.23 (0.88−1.68)	–	–	–	39	31.65	1.23 (0.88−1.68)
Prostate	86	63.65	1.35 (1.08−1.67)	86	63.65	1.35 (1.08−1.67)	–	–	–
Bladder	64	51.47	1.24 (0.96−1.59)	43	31.44	1.37 (0.99−1.84)	21	20.02	1.05 (0.65−1.60)

Patients and Methods: Retrospective analysis of all breast cancer patients treated at Mansoura University Cancer Center in the Nile Delta. Tumor clinico-pathological criteria were examined in relation to receptor status. The effect of receptor status on disease relapse and disease-free survival was examined with logistic regression and Kaplan Meier analysis.
Results: Hormone receptor positive tumors constituted 67% of cases, Hormone receptor negative-Her_2/neu positive was 14% and triple negative was 19%. Median age of the patients was 52 years and was equal across all receptor status types. Triple negative status correlated with increased risk of disease relapse (Hazards ratio= 1.8, $p = 0.03$, Logistic regression) and with shortened disease-free survival (Hazards ratio = 2.6, $p = 0.00$, Cox regression).
Conclusion: The age distribution and receptor status pattern in Nile Delta region does not explain the aggressive behavior of the disease. The age of the patients at diagnosis is older than earlier literature from Egypt emphasizing the importance of implementing mammographic screening programs.
No conflict of interest.

1429 POSTER

Peritoneal carcinomatosis of gastric origin: A population-based study on incidence, survival and risk factors

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Background: Peritoneal carcinomatosis (PC) is an important cause of morbidity and mortality among patients with gastric cancer. The aim of the current study was to provide reliable population-based data on the incidence, risk factors and prognosis of PC of gastric origin.
Methods: All patients diagnosed with gastric cancer in the area of the Eindhoven Cancer Registry between 1995 and 2011 were included. Incidence and survival were computed and risk factors for peritoneal carcinomatosis were determined using multivariate logistic regression analysis.
Results: In total, 5,220 patients were diagnosed with gastric cancer, of whom 2,029 (39%) presented with metastatic disease. PC was present in 706 patients (14%) of whom 491 patients (9%) had PC as the only metastatic site. Younger age (<60 yrs), female gender, advanced T- and N-stage, primary tumour of signet ring cells or linitis plastica, and primary tumours covering multiple anatomical locations of the stomach were all associated with a higher odds ratios of developing PC. Median survival of patients without metastases was 14 months, but only 4 months for patients with PC.
Conclusion: PC is a frequent condition in patients presenting with gastric cancer, especially in younger patients with advanced tumour stages. Given the detrimental influence of PC on survival, efforts should be undertaken to further explore the promising results that were obtained in preventing or treating this condition with multi-modality strategies.
No conflict of interest.

1430 POSTER

The effect of subsequent independent primary cancers on survival in patients with breast, lung and prostate cancer

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Introduction: Influence of including subsequent primary cancers on survival analyses are not well known. In this study, we planned to evaluate the impact of subsequent multiple primaries on the overall survival.
Methods: We analysed data on 6179 patients, who had lung, breast and prostate cancer as first primary. All patients were recorded in Antalya State Cancer Registry Office(South Turkey Region) between the years 2005 and 2011. Antalya State Cancer Registry Office followed SEER rules for the definition of multiple cancer sites. We utilised Kaplan–Meier survival analysis to compare overall survival figures of single primary tumours and multiple primary tumours. We analysed data with regard to each of the three first primaries. In addition, we stratified data according to age, gender, number of independent primaries, economic status and disease extent of the first primary (metastatic, non-metastatic). Lastly, all potential prognostic factors were separately evaluated in cox-regression models.
Results: 1928 of all patients had breast cancer as first primary and 29 (1.5%) of them had multiple primaries. 2513 of all patients had lung cancer as first primary and 29 (1.15%) of them had multiple primaries. 1738 of all patients had prostate cancer as first primary and 138 (7.94%) of them had multiple primaries. Estimated survival of lung cancer patients with single primaries was shorter than multiple primaries (HR: 2.73(%95 CI: 1.67 to 4.47), P: <0.001). On the other hand, estimated survival of prostate and breast cancer was higher in single primary cancers (HR: 0.75(%95 CI: 0.57 to 1.00), P: <0.051 and HR: 0.40(%95 CI: 0.22 to 0.74), P: <0.003, respectively). When multivariate analysis was done for lung cancer; age, gender, including subsequent primary tumours and disease extent were independently prognostic (HR: 1.02, P: <0.001, HR: 1.24, P: <0.001, HR: 2.53, P: <0.001 and HR: 0.54, P: <0.001, respectively). In addition, for cases with prostate and breast cancer; age, including subsequent primaries and disease extent were independently correlated with survival.
Conclusions: We found that inclusion of subsequent primary cancers in the overall survival analysis, resulted in higher survival for lung cancer primary first patients. Besides, it resulted lower survival for breast and prostate cancer primary first patients.
No conflict of interest.

1431 POSTER

Prospects for stratified cancer follow-up

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Background: Cancer prevalence is expected to increase by more than 50% in the next 10 years. The follow-up burden can be reduced by less frequent testing in patients with a low probability to die of cancer. The prospects for stratified follow-up are illustrated for five common cancer types.
Methods: The Netherlands Cancer Registry provided data on 214,173 patients diagnosed in the period 2003–2009 with in situ and invasive breast, invasive ovarian, invasive lung, or in situ, Ta or invasive bladder cancer, or invasive skin melanoma. Relative survival rates and risks of second primary cancers were calculated. Age and cancer specific co-morbidity rates were obtained from Janssen-Heijnen et al (2005).
Results: Five-year relative survival in early stage breast, bladder and skin cancer, comprising at least 50% of the incident cases, was close to 100%. Sixty five percent of ovarian and 84% of lung cancer patients were diagnosed at an advanced stage with five-year relative survival rates below 30%. Thirty five percent of breast, 47% of ovarian, 63% of lung, 65% of bladder cancer and 26% of skin melanoma patients were aged 80+ years or had at least 1 co-morbidity. Cumulative five-year risks of second primary cancers were below 5%.
Conclusions: Selecting patients for less intensive follow-up based on cancer stage, age and presence of co-morbidity has a large potential to reduce the follow-up burden. Before implementing less intensive follow-up in clinical practice, however, clinical studies are needed to classify patients as having a short life expectancy or low relapse rate.
No conflict of interest.

1432 POSTER

Genetic background and risk of lung adenocarcinoma in never smokers

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Background: The causative association between tobacco smoking and lung cancer is well-known.
However, the mechanism underlying the pathogenesis of lung adenocarcinoma in never smokers remains unclear. Recently, several driver oncogenes, such as *EGFR* and *EML4-ALK*, have been identified in lung adenocarcinomas of never smokers.
Material and Methods: This was a retrospective review of 588 patients with surgically resected lung adenocarcinomas between February 2009 and October 2012. The clinicopathological factors (age, gender, and pathological stage), *EGFR* and *KRAS* mutation status, a past history of any cancer or benign tumor, a family history of any cancer or lung cancer, and the presence of multiple primary lung cancers were compared between never smokers (n = 306) and smokers (n = 282).
Results: Lung adenocarcinomas in never smokers were more frequently found in females (P <0.001) and in patients with early stage disease ($P = 0.01$) than those in smokers. *EGFR* mutations were detected in 181

(59%) never smokers and in 88 (31%) smokers (P <0.001). *K-ras* mutations were detected in nine (3%) never smokers and in 57 (20%) smokers (P <0.001). The proportion of patients with a past history of any cancer was higher in smokers than in never smokers (28% vs 20%, P = 0.03). This may reflect the fact that tobacco smoking can cause various types of cancers. In contrast, the proportions of patients with any benign tumor and a family history of any cancer were higher in never smokers than in smokers (15% vs 4%, P <0.001 and 19% vs 12%, P = 0.04). These findings may suggest that a certain genetic background is involved in the pathogenesis of lung adenocarcinoma in never smokers. The frequencies of multiple primary lung cancers and a family history of lung cancer were not significantly different between never smokers and smokers (14% vs 11%, P = 0.2, and 7% vs 4%, P = 0.1). In never smokers, the *EGFR* and *KRAS* mutation status were not associated with a past history or a family history of any tumor, or the presence of multiple primary lung cancers.
Conclusions: A certain genetic predisposition is suspected to be involved in the pathogenesis of lung adenocarcinoma in never smokers. Further studies are thus needed to elucidate the genetic alterations associated with the susceptibility to lung adenocarcinoma in never smokers.
No conflict of interest.

1433 POSTER

Which colorectal cancer patients get venous thromboembolism?

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Background: Patients with colorectal cancer are considered at high risk of venous thromboembolism (VTE) and recent NICE guidelines have advised extended prophylaxis for these patients following surgery. The guidelines group highlighted the lack of understanding of which of these patients are at increased risk and what the magnitude of this risk is. The aim of this study was to determine the occurrence of VTE in patients with a diagnosis of colorectal cancer.
Materials and Methods: Population based cohort study using data from 4 linked databases; the Clinical Practice Research Datalink, linked to Hospital Episode Statistics, Cancer Registry data and Office for National Statistics cause of death data. We determined the incidence rates (cases per 1000 person-years) of VTE in colorectal cancer patients according to various risk factors. Data was extracted from 1997–2006.
Results: We identified 10,319 patients with colorectal cancer. The incidence of VTE was 15.8 per 1000 person years (95% Confidence Interval (CI) 14.5–17.1). The incidence increased from 7.3 per 1000 person years (95% CI 5.0–10.7) in Dukes A patients to 41.3 per 1000 person years (95% CI 33.4–51.2) in patients with Dukes D stage. This represented a threefold increased risk when accounting for other risk factors (HR 3.08, 95% CI 1.95–4.84). The risk of VTE following surgery varied by stage of disease. Those patients undergoing emergency surgery had a 40% increase in risk of VTE following surgery compared to those undergoing elective surgery (HR 1.43 95% CI 1.15–1.78). Patients who had chemotherapy had a significantly higher rate of VTE than those who did not (HR = 1.39 CI 1.14–1.69).
Conclusions: Tailoring risk assessment to include stage of disease, timing of surgery and chemotherapy may help identify patients at increased risk of VTE with colorectal cancer and direct appropriate thromboprophylaxis during treatment.
No conflict of interest.

1434 POSTER

Post code lottery in lung cancer incidence

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Background: Lung cancer is the most common cancer in the world with an estimated 1.6 million new cases diagnosed in 2008 but its incidence varies considerably within different areas in England. Socio-economic status of an individual has long been established a fundamental determinant factor in the incidence and prognosis of majority of illnesses and the aim of this study is to explore the impact socioeconomic status has on the incidence of lung cancer patients in Liverpool over a 3-year period.
Material and Methods: Hospital Episodes Statistics (HES) data from Liverpool Primary Care Trust (LPCT) was used to identify new cases of Lung cancer patients diagnosed between January 2005 and December 2007. Identified patients were later allocated into 5 classes (Quintiles) based on their residential postcodes using the Index of Multiple Deprivation, developed in 2007 by Department for Communities and Local Government (DCLG). This tool uses a weighting score on 7 aspects of deprivation for small areas (Lower Super Output Areas) and each quintile represents 20% of an identified population with similar deprivation characteristics.
Results: 80% of the patients diagnosed with lung cancer reside in the 5th quintile (the most deprived socioeconomically) and over 93% of the newly diagnosed lung cancer patients live within the 4th and 5th quintiles. There was no single case of a new lung cancer diagnosis from Liverpool residents living in the 1st quintile over the 3-year study (2004–2006) and only 7 (1.61%) cases were recorded in the 2nd quintile.
Conclusion: This study showed that lung cancer predominantly affects people with lower socio-economic status than their affluent counterparts and more public health work should be carried within deprived communities in order to reduce the inequalities gap for lung cancer.
No conflict of interest.

1435 POSTER

Potential risk of residential asbestos exposure: Japanese General Screening Study for Asbestos-related Diseases (JGSARD)

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Background: Currently, an argument about health risks by residential asbestos exposure as well as occupational asbestos exposure has been closed up in Japan. Therefore, the latest large-scale CT screening study reflective of a country's general situation of asbestos exposure will help citizens understand significant information about asbestos-related diseases.
Materials and Methods: JGSARD is a prospective cohort study for the general population representative of Japan designed to evaluate the actual situation of asbestos exposure and the prevalence of asbestos-related diseases through chest radiography and low-dose CT (LDCT) at baseline and after 2 years of follow-up. From 2006 to 2008, 9810 subjects (mean age, 57 years; 54% male and 50% smokers) underwent baseline screening in 26 institutions in Japan. Lifetime self-reported history of asbestos exposure (SHAE) was obtained.
Results: Occupational SHAE was definite and possible in 1103 (11.2%) and 1702 (17.3%) subjects, respectively, whereas residential SHAE was definite and possible in 262 (2.7%) and 931 (9.5%) subjects, respectively, although asbestos factory in their residential areas actually existed in 2870 (29.3%) subjects. The false negative rates of residential SHAE in all participants of this study (n = 9810), those with pleural plaque on LDCT (n = 264), and those with pleural plaque without occupational SHAE (n = 83) were calculated as high value of 85.6%, 76.0%, and 87.9%, respectively. Presence of pleural plaque was significantly correlated with male (odds ratio [OR], 2.32), age 60 years and older (OR, 1.75), smoking (OR, 1.60), occupational or residential SHAE (OR, 3.92), residential period in asbestos factory area (OR every 10 years, 1.13), and asbestos-related work period (7 works identified). Lung cancer was identified in 29 (0.3%) subjects. Presence of lung cancer was significantly correlated with age 60 years and older (OR, 2.67) and presence of pleural plaque (OR, 4.17) regardless of occupational and residential SHAE.
Conclusion: Our results indicate the potential risk of residential asbestos exposure and thus the importance of public relations and enlightenment for them among Japanese general population.
No conflict of interest.

1436 POSTER

Statin use as a moderator of metformin effect on overall survival in colorectal cancer patients with diabetes

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Background: Metformin has been associated with a decreased cancer risk and a decreased mortality in cancer patients. Individuals using metformin, frequently use statins as well. This study assessed whether the effect of metformin on overall survival varied by statin use among colorectal cancer patients.
Methods: Patients with primary colorectal cancer diagnosed between 1998 and 2010 in the South-eastern Netherlands were included from the Eindhoven Cancer Registry (ECR). The included patients were linked to data on drug dispensing from the PHARMO Record Linkage system. Colorectal cancer patients who started with diabetes medication in the five years prior to cancer diagnosis were included and the cumulative exposure

to diabetes drugs for this period was calculated. Cox proportional hazard analyses were conducted to assess whether overall mortality varied by statin use in patients using metformin.
Results: 289 colorectal cancer patients started with diabetes medication before cancer diagnosis, of whom 173 (60%) used statins and 220 (76%) used metformin as diabetes medication. Statin use was an effect modifier for the effect of metformin on overall mortality ($p = 0.04$), when taking into account cumulative exposure to the specific drugs and adjusting for patient-, tumour-, and comorbidity-related variables. However, the use of metformin was not significantly associated with a reduced overall mortality among colorectal cancer patients on statins (HR 0.87, 95% CI 0.73–1.03) when adjusting for the variables mentioned above and the additional cumulative use in days of insulin and sulfonylurea derivatives. The prognosis for those taking metformin and statins compared to those taking neither metformin nor statins was significantly better (HR 0.44, 95% CI 0.23–0.83).
Conclusions: The first results of this study showed that the effect of metformin on survival in colorectal cancer patients varied by their statin use. The combination of metformin and statins in colorectal cancer patients effected the prognosis positively in our study and may be due to synergistic effects. However, detailed information on laboratory function, such as LDL and Hba1C, was suboptimal, additional multivariate analyses should be performed and a relatively small number of patients was included.
No conflict of interest.

1437 POSTER

Castration-resistant prostate cancer (CRPC): Understanding disease progression and associated diagnostic procedures through a routine practice study in 13 medium-sized European countries

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Background: To examine CRPC, the natural course of disease progression and associated diagnostic procedures.
Materials and Methods: 167 physicians (100 oncologists and 67 urologists) completed a prospective 5-day workload form, an interview and an average of 8 patient record forms (PRFs, October 2012 through March 2013) for non-metastatic and metastatic CRPC patients. Final data from 142 workloads (not completed by all physicians), 167 interviews and 1,279 PRFs (including 475 CRPC patients at 'high risk' of bone metastases [BM], 505 CRPC patients with BM only, 102 CRPC patients with BM and visceral metastases [VM] and 197 CRPC patients with VM only) from 13 medium-sized European countries are reported.
Results: According to physician interviews, 61% of prostate cancer patients develop castration-resistance (where physicians specified a time-frame, this was most commonly 25−36 months post exposure to hormone therapy). Per the PRF data, multiple factors are involved in the diagnosis of castration resistance, the most common being elevated prostate-specific antigen (PSA) levels (79%), shortened PSA doubling time (39%) and no response to two different types of hormone therapy (32%).
According to the physicians, 78% of CRPC patients develop metastases. These data were further confirmed by the physician's daily workload outcomes which showed that among the CRPC population 82% had metastases. According to physicians, the factors associated with a high risk of developing BM in CRPC patients are: shortened PSA doubling time (78%), Gleason score (77%) and elevated PSA (74%). Per the physician daily workload results, the vast majority of metastatic CRPC patients have BM only or both BM and VM (94%). BM are commonly first suspected due to multiple factors such as symptomatic bone pain (31%), routine bone scan (29%) and elevated PSA (26%). However, BM are predominantly confirmed by a bone scan (69%).
Conclusions: Elevated PSA and shortened PSA doubling are the main factors involved in the diagnosis of CRPC and are also considered, as well as a high Gleason score, to be associated with a high risk of developing BM. Bone scans remain the main diagnostic procedure for confirming BM. These data highlight that the majority of non-metastatic CRPC patients in the 13 European countries will experience disease progression and develop BM in due course. There is a need for novel treatment strategies to delay metastatic progression to bone in patients with CRPC.
Conflict of interest: *Ownership: PV, GH, JA, JC, IH, AL − Amgen stock. Corporate-sponsored research: AR, AW, VC, RP − Amgen. Other substantive relationships: PV, GH, JA, JC, IH, AL − Employed by Amgen*

1438 POSTER

Epidemiological characteristics of liver cancer in Niamey

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Background: In Sub-Saharan Africa, liver cancer is a real public health problem. It is the third most common cancer and the second leading cause of cancer death (GLOBOCAN 2008). The aim of this study is to describe the epidemiological characteristics of liver cancer in Niamey, Niger's capital.
Material and Methods: This is a descriptive retrospective analysis of liver cancer cases, reported between 1992 and 2009 to the Niger Cancer Registry.
Results: A total of 555 liver cancer cases were recorded between 1992 and 2009, constituting 11.2% of all cancer cases reported in Niamey during this period. Of these, 60.7% were farmers. More than two-thirds were males with a male-female ratio of 2.21. The average age at diagnosis of liver cancer patients was 47 ± 14 years. Hepatocellular carcinoma was the most common histological type (98.6%). Among all detected cases, 206 (37.1%) died during the study period. The incidence rate of liver cancer was twice as high for men, with 5.89 cases per 100 000 men, compared with 2.80 cases per 100 000 women. The mortality rate was 1.59 deaths per 1000 000 population.
Conclusions: The absence of appropriate health policy prevents early detection of liver cancer and its management. This has a direct consequence on increasing in cancer incidence. Because of the seriousness of liver cancer in Niger; the health authorities should pay more attention to this pathology through efficient fight strategies.
No conflict of interest.

1439 POSTER

Cancer in Indians of the Brazilian Amazon

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Background: Cancer is currently a problem public health worldwide and is the second cause of death in many countries. The impact of this disease on indigenous peoples is poorly understood in Brazil and in the Amazon region. This research was conducted with the purpose to characterize the epidemiological profile of cancer in Indians of the Brazilian Amazon.
Methods: We conducted a descriptive, cross-sectional study based on retrospective analysis of medical records of the Indians diagnosed with cancer treated by Hospital Ophir Loyola, a referral center for oncology in the state of Pará, between January 2001 and December 2011. The medical records were evaluated for epidemiological data, diagnostic, and therapeutic response, according the protocol developed after literature review.
Results: We included 47 Indians with confirmed diagnosis of cancer. Women were more affected (68.09%), in the ratio of 2.12:1. The average age was 46.14 years, with the predominant age of 60−69 years (21.28%). Most patients were illiterate (46.81%), smokers (42.55%), from the municipalities of Altamira and Jacareacanga (17% each), of the indigenous ethnic group of Mundurukus (23.4%). Cervical cancer was the most frequent malignant tumour (48.93%), affecting 76.69% of women adults. Among adult men prevailed not any cancer. The haematological malignancies were the most detected in the paediatric age group (83.3%), with 50% of indigenous children diagnosed with Hodgkin's Lymphoma. The vast majority of patients was treated with modality cancer therapy (85.1%) and radiochemotherapy was the most used (23.4%). The time interval between diagnosis and cancer treatment was on average of 113 days; being more than 02 months in 60% of cases. Complete response and partial response was observed over the results after the first treatment (32.5% and 20%, respectively). We recorded 14 deaths among patients investigated.
Conclusions: From these data, it was possible to characterise the clinical and epidemiological profile of indigenous patients with cancer in the Amazon region. The data obtained could help in the implementation of public policies aimed at primary prevention, injury reduction and lower mortality for improvements in indigenous health in Brazil.
No conflict of interest.

1440 POSTER

The effect of prenatal factors on the development of colon cancer

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Background: There is some evidence that prenatal factors can play role in development of colon cancer. Children with an old parent age at the time of birth were observed to develop certain childhood cancers more frequently. This trial is designed to investigate the effects of some prenatal factors on colon cancer risk. Particularly, investigation of the effect of advanced parent age on colon cancer development risk was targeted.
Material and Methods: In this study 117 in or out patient diagnosed as colon cancer and 234 control patients included. Definitive diagnostic results and dates of diagnosis were determined from pathological reports. Groups were asked the parenteral age, smoking habits, sociodermographic, environmental, familial and reproductive traits. The results were compared between the patients and the control group.
Results: It was determined that children may have higher risk if mother and father are more than 30 at birth ($p = 0.018$, $p = 0.020$). While the mean mother age at birth was 25.6 ± 5.72 in patients, it was 24.7 ± 6.90 in the controls. The difference was not statistically significant ($p < 0.056$). While the mean father age at birth was 29.4 ± 6.58 in patients, it was 27.4 ± 7.47 in the controls. The difference was statistically significant ($p < 0.001$). Smoking of mother was one of the important risk factors of colon cancer ($p = 0.044$).
Conclusion: Our data supports that some prenatal factors such as high parental age at birth and smoker mother may be risk factors for some cancers for children. This is the first study reports that having high parental age at birth and exposure to smoke prenatally increase the risk or colon cancer.
No conflict of interest.

1441 POSTER

Pinnacle Study: Epidemiology and characteristics of neutropenic fever (NF) in cancer patients in Spain

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Background: The Pinnacle study aims to evaluate NF and its clinical management in Spain, further linking action protocols from medical oncologists with a patient's profile. The main objective is to describe the incidence of hospitalizations due to NF. Secondary objectives are to describe the characteristics of patients, NF, and describe its evolution and management.
Material and Methods: This study was designed as a retrospective analysis of hospital admissions of patients who developed NF over a 3-month period, involving 10 national tertiary care centers. Patients were included sequentially after providing informed consent, and data were collected on the underlying disease, treatment received and outcome.
Results: 119 patients were recruited. The most prevalent tumors were lung, breast and colorectal. The incidence of NF was 2.29%. The median duration of hospitalization was 7 days. Only 32% of patients had received prophylaxis with G-CSF, and these patients had a reduced duration of hospitalization (2.5 days shorter). On admission, the median neutrophil count was 260/mm^3. 61% of patients were receiving palliative chemotherapy and the remainder either curative or adjuvant treatment. 14% of patients were admitted without meeting the two NF criteria (temperature of 38.2^{o}C and neutrophil count <500/mm^3). Among patients receiving curative or adjuvant chemotherapy, 11% discontinued chemotherapy as a result of NF, 6% had dose reduction, 16% a dose delay, and 2% a dose reduction + delay (similar outcomes were noted in patients receiving palliative treatment). The most commonly used antibiotics were piperacilin-taxobactam,amoxicilin-clavulanic and cephalosporins. 8 patients died, 2 due to NF, 5 due to disease progression and one due to ventricular fibrillation.
Conclusions: NF is an important cause of chemotherapy delays and dose reductions, which can lead to reduced effectiveness of treatment. It is a serious complication of chemotherapy treatment, with a substantial proportion of death and a hospital stay of about seven days. Moreover, 14% of patients were admitted without fulfilling both NF criteria. Patients who were receiving palliative chemotherapy had a longer hospitalization, and the impact on their chemotherapy was the same as in patients receiving non-palliative treatment. On the other hand, patients receiving G-CSF had a shorter hospitalization. The number of died patients shows that patients with NF are patients mostly in progression and clinical instability.
Conflict of interest: *Board of directors: Sandoz Pharmaceutical*

1442 POSTER

Histopathologic characteristics and related variables in a study of 4,436 patients included in the Registry of Breast Cancer (Registro Cáncer de Mama- RCM) of the Argentine Society of Mastology (SAM)

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Background: In Argentina, more than 18,000 new cases of breast cancer are diagnosed every year. However, as we do not have adequately powered statistical registries in our country we cannot establish whether our local data are in concordance with international series. We present an analysis of the data collected in the web-database SAM-RCM regarding histopathological characteristics and basic therapeutic approaches.
Material and Methods: Descriptive, cross-sectional study of 4,436 patients (pts) included in the RCM until 31/12/2012.
Results: In this series, 9.8% were in situ carcinomas (Ca), 90.2% invasive Ca.
DCIS: 79.3% were treated with breast-conserving surgery (BCS) and 87.1% of these, with radiotherapy (RT); 20.7% required mastectomy. Regarding estrogen receptors (ER), 76.7% were positive, and 84.4% of them received tamoxifen.
INVASIVE CA: pT1 was found in 57.6% of pts. BCS was used in 81.5% of tumors $\leqslant 3$ cm. In 98.2% of these RT was added. Positivity of ER was similar in pre-(PrM) (78.5%) and post-menopausal pts (PoM) (83.7%), and also similar in the subgroup of age less than 40 years (70.5%). Lobular Ca was more frequently RE+ as compared to ductal Ca (91.6%vs81.3%, $p < 0.0001$). HER2 positivity was 13.5%, unrelated to menopausal status (MS). High Ki67 levels were detected more frequently in PrM as compared to PoM pts ($p < 0.0001$). We detected a direct association between Ki67 levels and tumor grade ($p < 0.0001$). Tumors were triple negative in 12.4% of PrM, 10.4% of PoM and 14.3% of women under 40.
pT1 SUBGROUP: Axillary lymph node involvement was similar for T1a and T1b (8.8%vs10.4%, p=NS), but greater for pT1c ($p < 0.0001$). As to pT1c tumors, PrM pts were node+ in 33.9% of cases and PoM in 26.9% ($p < 0.02$). This was not related to ER status. We found no association between adverse pathological features and MS. Chemotherapy (ChT) was used in 20.0% of stage I and 56.4% of stage IIA. Stratified by stage, ChT was used in a similar proportion in PrM and PoM pts for stage I, but not for stage IIA (74.5% in PrM vs 47.4% in PoM, $p < 0.05$). Hormone therapy was used in 88.3% of ER+ pts, regardless of MS. Only 61.1% of HER2+ pts received trastuzumab.
Conclusions: The variables we studied show no differences with the available published data, thus enabling us to extrapolate international data to our population. We find an exception regarding the lower incidence of HER2+, the higher utilization of BCS in small tumors, and the low use of trastuzumab in our series.
No conflict of interest.

1443 POSTER

Homeostasis model assessment to detect insulin resistance and identify patients at high risk of breast cancer

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Background: Altered insulin signalling is thought to play a major part by increasing cancer cell growth, proliferation and survival. Therefore, to investigate clinically the potential role of insulin in breast carcinogenesis we studied a large cohort of breast cancer patients and controls to

assess which correlations existed with MS criteria and, specifically, insulin resistance measured through Homeostasis Model Assessment (HOMA-IR).
Materials and Methods: 975 women have been enrolled of which 410 underwent surgery for breast cancer (cases), whereas 565 were healthy women (controls). After obtaining informed consent, for each woman anthropometric features were measured, arterial blood pressure was taken and venous blood was collected. Insulin levels were defined in the normal range when between 5 and 25 mcU/ml, whereas concentrations above 25 mcU/ml were considered corresponding to hyperinsulinemia. The HOMA-IR index was calculated as the product of the fasting plasma insulin level (mcU/mL) and the fasting plasma glucose level (mg/dl), divided by 405. The cut off value to define insulin resistance was HOMA-IR $\geqslant$2.50. Chi-squared test and logistic regression analyses were used to confirm the association between MS and breast cancer and to calculate the risk. Statistical significance was considered at $p < 0.05$.
Results: We found a higher prevalence of MS (35%) among post-menopausal women with breast cancer compared to healthy women (19%). Waist circumference >88 cm was measured in 53% of cases OR 1.58 (95% CI 0.8−2.8) and in 46% of controls. Hyperinsulinemia was detected in 7% of cases and only in 3% of controls. HOMA-IR was $\geqslant$2.50 in 49% of cases (C.I.95% =0.42 to 0.52) respect to 34% of controls (C.I.95% =0.03 to 0.38), showing a positive trend for breast cancer patients. 80% of insulin resistant cases were postmenopausal, whereas premenopausal were 20%. HOMA-IR and insulin were positively associated to at least three other MS criteria in 89% of cases compared to 50% of controls.
Conclusions: Our results further support the hypothesis that MS, in particular insulin resistance and abdominal fat, can be considered as risk factors for developing breast cancer in postmenopause. Moreover, we suggest that HOMA-IR, rather than fasting plasma glucose and fasting plasma insulin levels, could be a valuable tool to identify patients with subclinical insulin resistance, which could be relevant for primary prevention and for screening of patients at high risk.
No conflict of interest.

1444 POSTER

Pattern of cancer incidence in Yemen (2000–2011)

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Background: Hadhramout Sector in Yemen constitutes of three governorates (Hadhramout, Shabwa, & Almahra) with a population of 1,684,373 inhabitants. Cancer cases reported from the different health care facilities are registered in Hadhramout Cancer Registry (HCR) as a population based cancer registry. This paper describes the incidence of cancer in the period of 10 years' time (2000–2011).
Methodology: The data was analyzed using the CanReg4 Programme and the incidence rate was calculated based on mid-time total population in each period.
Results: The cancers were more frequent in females with age standardized incidence rate (ASR) for them of (28) while for males was (22.1). The three most common types were breast (15.6%), leukemia (6.2%), and Non-Hodgkin's Lymphoma (6%). In the pediatric group, leukemia (20.5%) was most common cancer.
Conclusions: Breast cancer in females and hematological malignancies in males were the most frequent types of malignancies. Leukemia were the most common cancers in children.
Our results generally indicate that the pattern of the most common registered cancer bears some similarities with the Aden and Gulf's data with some differences that necessitate further evaluation.
No conflict of interest.

1445 POSTER

Epidemiological aspects of breast cancer: Multicentric study of 4,041 patients. Argentine Society of Mastology, RCM (registro cáncer de mama − breast cancer registry)

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Background: In Argentina, more than 18,000 new cases of breast cancer are diagnosed every year. However, we do not have adequately powered statistical registries in our country. For this reason the Argentine Society of Mastology saw the need to create a database. Here we present an analysis of the data we collected in the participating centers in the first two years, describing some epidemiological characteristics, as well as clinical presentation, stage and surgical treatment of breast cancer in Argentine women.
Material and Methods: Descriptive, cross-sectional study, analyzing data of 4,041 patients, which was entered in the web-database RCM until September 30th, 2012.
Results: 99.6% of patients were women, with a mean age of 57.7$\pm$13.2 years. Mean age at menarche was 12.5$\pm$1.4 years, and 48.6$\pm$4.1 years at menopause. Post-menopausal women accounted for 68.8% of patients. Twenty percent of patients were nulliparous. A family history of breast cancer was identified for 19.3% of patients. The main reason for consultation was an unusual finding in breast self-examination (54.3% of patients). Clinical stages were as follows: 11.6% stage 0, 40.6% stage I, 36.5% stage II, 10.3% stage III, and 1.0% stage IV. In 69.4% of cases a segmental resection of the breast was performed. Axillary lymph node dissection was the most frequent treatment of the axilla before the year 2000 (67.9%), but the sentinel lymph node biopsy was used for 63.6% of patients in more recent years.
Conclusion: Demographic variables associated with breast cancer analyzed in this series are no different to those published in most of the literature.
No conflict of interest.

1446 POSTER

Self-examination and risk groups in screening breast cancer

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Background: There is a consensus that routine screening mammography should be offered to women ages 50 to 69. Consensus is not as strong for routine screening among women less age 49, over age 70 and for screening with clinical breast examination (CBE) or breast self-examination (SE).
Methods: A retrospective review of firstly diagnosed primarily breast cancer patients over the period 2010–2012 was perform.
We divided patients based on age at presentation: <50, 50−69, >69 and way of presentation of breast cancer: self-examination (SE), mammography (MM) and clinical breast examination (CBE). The research was performed using medical records review.
Results: Among 766 patients diagnosed in this period, the mean age was 60 years (30−93) and 85% of the tumors were invasive ductal carcinomas. Age groups included: 29% <50, 44% 50−69 and 27% >69. Presentation groups included 44% SE, 41% MM and 15% CBE.
Self-palpable mass was the most frequent way of presentation in <50 (50%) and >69 (66%), and the second in 50−69 (27%) after mammography.
More patients in <50 group had had a history of benign breast pathology (20%, $p < 0.01$), no parity (19.5%, $p < 0.01$), age at first birth >30 (39%, $p < 0.05$), use of contraceptive pills (44%, $p < 0.01$) and more breast density on mammography (72%, $p < 0.01$), compared with 50−69 group (13%, 15%, 20%, 23% and 40% respectively).
Tumors diagnosed in <50 group tended to have more aggressive features than those diagnosed in 50−69 group: T3−4 (14% vs 8%, $p < 0.01$), negative hormonal receptors (16% vs 15%, $p = 0.9$), her2 overexpression (30% vs 18%, $p < 0.01$), ki67 $\geqslant$14% (72% vs 60%, $p = 0.04$), high grade (39% vs 27%, $p = 0.04$), positive nodes (44% vs 35%, $p = 0.096$).
Conclusions: A significant number of women were diagnosed out of screening group and with palpable masses or abnormal clinical breast examination, many with aggressive tumors. It would be necessary more studies to better select patients at risk, although they are not included in screening age.
No conflict of interest.

1447 POSTER

Epidemiological aspects of cervical cancer incidence in mountainous region of Kyrgyz Republic

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Background: To study influence of high altitude on cervical cancer incidence in the Naryn region of Kyrgyz Republic.
Methods: Patients with the primary diagnoses of cervical cancer received treatment at the National Center of Oncology of Kyrgyz Republic during the period of 1996–2005.
Results: Altitude factors in Naryn were divided into 3 levels: first level − up to 2000 meters above the sea level; second level − 2000 to 3000 meters; and third, 3000 meters and higher.

Patients during the treatment period were divided by age: up to 30-years old − 5 cases (1.8%); 31−40-years old − 50 cases (18.5%); 41−50-years old − 140 cases (51.8%); 51−60-years old − 45 cases (16.6%); and, 61-years old and older − 30 cases (11.1%).
Cancer incidence rate for the first altitude level (up to 2000 meters above the sea level) was 18.8 per 100 000 people, for the second (2000–3000 meters) − 23.9; and for the third (3000 and higher) − 4.2 per 100 000 people.
Of the total number of patients with cervical cancer, only 2 patients were registered with I stage of cancer (0.7%); 80 patients were registered with II stage (or, 29.6%); 130 patients had III stage cancer (48.1%); and 58 patients were discovered with IV stage (21.4%).
Conclusion: Accordingly, the incidence rate for cervical cancer in the mountainous region of Naryn is relatively high, at 13.2 per 100 000 people. The highest rate of cervical cancer in the focused region is observed for the age group of 41−50-years olds where patients are mainly diagnosed at the III and IV stages. The study concluded that altitude factors can favorably influence incidence rates of cervical cancer − the higher the altitude above the sea level, the less the incidence rate.
No conflict of interest.

1448 POSTER

21-year-long trends in cancer mortality in Tomsk population

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Background: To study 21-year-long trends in cancer mortality in Tomsk population.
Material and Methods: The study was performed as a part of international investigation 'Epidemiological study of the causes of the dramatic fall in life expectancy in Russia in 1990'. Russian Centers (Moscow, Tomsk, Barnaul, Biisk − prof. D.Zaridze, prof. R. Karpov), centers of France (IARC, Lyon − d-rs P.Bofetta and P.Brennan) and of Great Britain (Oxford University − prof. R.Peto) were participants of the study. The following study steps were used: working meetings in Tomsk, in Moscow and in Lyon (collaboration agreement, contract 043905), training of interviewers (practical seminars for 45 physicians of primary medical stuff for screening population, instructions, using standardized questionnaires, screening families, identity cards), receiving of Ethical Committee permission, informing population (newspapers, radio, TV, advertisement), collaboration with Forensic Medicine Department of experts. Standard protocol was used for the study.
Results: A total of 90 745 persons aged from 15 to 74 years who died in 1990–2010 were investigated. Apart from the standardized questionnaires, we used archival data from Tomsk Statistical Administration, Forensic Medicine Department, and Civil Registry Office. The total mortality rates ranged from 889 to 1588 in men and from 509 to 784 in women per 100,000 of population. Mortality in women was 2-fold lower than in men. Cancer death took the 2nd place (17.5% in women) and the 3rd place (15.7% in men) in the total mortality. Mortality dynamics from neoplasm's varied from 181 (in 1991) to 244 (in 2009) in men and from 127 (in 1992) to 205 (in 2008) in women. It should be noted that mortality in women was by 27% lower than in men. Mortality risk from cancer was associated with smoking, profession status, alcohol and education.
Conclusion: The study showed feasibility of retrospective analysis of death cases in the population of a moderately urbanized city of West Siberia. Methodology of studying death cases was successfully implemented into practical health care system. An array of documents (form of informed consent from family members; informational and methodical instructions for interviewers; questionnaire; other tools for acquiring information about the living and deceased individuals; interviewer's certificate; announcements; etc.) was worked out and implemented in Tomsk hospitals. The cancer mortality rates ranged from 181 to 244 in men and from 127 to 205 in women per 100,000 inhabitants. Mean age of mortality in Tomsk was significantly lower (by 6.6–19.8 years) than in the population of the West.
No conflict of interest.

1449 POSTER

The role of alcohol consumption on overall and cause-specific mortality in the European Prospective Investigation into Cancer (EPIC) study: A competing risks analysis

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Background: In 2005, it was estimated that alcohol caused 3.2% of all deaths worldwide (WHO 2007). An exhaustive evaluation on the relationship between alcohol use and mortality was carried out in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, a large prospective cohort in 10 Western European countries, using a competing risks analysis.
Methods: Multivariable Cox regression models were used to quantify the association between baseline alcohol intake and risk of overall and cause-specific mortality, i.e. alcohol-related cancers, cardiovascular disease and deaths due to injuries/violence. Models were adjusted for relevant confounding factors. Participants with prevalent diseases at baseline (anyone of cancer, stroke, heart disease, diabetes, or hypertension) were excluded. The analyses used information on 288,406 study participants with over 3.7 million Person-years and 15,174 fatal events. An augmented dataset was used to evaluate the association categories of baseline alcohol (coded as never, former, (1−5] (reference category), (5−15], (15−30], (30−60], >60 g/day) and cause-specific mortality. The effect of alcohol across causes of death was compared.
Results: A total of 1 781 deaths due alcohol-related cancers (including cancers of upper aero-digestive tract, breast [women], liver and colorectum), 2 613 cardiovascular disease (CVD) deaths, and 694 injuries and violent death were used. In men, alcohol use was positively associated to death due to injuries, and to alcohol-related cancers. In women associations were overall less pronounced. Alcohol consumption showed an inverse relationship with CVD mortality, both in men and women. The alcohol/mortality relationships were heterogeneous ($p < 0.001$) and across specific causes and non-linear, both in men and women. Based on a competing risks analysis, at the age of 60 years a heavy drinker woman had a chance of dying within the next 10 years from an alcohol-related cancer, CVD or injuries/violence equal to about 0.6%, 0.5%, and 0.3%, respectively. Corresponding figures in men were 2%, 2% and 1%.
Conclusion: Alcohol use was positively associated to death due to injuries/violence, and to mortality due to alcohol-related cancers in men. A non-linear J-shaped association was observed for CVD mortality, particularly in men.
No conflict of interest.

1450 POSTER

Triple-negative breast cancer − a Hispanic experience

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Background: Breast cancer is known to be a heterogeneous group of tumors that gene studies identified in different subtypes. Triple negative (TNBC) reflect the worst prognosis of the disease and represents 15% of all invasive breast cancers, but some studies have suggested that its prevalence differs between races. In Mexico there is a high TNBC incidence reported. There most be an association with risk factors. Although there are multiple risk factors documented with TNBC, age, African-American origin, obesity and overweight, hypertension, diabetes mellitus, smoking and alcoholism, age at menarchea and age at first pregnancy, there is some information of prevalence of TNBC among Hispanic women.
Methods: We identified 145 patients with triple-negative breast cancer collected from 2005 to 2011 in Centro Oncologico Estatal ISSEMyM. All histopathologic and immunohistochemical diagnoses were reviewed by a breast cancer pathologist. The prevalence of TNBC, its association with clinicopathologic characteristics and risk factors were determined.
Results: The mean age at diagnosis of TNBC was 47 years and was more commonly in locally-advanced stages. There was an incidence of 66 patients with body mass index (BMI) >25 kg/m^2 (45%), 35 patients with body mass index (BMI) >30 kg/m^2 (28.1%). BMI mean was 27 kg/m^2. The presence of less than 40 years old was found in 20 patients (13%), all were mexican, 83 patients were with ISSEMyM social securance and 63 with social securance (seguro popular), there were 34 patients documented with hypertension, 18 with diabetes mellitus. The mean age at menarche was 14 years old, first pregnancy mean 20 years (15−41). Clinical stage was distributed as follows: 2.7% of patients had bilateral diseases, 6.8% of patients had stage I disease, 43.4%of patients had stage II disease, 37.9% of patients had stage III disease, and 11% of patients had stage IV disease at diagnosis. 83 patients were able to receive adjuvant treatment and 62 were evaluated after neoadjuvant treatment. Of these patients were histologically documented complete pathological responses 14 (15.3%) and 48 overall responses (52%). Was identified primarily ductal histological type and well differentiated. 26 patients had lymphovascular infiltration. Mean follow-up of our patients was 1184 days, with a median relapse free-survival of 601 days and a median overall survival of 765 days. At the moment of the analysis only 21 deaths were reported.
Conclusions: In our cancer center we observed a similar distribution to that reported in large series of triple negative breast cancer and we also demostrate a high incidence of diabetes and hypertension, both of them relacionated with metabolic syndrome. In our study population, we

observed that the prevalence of TNBC was 8.3% in our cancer center but we detect a high incidence of metabolic syndrome or its variants in the TNBC patients so we need to search strategies in the Hispanic population to improve outcome in TNBC patients.
No conflict of interest.

1451 POSTER

Prevalence of cervical and uterus cancer and ovarian cancer in Andijan region

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Objective: To investigate the prevalence of cancer of the cervix and uterus and ovaries in Andijan region.
Materials and Methods: We analysed and compared materials of oncological service bulletins and registration of malignant tumours. 953 records were examined. Age of the patients was ranged from 13 to 86 years.
Results: The highest number of women suffering from various tumours of the reproductive system, are observed in 2011–2012 y (234–216 people per year), the least − in 2008 (145 people). In 2008–2009, the number of women affected was less than 160 per year, and in 2008–2012, respectively 200. The smallest number of women (14), suffering from tumours of the body of uterine, it was in 2008–2009, the highest number − in 2011 (36). In the period 2008–2009, the number of patients was less than 15 per year, and in 2011–2012, more than 30. The smallest number of patients with tumours of the cervix were in 2008 (104), the highest number (149) in 2010. The largest number of women (55) suffering from ovarian neoplasms was revealed in 2011, the lowest (27) in 2008–2009, and over the years there is a tendency to increase, and the rejuvenation of ovarian cancer among women.
The largest number of women suffering from cervical cancer is at the age of 17−49 years (317), and more than half of all patients in the age range 32−59 years (512). The largest number of patients with cancer of the corpus uteri was aged in range of 50−59 years (55), and more than half of all patients are in the age range 50−69 years (81). The largest number of women suffering from ovarian cancer is at the age of 17−49 years (94), the least-in the age range 70 years and over (9) and <17 years (3). More than half of patients with this pathology are in age range from 40 to 59 years inclusive.
Conclusions: The number of people in Andijan region suffering from cancer of the body and cervix of uterus, and ovarian cancer in the last three years has increased dramatically. Women of working age (30 to 59 years) are most susceptible to malignant tumours of the reproductive system.
No conflict of interest.

1452 POSTER

Incidence, survival and clinical characteristics in adult acute lymphoblastic leukemia in a single institution: SOLCA-Guayaquil-Ecuador

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Background: Adult patient with Acute Lymphoblastic Leukemia (ALL) were 52.5% of acute leukemias admitted in the Hospital, with an annual incidence of 18 new cases, the objective of the study was to determine incidence, clinical and biological characteristic, treatment response and overall survival with the institutional protocol.
Material and Methods: A retrospective study was conducted from 2008 to 2011, included all adult patients >15 años, with at least cytomorphologic diagnosis of leukemia who received intitutional protocol consists of four phases: Induccion 1, Induccion 2, Early Consolidation and standar maintenance up to 2 years, if found t(9;22), imatinib was added. Data were analyzed by SPSS v13.
Results: 74 patients with ALL >15 years were admitted at Institute from 2008–2011. The median age was 31 years (range: 15 to 81 years) and 48 patients (64.9%) were males. FAB morphologic diagnosis: ALL-L1: 40.5%(30), ALL-L2: 13.5%(12), ALL unspecified: 13.5%(12), according to the immunophenotype: B-common ALL: 50%(37), Pre B-ALL: 12.2%(9), T-ALL: 5.4%(4), and in 32.4% (24) was not performed flow cytometry for economic reasons, molecular biology studies and/or cytogenetic were available only in 37.8% (25), and in 32% was found some alteration: t:(9;22): 20%(5); t:(12;21): 8% (2), inv(16): 4%(1). Unfavorable prognostic factors such as age ocurred in 36.5% (27); leukocytosis $\geqslant$25.000: 60.8% (45), CNS involvement: (2.7%) 2. Sixteen patients (21.6%) died before starting treatment for infectious complications and/or bleeding, one patient received palliative treatment and six patients discontinued treatment. In 51 evaluable patients, 72% achieved complete response (CR) with induction, however during the course of treatment continuous CR only occurred in 13.7% (7) in an median follow-up of 38 months (range: 16 to 59 months), 62.7%(32) relapse/refractory, 23.5%(12) died by toxicity. The median overall survival (OS) was 17.6%; patients with a poor prognosis factor had an OS of 10%, and standard risk factor: 45.5%.
Conclusions: Clinical, immunophenotype and genetic abnormalities are essential to provide treatment according to risk and therapeutic targets. Currently efforts are being made to improve diagnostic techniques in the Institute. In our environment remains an aggravating factor deficiencies economic, isolation measures, availability of blood products, and supportive care, increasing mortality.
No conflict of interest.

1453 POSTER

Strategies to develop personalised screening programmes: A request for discussion

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Background: Currently, it is debated whether risk-based screening programmes are more (cost-)effective than 'one-size-fits-all' programmes. Most studies focus on risk stratification according to absolute risk of event. We would like to discuss whether this is the only and best approach.
Methods: We will theoretically compare the potential impact of stratification according to absolute risk of event, screening test characteristics and life expectancy.
Results: In primary and secondary screening event rates are generally low and the discriminating power of predictive profiles limited. As a result, the absolute risk difference between person subgroups with a low or high risk of event is small. This small difference will lead to quite similar 'optimal' screening programmes for low and high risk groups. Besides risk of event, the potential benefit of a screening programme depends on the sensitivity of the screening modality. This sensitivity differs between persons. Therefore, adaptation of screening programmes according to subgroups' sensitivity may result in differential optimal screening programmes. Furthermore, screening may be minimised in persons with a short life expectancy. Co-morbidity, for example, may preclude the benefit of screening initiatives. During the presentation at the ECC2013 conference, we will give illustrations of these three approaches based on published studies.
Conclusions: Stratification attempts based on absolute risk of event will not guide personalised screening if event rates are low. Stratification based on screening test characteristics or identification of persons with a short life expectancy are more promising. *We invite the ECC2013 attendees to discuss strategies to design personalised cancer screening programmes.*
No conflict of interest.

1454 POSTER

PIK3CA mutations, aspirin use and mortality in patients with women's cancers or colorectal cancers treated in early-phase clinical trials

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Background: Aspirin reduces the risk and mortality from breast and colorectal cancer (CRC). Aspirin down-regulates phosphatidylinositol 3-kinase activity by inhibiting cyclooxygenase-2 and is associated with improved survival in patients with mutated, but not wild-type *PIK3CA* CRC. The prevalence of *PIK3CA* mutations is known to be high in breast cancer, gynecologic cancer, and CRC.
Material and Methods: Total of 536 patients with CRC (242, 45%), ovarian (137, 26%), breast (65, 12%), endometrial (63, 12%), and cervical cancer (29, 5%) participating in early-phase clinical trials at the University of Texas MD Anderson Cancer Center from 10/2008 were tested for *PIK3CA* mutations and their survival outcomes with respect to regular aspirin use, defined as at least three months of use at the time of initial referral visit, were analyzed. Adjusted hazard ratio (AHR) for mortality was computed controlling for the Royal Marsden Hospital (RMH) score, which was validated in our cohort.
Results: Median age of the cohort was 56 years [range: 20−91 years]. 76% (405) were female and 72% (408) were Caucasian. Median survival was 8.8 months, 10% (54) of patients used aspirin and 17% (88) had *PIK3CA* mutation. Aspirin users and nonusers were similar except for older

age in aspirin users (mean difference of 8 years, p < 0.001). Aspirin use was not associated with difference in survival (AHR 0.82, 95% confidence interval [CI] 0.57–1.18, p = 0.29). However, in patients with breast and gynecological cancers, aspirin use independent of *PIK3CA* status was associated with prolonged survival (AHR 0.59, 95% CI 0.35–0.98, p = 0.04). Of note, in patients with wild-type *PIK3CA* CRC, aspirin was associated with shorter survival (AHR 1.80, 95% CI 1.01–3.23, p = 0.04). In contrast, in patients with mutated *PIK3CA* CRC, aspirin did not impact survival (AHR 0.75, 95% CI 0.17–3.20, p = 0.70).
Conclusions: In early-phase clinical trial setting, aspirin was associated with prolonged survival in patients with breast and gynecological cancers irrespective of *PIK3CA* status and shorter survival in patients with wild-type *PIK3CA* CRC. Larger studies are required to validate possible interactive effect between *PIK3CA* mutations and aspirin use on survival outcome.
No conflict of interest.

1455 POSTER

Genetic variants in the myeloid derived suppressor cells pathway and susceptibility to breast cancer in the Breast Cancer Association Consortium

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Background: Breast cancer is the most common cancer in women in Europe with an incidence of 425,000 per year. Evading Immune destruction is considered as a new hallmark of cancer. Myeloid derived suppressor cells (MDSCs) promote tumor-associated immune suppression and therefore the MDSCs pathway could harbour susceptibility loci for breast cancer.
Material and Methods: This study included 40,987 invasive breast cancer cases and 39,452 cancer-free controls of European ancestry from 36 studies in the Breast Cancer Association Consortium. 27 candidate genes were identified by extensive literature review and 735 tagSNPs genotyped using the custom Illumina iSelect array passed quality controls. We used logistic regression analysis to assess the main effects of single SNPs for overall breast cancer and for ER+ and ER− subtypes respectively. Furthermore, we applied a new pathway score which models independent signals from the same gene in a regression framework to assess pathway association using the INTERSNP program. All analyses were adjusted for study, age and population structure.
Results: Two SNPs (rs470747 A>G and rs470132 C>A) at 11q22.3 (matrix metallopeptidase-1 gene, *MMP-1*) showed the most significant association with overall breast cancer. They were highly linked, showing linkage disequilibrium (LD) of r^2=0.99 and were associated with elevated per allele ORs of 1.03 (95% CI = 1.01–1.06, p = 0.002). Another SNP (rs7125320 A>C) at the same region but not in LD with the other two SNPs (r^2=0.04) was associated with a reduced OR of 0.95 (95% CI = 0.91–0.99, p = 0.007). *MMP-1* is a zinc-dependent endopeptidase belonging to the Metzincin superfamily and has been reported to play an important role in breast cancer carcinogenesis. In addition, rs25645 (G>A) as well as two other SNPs in high LD located at 17q11.2-q12 (granulocyte colony-stimulating factor gene, *G-CSF*) was also associated with elevated per allele ORs of 1.03 (95% CI = 1.01–1.05, p = 0.004). *G-CSF* can affect myeloid lineage in tumor microenvironment. Analysis of the overall MDSCs pathway did not yield a significant association with breast cancer susceptibility overall (p = 0.12).
Conclusions: Of genes in the myeloid derived suppressor cell pathway, we found strongest evidence of association with susceptibility of breast cancer for *MMP-1* and *G-CSF*. Pathway analysis suggests that genetic variation in the MDSCs pathway may not play a strong role in breast cancer susceptibility.
No conflict of interest.

1456 POSTER

PTCH1 g.79755C>T and g.79456C>T polymorphisms, enrolled in proliferation cell control, are risk factors for head and neck squamous cell carcinoma

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Background: The *PTCH1*, a tumor suppressor gene, encodes a transmembrane protein that controls cell proliferation. Alteration of *PTCH1* expression was associated with the onset of tumors. The roles of the *PTCH1* g.79755C>T (rs16909856) and g.79456C>T (rs16909859) genetic polymorphisms in the risk of head and neck squamous cell carcinoma (HNSCC) have never been described in the literature, and therefore, to analyze their impacts in the disease was the aim of this study.
Materials and Methods: Genomic DNA from 150 HNSCC patients and 150 controls matched to patients by age, gender and race was analyzed by real-time polymerase chain reaction, using TaqMan® genotyping assays. The differences between groups were analyzed by the logistic regression model. Power analysis (PA) was used to verify the effect of sample size on the results obtained in the study.
Results: HNSCC patient's and control's samples were in Hardy–Weinberg equilibrium for *PTCH1* g.79755C>T (χ2= 0.31, *P* = 0.58; χ2= 1.04, *P*= 0.31) and *PTCH1* g.79456C>T (χ2= 2.2, *P* = 0.13; χ2= 1.29, *P* = 0.26) loci. The *PTCH1* g.79755CC (82.0% *vs* 65.3%, *P* = 0.002; PA= 94%), *PTCH1* g.79456CC (82.6% *vs* 66.0%, *P* = 0.003; PA= 92%), *PTCH1* g.79755CC + *PTCH1* g.79456CC (82.9% *vs* 65.7%, *P* = 0.002; PA= 95%) genotypes were more common in patients than in controls. Individuals with the respective genotypes were under a 2.62-fold (95% CI: 1.43–4.80), 2.52-fold (95% CI: 1.37–4.64), and 2.70-fold (95% CI: 1.45–5.00) increased risks for HNSCC than those with the remaining respective genotypes. In addition, the frequency of *PTCH1* g.79755CC genotype was higher in male patients than in female ones (84.3% *vs* 62.5%, *P* = 0.04; PA= 56%). The *PTCH1* g.79755CC genotype in male patients was also more common than in controls (84.3% *vs* 65.3%, P= <0.001; PA= 96%). Male individuals with the *PTCH*1 g.79755CC genotype had a 3.55-fold (95% CI: 1.79–7.04) increased risk for HNSCC than others. Similar frequencies of the *PTCH1* g.79755C>T and *PTCH1* g.79456C>T genotypes were seen in patients stratified by age and race.
Conclusions: Our results suggest, for the first time, that *PTCH1* g.79755CC and *PTCH1* g.79456CC genotypes are important inherited risk factors for HNSCC. Analyzes of proteins encoded by the alleles of the polymorphisms should be conducted to clarify their roles in tumor. We believe that healthy individuals with the above genotypes, particularly males, deserve additional recommendations for disease prevention and early diagnosis.
No conflict of interest.

1457 POSTER

Differences in incidence trends of estrogen receptor positive/ negative breast tumours in the Girona province, 2000–2009

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Background: Expansion of mammopgraphy screening and variations in lifestyle risk factors have lead to changes in invasive breast cancer (IBC) incidence trends in several countries. Positive estrogen receptor (ER) cancers have better prognosis than negative ER tumours. The aims were to determine whether clinicopathological features differed among positive and negative ER, and to analyze IBC incidence trends according to ER status in the Girona province, 2000–2009.
Methods: Women diagnosed with primary IBC (*n*=3513) during 2000–2009 were extracted from the population-based Girona Cancer Registry. ER immunohistochemical status was collected from pathological reports. Clinicopathological features (histological grade, stage, age, mean tumour size and positive nodes) were compared among ER positive and negative tumours. The estimated annual percent change (EAPC) was estimated using joinpoint analysis.
Results: The proportions of ER positive, negative and unknown tumours were 70.5%, 18.4% and 11.1%. ER positive tumours correlated to a lowest histological grade, early stage, mean tumour size and mean positive nodes, and a higher mean age compared to ER negative tumours. IBC incidence showed a non-statistically significant EAPC of −1.0% (−2.2; 0.2). Women diagnosed with ER positive tumour showed an upward incidence trend of 1.6% (−0.2; 3.5) and ER negative tumours presented a significant EAPC of −6.0% (−8.6; −3.4).
Discussion and Conclusions: Differences in incidence trends in ER positive/negative tumours could be explained by changes in lifestyle risk factors as obesity. During the study period in Spain the percentage of overweight and obese women has increased. Also, changes in RE immunohistochemical assessment have to be considered.
No conflict of interest.

1458 POSTER

Clinical significance of triple negativity in young breast cancer patients (⩽35 years): A single-institute study from India

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Background: Triple negative breast cancer (TNBC) has been identified as an independent poor prognostic factor for survival. The aim of this study was to compare the clinico-pathological characteristics and treatment outcomes of patients with young TNBC (yTNBC) and young non-TNBC (y-non TNBC).
Methods: We carried out a retrospective study of 299 young invasive breast cancer patients registered (whom receptors status were available) between 1999–2012 at Institute Rotary Cancer Hospital, All India Institute of Medical Sciences (AIIMS), India.
Results: One hundred and five patients (35%) had yTNBC and 194 (65%) had y-nonTNB. Patients with yTNBC had significantly lower median age 29 vs 33 yrs ($p = 0.049$) and higher proportion of high grade tumors as compared to y-non TNBC group (40% vs 23.5%; $p < 0.0001$). The median tumor size (5.0 vs 5.1 cms), node positivity rate (61.7% vs 65.2%), stage distribution (2.7%, 27.3%, 53.4%, 16.6% vs 3.3%, 23.6%, 52.7%, 20.2% for Stage I, II, III and IV respectively) were not statistically significant between yTNBC and y-nonTNBC groups. Fifty seven patients presents with upfront metastasis. The most common site of relapse was lung followed by liver and loco-regional. After a median follow-up of 36 months, relapse rate was 33% for yTNBC and 19% for non-yTNBC ($p = 0.003$). The 3 year RFS and OS for non metastatic group was significantly lower in TNBC group (50.2% vs 65%; HR = 2.38, 95% CI:1.21–3.60,$p = 0.001$) and (66.4% vs 77.2%, HR = 1.9, 95% CI: 1.02–2.80, $p = 0.049$) respectively. With a median follow up of 36 months (non metastatic group), three years disease free survival (DFS) and overall survival (OS) was 50% and 60%. Higher Nodal stage, tumor size (>5 c.m) and negative hormonal status (triple negative) predicted poor outcome.
Conclusion: Young breast TNBC constituted 35% cases of young breast cancer patients (</=35 years) and had higher relapse rate and more aggressive clinicopathological characteristics than non TNBCs. Triple negativity is independent prognostic factor for RFS, OS in nonmetastatic and PFS and OS in metastatic setting in young breast cancer patients and might be integrated into risk factor analysis as base line workup.
No conflict of interest.

1459 POSTER

Risk of breast cancer in ovarian cancer patients non-carriers of BRCA1 and BRCA2 mutations with a family history of breast and ovarian cancer: A population-based cancer registry study

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Background: A family history (FH) of breast and/or ovarian tumor is a well-established risk factor for breast and ovarian cancer, and for BRCA mutations. BRCA1/2 mutation carriers diagnosed with ovarian cancer (OC) have a strong life time risk of developing breast cancer (BC). No studies to date have examined the predictive contribution of FH in relation to the risk of BC for OC patients in whom no BRCA1/2 mutation has been identified. The objective of this study was to address the risk of BC in OC patients with a FH who test negative for BRCA1/2 mutations.
Materials and Methods: We identified 89 patients (pts) with both OC and BC (OC-BC) from a cohort of 1497 women with a primary OC systematically collected by the Cancer- Registry of Parma Province from 1978 to 2010. We selected women with FH who tested either positive (12 pts with OC-BC vs. 11 control pts with OC) or negative (15 pts with OC-BC vs. 20 control pts with OC) for BRCA1/2 mutations. The association between FH and risk of OC-BC was examined. Age- and family history-specific 10-year cumulative absolute risks of OC-BC were estimated using the entire Cancer Registry cohort.
Results: FH was associated with increased OC-BC risk; risk was highest among young women (<45 years) with first-degree relatives with breast and ovarian cancers. Women diagnosed with OC before age 45 years with a first-degree FH of OC-BC had a 10-year risk of OC-BC of 12.5%.
Conclusions: Young women with ovarian cancer who have a FH of breast and ovarian cancer and who test negative for BRCA1/2 mutations are at significantly greater risk of OC-BC than other OC survivors. This has important implications for the clinical management of these pts.
No conflict of interest.

1460 POSTER

Breast cancer screening controversy: Too much or not enough?

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Background: The Cochrane analysis revisiting the risk/benefit of breast cancer screening resulted in a worldwide controversy spread by the mass media. The objective of our survey was to assess the impact of this controversy in terms of perception, opinion and intent in the average risk population.
Material and Methods: A nationwide observational study, recorded in the EDIFICE iterative surveys, with a representative sample of 451 women living in France aged 40−75 years old, was carried out in January 2013, using the quota method. The survey questionnaire was conducted using a computer-assisted telephone interviewing technique (CATI) 3 months after the beginning of the controversy. The following analysis focused on women without a history of cancer, taking into account positive awareness (AC+ group) or negative awareness (AC- group) of the controversy.
Results: Among the 405 women with no personal history of cancer, 69 (17%) belong to the AC+ group. There was a negative relationship between awareness of the controversy and being underprivileged, having a lower level of education and lower socioeconomic status. Among the 69 women of the AC+ group, 73% vs. 8% remembered the reasons for and against screening respectively. The most frequent reasons against screening were over-diagnosis (38%), unreliability (16%), and radiation risk (9%). The breast cancer screening limits were better known by the AC+ group, such as undiagnosed cancers (20% vs. 7%, $p < 0.05$) and risk of false positives (20% vs. 2%, $p < 0.05$). In the AC+ and AC- groups, opinion on breast cancer screening did not change in 86% and 88% of cases respectively. Negative opinion increased in the AC+ versus the AC- groups (8% vs. 1%, $p < 0.05$). Nevertheless, In the AC+ group, there was no change in the intention of screening in 91% of cases. In the overall population, only 1% stated that they would plan to attend screening less often.
Conclusion: Few women were aware of the controversy spread by the mass media (17%). The impact of the controversy on screening intention is very low (1%). However, in women with an awareness of the controversy, a better knowledge of the breast cancer screening limits was observed. Unexpectedly, it seems this better knowledge does not impact on the personal decision-making about screening.
No conflict of interest.

1461 POSTER

Trends in cancer care and outcome in the Netherlands: A population based approach

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Background: Large variation exists in patterns of cancer care between regions, hospitals, and over time. Monitoring the variation in care delivered and linking this variation to outcome provides important insight into guideline adherence, medical practice in case of clinical equipoise, and implementation of new diagnostic tools and treatments. Valid, reliable and complete data is needed to obtain reliable indicators of cancer care. The IKNL Cancer Registry covers all newly diagnosed cancers since 1989 in the total population of the Netherlands (17 million inhabitants). It gathers data in all hospitals based on pathology reports with increasing data over the years on stage, treatment, and outcome. The IKNL cancer registry enables us to evaluate patterns of cancer care over time and give detailed yearly feedback to hospitals.
Methods: Crucial indicators per tumor type were based on national guidelines for breast, colorectal, pancreas, esophagus, stomach, bladder, kidney, lung, brain, neuroendocrine, melanoma, testis, endometrium, cervix, and lymphoma. Trends over time (2001–2011) between hospital volume and hospital type (academic, top clinical, general) were determined per indicator. Relative survival was determined with complete follow-up until 2013.
Results: Survival has increased over time for almost all tumor types. The number of patients per hospital per tumor type is increasing and the variation in volume is decreasing. These effects are caused by increases in

incidence of various tumor types, hospital mergers, and changing regional referral patterns. The effects are not only seen for low-incidence tumors but also for high-incidence tumors such as breast cancer.
If the national guidelines allow choosing between two or more equivocal treatments, a large variation between treatments provided is indeed seen. In addition, however, variation also exists if the guidelines do provide clear treatment recommendations.
Detailed results per tumor type will be presented during the meeting.
Conclusion: Providing insight in differences in cancer care between hospitals is a strong incentive for hospitals to improve their quality by prioritizing the care they can deliver and choosing whom to refer elsewhere. In addition, it facilitates patients and health insurance companies to choose between hospitals.
No conflict of interest.

1462 POSTER

Time-to-Antibiotics (TTA) and outcomes in cancer patients with febrile neutropenia (FN)

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Introduction: Febrile neutropenia (FN) is an oncologic emergency that requires prompt initiation of antibiotics. A prolong time-to-antibiotic (TTA) may result in adverse outcomes in immune compromised patients. The study aims to determine TTA in hospitalised patients with FN, a quality measure in cancer care, and to assess relationship between TTA and outcomes.
Methods: The study population was comprised of a cohort of adult cancer patients with FN who were hospitalised at a tertiary care hospital between 2010 and 2012. Pearson correlation and multivariate analysis using linear and logistic regression models were done to assess relationship between TTA and length of hospital stay and mortality.
Result: 105 eligible patients with a median age of 60 (18−89) and M:F of 43:62 were identified. 50% had a comorbid illness, 44% had a haematological malignancy and 60% had advanced disease. 85% were presented to the emergency department and remaining were hospitalised from ambulatory clinics. Median TTA was 2.5 hrs (0.03−50). 84% patients were treated with broad spectrum penicillin. 30% patients each received prophylactic filgrastim or antibiotic. Of 105 patients, 75 met American Society of Clinical Oncology (ASCO) criteria for primary prophylaxis with filgrastim and only 24 (32%) received prophylaxis. Median length of stay was 6 days (1−57). 4 patients died and 2 required ICU admission. A source of infection was identified in 23 patients. Pearson correlation between TTA and length of stay was 0.258 ($p = 0.008$). In univariate analysis TTA, known source of infection, filgrastim prophylaxis, anaemia, thrombocytopenia and elevated urea were significantly correlated with length of stay ($P<0.05$). In the multivariate analysis TTA (regression coefficient [RC] 0.335 $\pm$ standard error [SE] 0.092, $p < 0.001$), known source (5.07 ± 1.62, $p = 0.003$), filgrastim prophylaxis (3.93 ± 1.42, $p = 0.007$) and elevated urea (0.312 ± 0.158, $p = 0.05$) were significantly correlated with length of stay. One hr delay in TTA resulted in 8 hrs prolongation of hospital stay. No variable significantly correlated with hospital morality.
Conclusions: A prolonged TTA is independently associated with prolonged hospital stay but not with hospital mortality in cancer patients with FN.
No conflict of interest.

1463 POSTER

Non-AIDS malignancies and co-infections among HIV/AIDS patients in our registry

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Background: Malignancies among people living with HIV/AIDS as a complication of immunodeficiency have been well described in different studies. In time of the beginning of the HIV epidemic, it was observed high incidence of Kaposi's sarcoma, non-Hodgkin's lymphoma and invasive cervical carcinoma, which strongly suggested a causal relationship between immunodeficiency and the development of these kind of malignancies. The Centers for Disease Control later defined list of the conditions for malignancies in the AIDS definition where called 'AIDS-defining' malignancies. In the era of highly active antiretroviral therapy (HAART) the epidemiology of malignancies among HIV infected population has changed significantly. Currently it's observed rising incidence of non-AIDS-defined malignancies (NADM) among adults but also children.
Method: Between 1/2009 and 2/2013 data collected from 6 International HIV/AIDS Projects (Slovakia, Russia, Romania, Kirgiz Republic, Uganda and Argentina) was analysed on the development of malignancy in HIV positive children, adolescents and adults. The three projects have been oriented to the street and marginal population. After a biopsy were the samples fixed immediately in buffered 5% formalin and embedded in paraffin. Hematoxylin-eosin stain was performed and specimens from tumors or biopsies (e.g. lymph nodes) were separated for DNA preparation. Serum of all patients was collected and investigated at Health Initiatives Association/St. Elizabeth University laboratory to co-infections.
Result: There were enrolled 129 HIV-positive patients with cancer. In this study the majority of patients had NHL, however 23% of the patients were identified with NADM e.g. leukaemia, colorectal carcinoma, breast cancer, hepatocellular carcinoma, rhabdomyosarcoma, melanoma and leiomyosarcoma. We have found also co-infections with HHV-8, EBV, CMV, HBV, HCV and HPV.
Conclusion: Other studies have reported similar EBV findings in NADM among AIDS patients. Thus EBV appears to be an important cofactor in development of malignancy in paediatric and adolescent AIDS patients. Co-infections have shown an important impact on increase rate of the incidence of NADM among this group of vulnerable population.
No conflict of interest.

1464 POSTER

A professionals education program on cervical cancer prevention: Results of an e-learning experience

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Background: Cervical cancer remains the second most important cancer in women worldwide and the cancer priority in most developing countries. Cervical cancer is largely preventable and if diagnosed and treated at an early stage is a highly curable disease. In the absence of efficient preventive action, cervical cancer is usually diagnosed in advanced stages and results in a major cause of death among young women. The advent of HPV vaccines and the impact of HPV technology for cervical cancer screening represent a milestone in our opportunities for prevention. The introduction of a new vaccine targeting women worldwide requires that literally tens of thousands of health professionals and decision makers understand its value and mode of use. Information on a new vaccine and novel screening options should be scientifically accurate, and technically unbiased. A virtual course has been designed to provide such information to health professionals worldwide without costs to the participant and overcoming the limitations of travelling, time availability or language.
Objectives:
1. Create and promote an e-learning educational program on HPV and cervical cancer epidemiology and prevention suitable for a wide audience of health professionals.
2. Create an international network of professionals qualified as key trainers in cervical cancer prevention in critical countries in the world.

The Project was supported by various unrestricted educational grants.
The technological platform and the scientific and pedagogical methodology were provided by e-oncología, the e-learning platform from Catalan Institute of Oncology, (ICO) Barcelona, Spain.
Results: Output was an 18 hours distance course in Spanish, English, French and Russian. The course contents are largely based on the ICO HPV Monograph series. The program was scientifically validated and endorsed by the International Federation of Gynecology and Obstetrics (FIGO), the International Union against Cancer (UICC), the International Atomic Energy Agency (IAEA), the International Agency for Research on Cancer (IARC), and the World Health Organization (WHO), the course is being freely distributed.
In the first 18 months of operation more than 7.000 professionals worldwide have registered to the course, a pool of 32 international tutors have been certified and acted as course professors in their own environment, and 70% of the students have been certified.
Conclusions: E-learning methodology with a tutorial support can be a good and cost affordable solution to the medical education in low income countries. The contents are easily adapted to each country particularities including translation to other languages.
No conflict of interest.

1465 POSTER

Non-presencial genetic counseling for BRCA1/2 families

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Background: BRCA1/2 genetic screening is recommended when there is a suspicion of breast/ovarian cancer hereditary syndrome. Although commercially available, the decision to screen for BRCA1/2 mutations must be done in the context of appropriate genetic counseling. Several barriers difficult the access to BRCA1/2 genetic counseling: increased demand, reduced number of specialized centers and genetic counselors, schedule of the outpatient visits consultations, and geographic limitations. These difficulties led to the development of new methods of counseling and there is some published data showing satisfactory results with telephonic genetic counseling.
Material and Methods: Review of all cases that included, during the counseling process for BRCA1/2 mutations, some form of non presencial communication. In our Clinic, genetic counseling includes pre and post test counseling and, in BRCA1/2 carriers, distress evaluation one month after the diagnosis disclosure.
Results: Since 2000, and after 2097 pts screened only 9 patients, 4 man and 5 women aged 40−68 years had some non-presencial communication during their counseling (0.4%). All but one were identified as candidates for screening in already registered families; the other was an index pt identified as high-risk by her physician. With 1 pt pre and post test counseling was made by phone, with another one only pre-test was by phone and for 6 pts only post test counseling was made by phone. In two male pts (one BRCA1, the other BRCA2) distress evaluation (validated questionnaire) was sent and returned to the Clinic by mail.
Five pts were cancer survivors of breast or ovarian cancer, one male pt was a prostate cancer survivor and 3 were healthy at risk. Three pts were BRCA2 positive, 1 BRCA1 positive, 1 BRCA1 negative, 1 BRCA2 negative, 2 index pts had inconclusive results(non pathogenic BRCA1/2 mutations). One pt is waiting for the test result.
All non presencial counseling was motivated by geographic limitation. The BRCA1/2 pts evaluated for distress did not have evidence of need for specialized psychological support.
Conclusions: In our practice non presencial genetic counseling is used rarely. This option, however, should be acknowledged as a valid one.
No conflict of interest.

1466 POSTER

Outbreaks of hospital infections at the Institute for Oncology and Radiology of Serbia

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Background: Active surveillance of hospital infections at the Institute for Oncology and Radiology of Serbia includes monitoring of patients and microbiology reports, outbreak investigations and other activities carried out by the Department for Epidemiology and Prevention in collaboration with hospital wards. From time to time, outbreaks of infections are registered.
Material and Methods: Data from the hospital infections surveillance, including microbiology results of samples taken from patients, staff and environment in the period 2010–2012 were analyzed. Unusual outbreaks of infections or outbreaks that triggered changes in the everyday hospital practice were analyzed.
Results: At the radiotherapy department there is and increasing incidence of Clostridium difficile diarrhoea (CAD)among patients undergoing gynecological radiotherapy. In 2012, an outbreak of CAD cases among patients but also among doctors and nurses was registered.
At the Pediatric oncology department, in 2010 there was an outbreak of 4 febrile neutropenia patients with bloodstream Fusarium infection; all patients had bone tumors and previous surgery in other hospital. This year, 2 strains of multi-resistant bacteria (Pseudomonas, Klebsiella) and Acinetobacter resistant to all antibiotics were isolated from urine and decubital wound of a patient previously treated at other hospitals.
At the Surgical oncology clinic, there were occasional outbreaks of vancomicin-resistant infections, mostly at the post-operative intensive care unit in patients that had gastrointestinal surgery, that required additional education of staff and other measures.
At the Department for radiotherapy of head and neck cancers, tracheostoma colonization and infections are very frequent in patients with tracheostoma. The majority of infections are present on admission. Most frequently, S.aureus and Klebsiella are isolated; occasionally, multi-resistant strains are found, particularly in patients that previously had surgical intervention in other hospitals. Therefore, the sample for microbiology analysis is always taken on admission in order to identify and prevent spread of multi-resistant strains.
Conclusion: In cancer patients there is a higher risk for infections due to the disease and specific treatment modalities. There is also a risk that antibiotic-resistant bacterial strains will be introduced into hospital settings through patients with long-term cancer treatment and interventions in various hospitals. Therefore, active surveillance of hospital infections by a multiprofessional team is necessary.
No conflict of interest.

1467 POSTER

Individualised or guideline concordant G-CSF usage − Data from the non-interventional study HEXAFIL

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Background: Chemotherapy (CT)-induced neutropenia (CIN) is a common complication of cancer treatment and often leads to CT modifications. Granulocyte-colony stimulating factors (G-CSF) are often used to prevent or treat CIN in cancer patients. The non-interventional observational study HEXAFIL was conducted to provide further insight into the therapeutic efficacy and routine clinical use of biosimilar filgrastim (EP-2006) in Germany, especially in compliance with guidelines on G-CSF use.
Materials and Methods: Data is documented for up to 3 consecutive filgrastim-supported CT cycles. Rates of modified CT treatments (dose modification/discontinuation of drug) are calculated by the number and % of patients affected. A total of 709 breast cancer patients were included in this interim analysis. Data presented are based on the first CT cycle. Inclusion/exclusion criteria: www.germanctr.de.
Results: Only 2% of all patients experienced febrile neutropenia (FN), 8.7% had neutropenic complications and 43.4% had leukopenia CTC 3/4 at nadir. The majority of patients received primary (49.4%, PP) or secondary prophylaxis (33.6%, SP) with biosimilar filgrastim; 17.1% were treated on demand (ie, after having experienced neutropenic complications in the first documented CT cycle or a drop in leukocytes putting the patient at acute risk of neutropenic complications). Median filgrastim treatment duration was 4 d (range 1−14) with median start on day 6 after CT (range 1−21). 96.3% of all documented patients received CT without modification, 3% received a modified CT dose and 0.8% discontinued a CT drug. The following populations were compared to assess the impact of individualised (IND) or guideline-concordant (GUI) filgrastim treatment: patients with FN risk >20% and (1) G-CSF initiation within 5 d after CT (GUI; N = 104) or (2) G-CSF initiation starting at day 6 after CT or later (IND; N = 169). IND patients experienced FN more frequently than GUI patients (4.1 vs 1.9%). CT was modified in 6.5% of IND but only 1% of GUI patients.
Conclusions: 96% of patients received biosimilar filgrastim-supported CT cycles without any modification of the CT regimen. Patients with individualised G-CSF treatment showed more CT disturbances and FN. There remains room for improvement in prevention of CIN/FN in cancer patients as reflected by median start/treatment days and number of neutropenic complications. Further data are warranted to detail the impact of individualised G-CSF treatment.
Conflict of interest: *Ownership: No. Advisory board: Amgen, Boehringer Ingelheim, Hexal/Sandoz, Novartis. Board of directors: No. Corporate-sponsored research: No. Other substantive relationships: No*

1468 POSTER

Overview of meta- and pooled analyses of nutrition and breast, colorectal and prostate cancer risk

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Background: Twenty years ago, recommendations for prevention of cancer by nutritional modification were based on decreased fat consumption, and increased consumption of dietary fibers, fruits, vegetables and vitamins. Subsequent literature is replete with reports of studies of nutrition often containing widely varying advice regarding reducing cancer risk.
Methods: A systematic search in PubMed was conducted to identify meta- and pooled analyses relating breast, colorectal and prostate cancer risk to nutritional components. Cancer risk was related to intake of coffee, dairy, dietary fibers, eggs, fat components, fruits and vegetables, glycemic index and load, meat components, minerals, seafood, soy, tea, and vitamins.

Inclusion criteria were: published in English, time period 2000–2011, and prospective studies. All published relative risks and confidence intervals were abstracted.
Results: The search retrieved 120 meta- and pooled analyses concerning alcohol (7), carbohydrates (1), coffee (7), dairy (9), dietary fibers (4), eggs (1), fat components (15), flavonoids (1), fruits and vegetables (7), glycemic index and load (6), meat (23), minerals (6), proteins (1), seafood (5), soy food (3), sugar-sweetened beverages (1), tea (6), and vitamins (17). In total 1,211 relative risks were computed by meta- and pooled analyses, with 830 (69%) statistically not significant, 164 (14%) showing an increased risk and 217 (18%) showing a decreased risk of cancer. 129 relative risks were less than 0.90 and 83 were greater than 1.25. Of the 70 estimates for alcohol, 44 (63%) showed statistically significant increased risk for breast and colorectal cancer. 9 (64%) of the risk estimates showed an increased risk of prostate cancer with dairy consumption, and 47 (47%) showed a decreased risk for colorectal cancer. Red meat risk estimates related with colorectal cancer were increased in 63%, and for 52% for processed meat. For other food items, proportions associated with non-significant risk were for fat consumption (88%), dietary fibers (60%), fruits and vegetables (74%), glycemic index/load (91%), and vitamins (78%).
Conclusions: No individual nutritional item has been consistently related to cancer risk, but alcohol and meat for which a modest increase of colorectal cancer seems to exist. Probably that energy balance and dietary patterns (eg the Mediterranean diet) rather than food items are the key nutritional aspects relevant to cancer prevention.
No conflict of interest.

1469 POSTER

An innovative approach to raising awareness and encouraging early diagnosis of neuroendocrine cancers in the UK

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Early diagnosis of neuroendocrine cancers, and subsequent referral to a multi-professional team, greatly improves the outcome for the patient.
We conducted a nationwide survey of 200 patients with neuroendocrine cancers in the UK to determine routes and challenges to diagnosis. The findings show that a significant number of patients (47%) had to wait at least a year before being diagnosed, and that the majority of patients (51%) visited their GP 4 times or more before being diagnosed. 61% of respondents had been treated for the wrong disease prior to diagnosis.
In response to the survey results we designed a tool to support GPs and encourage the suspicion of a neuroendocrine cancer as a differential diagnosis. In conjunction with the tool, we produced engaging and educational posters about neuroendocrine cancers for GP surgery waiting rooms. In order to save costs whilst ensuring a higher viewing rate than through more traditional distribution methods such as post or email, we sought the help of patients and family members throughout the UK to deliver the materials. This innovative approach has proved to be both cost efficient and highly successful, with these materials having been personally delivered to over 3,500 GP practices since October 2012. Distribution target is 15,000 practices by October 2013.
No conflict of interest.

1470 POSTER

Lung cancer and occupation

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Introduction: Association between tobacco smoking and lung cancer is clear and well-studied. Other factors of importance for prevention, early diagnosis and treatment of lung cancer have received little attention. We present a case-control study focusing on social variables and occupation; comparing lung cancer patients with those with large bowel cancer.
Patients and Methods: A written questionnaire was completed by 377 consecutive patients with lung cancer and 374 patients with large bowel cancer. Data on place of birth, smoking history, diet and alcohol intake, body weight and height, profession, housing conditions and family income were collected and analysed. Statistical analysis was performed by using descriptive statistics, Mann-Whitney U test, chi-square test and logistic regression.
Results: The groups were balanced as regards gender and age distribution. As expected, there were significant differences between the groups regarding smoking status: non-smokers 9.9% vs. 52.1%, ex-smokers 67.9% vs. 36.9%, and current smokers 21.4% vs. 9.9% for lung and large bowel cancer respectively ($p < 0.001$). The proportion of patients working as industrial workers, construction workers or in other polluted working environment was also higher among lung cancer patients, as compared to large bowel patients (65.4% vs. 43.7%%, $p = 0.004$). Especially striking is the difference in metal industry workers (28.2% vs. 15.8%, $p < 0.001$). The share of immigrants, although not statistically significant, was higher (17.1% vs. 12%, $p = 0.08$) in patients with lung cancer. There were no statistically significant differences regarding housing conditions, family income, diet and alcohol consumption. The importance of smoking and polluted working environment was confirmed by a multivariate analysis.
Conclusions: The association between tobacco smoking and lung cancer is clear; more than 80% of lung cancer patients are current or former smokers. This very high figure leads to under-estimation of other preventable co-factors involved in etiology of the disease. Environmental pollution is an independent risk factor for lung cancer, both in smokers and in non-smokers. Our trial confirmed the role of occupational exposure to carcinogens in the etiology of lung cancer. When compared to patients with cancer of the large bowel, the group of lung cancer patients included a higher higher proportion of those working in polluted environment.
No conflict of interest.

1471 POSTER

Long term consumption of flaxseed enriched diet decreased ovarian cancer incidence and prostaglandin E2 in hens

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Ovarian cancer is the most lethal gynecological malignancy. Prevention of ovarian cancer is the best approach for reducing the impact of this deadly disease. Progress in the treatment and prevention of ovarian cancer has been hampered due to the lack of a valid and appropriate animal model, and absence of effective chemo-prevention strategies. The domestic hens spontaneously develop ovarian adenocarcinomas that are similar in histological appearance to human ovarian carcinomas and share similar symptoms of the disease, such as perfuse ascites fluid and peritoneal metastatic dissemination. Flaxseed is the richest vegetable source of omega-3 fatty acids which may be effective in the prevention of ovarian cancer. There is a link between chronic inflammation and cancer. Prostaglandin E_2 (PGE_2) is the most pro-inflammatory ecoisanoid and one of the downstream products of two isoforms of cyclooxygenase (COX) enzymes: COX-1 and COX-2. Our objective was to determine if long-term consumption of a flaxseed enriched diet decreased ovarian cancer severity and incidence in the laying hen and to investigate its potential correlation with the expression of COX enzymes and PGE_2 concentration. 1200 white Leghorn hens were fed 10% flaxseed-enriched or standard diet for 4 years. The severity and incidence of ovarian cancer were determined by gross pathology and histology. COX-1 and COX-2 protein and mRNA expression and PGE_2 concentrations in ovaries were measured by Western blot, quantitative real-time qPCR and ELISA, respectively. Our results indicated that similar to humans, the incidence of ovarian cancer was increased in hens which further validates the chicken as a suitable model to study human ovarian cancer. In correlation with ovarian cancer incidence, the expression of both COX enzymes and concentrations of PGE_2 were elevated with age. The results demonstrated that there was a reduction in ovarian cancer severity and incidence in hens fed flaxseed diet. In correlation with decreased ovarian cancer severity and incidence, concentration of PGE_2 and expression of COX-2 were diminished in ovaries of hens fed flaxseed. Our findings suggest that the lower levels of COX-2 and PGE_2 are the main contributing factor in the chemo-suppressive role of long-term flaxseed consumption in ovarian cancer in laying hens. These findings may provide the basis for clinical trials of dietary intervention targeting prostaglandin biosynthesis for the prevention and treatment of ovarian cancer.
Supported by NIH (1R01 AT005295) National Center for Complementary and Alternative Medicine Grant AT004085 (DBH) and American Institute for Cancer Research Grant 06-A043 (DBH).
No conflict of interest.

1472 POSTER

Clinico- pathological differences in breast cancer in women from rural and urban areas

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Background: Breast cancer is themost commonly diagnosed neoplasm among women and second cause of death becauseof malignancy. Levels of living conditions and medical education in rural andurban areas may have influence on early cancer detection, access to the medicalcare, screening programs and successful outcome of therapy.
The aim of this studyis to analyze clinical and pathological differences of breast cancers amongoperated women living in rural and urban areas.

Materials and Methods: One thousand fivehundred five women, aged 23 to 93 years (median 56), with breast canceroperated between 2001 and 2011, were evaluated. The analyzed parameters were:place of living (urban/rural), age (in subgroups: 1. <50 y.; 2. between 50and 70 y.; >70 y.), histological type, tumor size (T), state of regionallymph nodes (N), grading (G), estrogen, progesterone and HER2 receptor status,stage of cancer (TNM VII ed. 2010) and type of surgical procedure. The resultswere statistically analyzed by Statistica (Statsoft, ver. 9.0).
Results: Out of1505 patients, 958 (63.6%) lived in urban and 547 (36.3%) in rural areas. Themost common diagnosed histological type of cancer was ductal carcinoma. Amongthe urban patients, most common were Tis and T1 tumours, and in the rural womenT2 and T4 tumors ($p = 0.007$). Proportion of T3 tumors was similar in both groups(1.6% rural vs 2.2% urban). Higher percentage of rural women was diagnosed inII and III stage of cancer (63.4% vs. 58.1%), whereas among urban patientsstages 0 and I were more common (35.9% vs 30.9%; $p = 0.039$). Mastectomies hadbeen proceeded on 50% women from urban and 55% rural patients. Breastconserving treatment was applied to 49% urban and 45% rural women ($p = 0.11$).
Conclusions: Women living in therural areas had significantly higher stage of breast cancer, which may haveinfluence on the prognosis. Major impact should be focused on heath educationand prevention. Women living far from the oncological centers should haveeasier access to the diagnostics and earlier treatment.
No conflict of interest.

1473 POSTER

Quercetin-3-glucoside, a potential dietary supplement to prevent cancer, is secure to normal cells?

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Background: Cancer is one of the leading causes of death in the human population worldwide. Prevention consisting in a healthy lifestyle and a natural diet is suggested to approaches to reduce cancer risk. In recent years, the use of flavonoids present in foods and dietary supplements has the greatest potential to modulate activity of tumor cell. However, since phytochemicals are foreign compounds, their consumption in large quantities should be carefully considered. The negative properties of these dietary supplements may have origin in their own toxicity, metabolic conversion into cytotoxic or mutagenic agents, induction of carcinogen activating enzymes, or effect on human microflora. The objective of this study is investigate the mutagenicity, antimutagenicity and antiproliferative effects of quercetin-3-glucoside, obtained by rutin hydrolysis with hesperidinase from Penicillium sp.
Materials and Methods: The enzymatic reaction was catalysed by heated hesperidinase from *Penicillium sp* for the bioconversion of rutin to its mono-glycoside form, quercetin-3-glucoside. The antiproliferative activity of the samples was performed on human tumor cell lines [breast (MCF-7), ovarian (OVCAR-3) and resistant ovarian (NCI-ADR/RES), kidney (786−0), prostate (PC-3), colon (HT-29)] and normal human keratinocytes (HaCat). The micronuclei assay (CBMN) had followed OECD guide using normal hamster ovarian cells (CHO-K1).
Results: Q3G exerted antiproliferative effect in human carcinoma cell lines (GI_{50} <10 μg/mL). At 2.5 μg/mL, Q3G did not improve micronuclei incidence besides a protective effect against MMS genotoxic effect.
Conclusion: The Q3G has a great potential to modulate activity of tumor cell lines; moreover, Q3G does not induces mutagenic risk by itself and can protect against xenobiotic mutagenic effect at the concentration considered.
No conflict of interest.

1474 POSTER

Knowledge about smoking-related cancer, health risk perception and role of nurses and physicians in smoking prevention among school children

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Background: In Latvia more than 30% of school children (age 13−18) are smokers. Seven in ten have an experience in tobacco smoking at the age of 16. The proportion of smoking girls increased from 2% in 1991 to 24% in 2010. There are several ongoing programs and campaigns focused on decrease of smoking habits among school children, which seem to be not working due to problems in health care system. The aim of this study was to examine knowledge about smoking-related diseases, risk perception and what should be changed in health care workers behavior to increase smoking prevention among school children.
Methods: A questionnaire-based survey was carried out among 566 school children smokers. Knowledge about smoking-related diseases was assessed with a questionnaire created for this study. Children rated their risk perception and role of physician in their health control. A cross-sectional survey was given to 238 nurses and 126 physicians to assess knowledge and identify factors that affect their anti-smoking behavior.
Results: School children are aware that smoking could cause lung cancer (29% of boys and 21% of girls), bladder cancer (6% and 8% respectively), cancer of the larynx and cancer of the oral cavity (10% and 3%), kidney cancer (2% and 1%), cancer of the cervix and uterus (1% and 5%), cancer of stomach and esophagus (2% and 1%), respiratory diseases (4% and 2%), heart diseases (2% and 5%), infertility and pregnancy complications (4% and 10%). Risk perception mean (SD) level was significantly higher in non-smokers school children (age 16−19). About 65% of boy (age 13−15) said they trusted their doctor ‘a lot,’ 30% said they had ‘some’ trust, while only 5% said they didn’t trust the doctor. About 82% of elder teenagers (age 16−19) trust doctors ‘a lot’, 10% have ‘some’ trust and 8% don’t trust the doctor. Cross-sectional survey among health care professionals showed that 147 nurses (61.7%) and 100 physicians (79.3%) neglected to speak about smoking-related diseases with teenagers or ask about smoking habits. Among them ‘was too busy’ were 91% of nurses and 67% of physicians, ‘forgot’ 6% nurses and 32 % of physicians, ‘do not recognize the necessity’ 3% nurses and 1% of physicians.
Conclusions: The results indicate an unsatisfactory knowledge about smoking-related diseases, low risk perception, absence or ignoring of prevention plan among school children as main causes of high prevalence of smoking in schools. Teenagers smokers must be informed about risk of smoking-related diseases by physicians and nurses during annual medical observation or every visit to doctor and educational strategies need to be focus on prevention plan immediately after confirmation of smoking habits. Prevention of smoking in schools does not work because doctors are neglecting their duty to speak with smokers about smoking-related diseases. Nevertheless, the results of this study show that school children respond far better to anti-smoking messages from doctors and nurses than they do from teachers, parents or government anti-smoking programs.
No conflict of interest.

1475 POSTER

Knowledge and awareness of breast cancer and practice of breast self-examination among female health workers in Al-Mukalla city

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Introduction: Breast cancer is the most common cancer among women worldwide, comprising 16% of all female cancers. The prevalence of breast cancer in Yemen was 20.8/100 000 women Thus, World Health Organization(WHO) has emphasized raising awareness among women for early detection and reporting of breast cancer in order to increase life quality, survival rate and to overcome the ever-increasing burden of this deadly disease. Therefore, this study was designed to evaluate the knowledge regarding breast cancer (BC) and breast self examination (BSE) and the practice of BSE among female health workers in order to introduce the best intervention.
Methodology: A cross-sectional study was carried out from 15th January to 31st May 2012 in three public hospitals in Al-Mukalla city: Al Mukalla Hospital for Mother & Child, Ibin Sina General Hospital and the University Hospital. All female health workers practicing in hospitals were selected (total number of 182 females employed as doctors, nurses and midwives). The data was collected by pre-tested self report questionnaires. Interpretive description was used in the data analysis.
Results: Out of 182 female health workers registered in hospitals, 151 returned their questionnaires, giving a response rate of 83%. More than half (60%) of the female health workers in Al-Mukalla city had a high knowledge regarding BC and BSE. Doctors had more knowledge than the nurses and midwives. The study found a significant relationship between socio-demographic characteristics and BC knowledge, and also between family history of BC and BC knowledge. Majority of respondents were aware that BSE is a method for early detection of BC. Although only 54% of the female health workers were performing BSE (65% of doctors, 59% of midwives and 37.7% of nurses). Ninety % of those who practice BSE had high knowledge about BSE technique. ‘forgetfulness (43.4%)’and ‘absence of symptoms (40.6%)’ were main reasons that prevented respondents from practicing BSE.There was a statistically significant correlations between BSE practice and educational level, occupation, and level of knowledge.
Conclusion: The results point out that female health workers in Al-Mukalla city have a satisfactory level of knowledge regarding BC and BSE which was reflected in high percentage of practice of BSE. Significant correlation was found between the respondents’ knowledge and BSE practice. Our findings suggest that there is a need for continuing education programs to change attitudes and behavior towards BSE.
No conflict of interest.

1476 POSTER

Mediterranean dietary pattern and breast cancer in women: the modifying role of physical activity

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Background: The aim of this study was to investigate the association of the adherence to the Mediterranean diet with breast cancer development.
Material and Methods: An age-matched case-control study was conducted; 250 newly diagnosed breast cancer patients (56±12 yrs) and 250 controls were consecutively enrolled during 2010–2012 from 5 major hospitals. Participants completed a standardised questionnaire that also included a validated 86-item food frequency questionnaire. Adherence to the Mediterranean diet was evaluated using the MedDietScore (theoretical range 0−55). Anthropometric characteristics, family history, dietary and smoking habits and physical activity were also evaluated.
Results: Patients with breast cancer were less likely to be adherent to the Mediterranean dietary pattern as compared with controls (Odds ratio by 1-unit increase in the MedDietScore =0.923, 95% CI 0.879–0.968), adjusting for age, socioeconomic level, family history of breast cancer, body mass index (BMI), physical activity (IPAQ score), smoking and menopausal status. Physical activity status seems to enforce the aforementioned results, since adoption of a more physically active lifestyle was associated with greater reduction of the odds of having breast cancer. Specifically, patients with low physical activity status (i.e. IPAQ score<600 MET-minutes/week) were less likely to be adherent to the Mediterranean dietary pattern (OR=0.928, 95% CI 0.868–0.993), moderately physically active (i.e., IPAQ score=600–3000 MET-minutes/week) were 0.909 times (95% CI 0.835–0.989) less likely to be adherent to the Mediterranean dietary pattern, and women with health enhancing physical activity status (HEPA active, i.e., IPAQ score>3000 MET-minutes/week) were 0.847-times (95% CI 0.710–1.00) less likely to be closer to the Mediterranean diet.
Conclusions: These findings highlight the protective effect of the adherence to the Mediterranean dietary pattern in relation to breast cancer, irrespective of physical activity status.
No conflict of interest.

1477 POSTER

Mediterranean dietary pattern and breast cancer in women: the modifying role of obesity

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Material and Methods: An age-matched case-control study was conducted; 250 newly diagnosed breast cancer patients (56±12 yrs) and 250 controls were consecutively enrolled during 2010–2012 from 5 major hospitals. Participants completed a standardised questionnaire that also included a validated 86-item food frequency questionnaire. Adherence to the Mediterranean diet was evaluated using the MedDietScore (theoretical range 0−55). Anthropometric characteristics, family history, dietary and smoking habits and physical activity were also evaluated.
Results: Patients with breast cancer were less likely to be adherent to the Mediterranean dietary pattern as compared with controls (Odds ratio by 1-unit increase in the MedDietScore =0.923, 95% CI 0.879–0.968), adjusting for age, socioeconomic level, family history of breast cancer, body mass index (BMI), physical activity (IPAQ score), smoking and menopausal status. Obesity status masked the aforementioned results; particularly, adherence to the Mediterranean dietary pattern maintained its protective role in normal weight (BMI<25 kg/m^2) (OR=0.903, 95% CI 0.827–0.987) as well as in overweight women (BMI=25–29.9 kg/m^2) (OR=0.875, 95% CI 0.805–0.950); however, in obese women (BMI>30 kg/m^2) there was no significant association (OR=0.974, 95% CI 0.884–1.073, p = 0.59).
Conclusions: These findings highlight the protective effect of the adherence to the Mediterranean dietary pattern in relation to breast cancer, especially for normal weight and overweight women; and underline the detrimental role of obesity on diet-disease association.
No conflict of interest.

1478 POSTER

Mediterranean dietary pattern and breast cancer in women: the modifying role of menopausal status

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Background: The aim of this study was to investigate the association of the adherence to the Mediterranean diet with breast cancer development.
Material and Methods: An age-matched case-control study was conducted; 250 newly diagnosed breast cancer patients (56±12 yrs) and 250 controls were consecutively enrolled during 2010–2012 from 5 major hospitals. Participants completed a standardised questionnaire that also included a validated 86-item food frequency questionnaire. Adherence to the Mediterranean diet was evaluated using the MedDietScore (theoretical range 0−55). Anthropometric characteristics, family history, dietary and smoking habits and physical activity were also evaluated.
Results: Patients with breast cancer were less likely to be adherent to the Mediterranean dietary pattern as compared with controls (Odds ratio by 1-unit increase in the MedDietScore =0.923, 95% CI 0.879–0.968), adjusting for age, socioeconomic level, family history of breast cancer, body mass index (BMI), physical activity (IPAQ score), smoking and menopausal status. Stratified analysis by menopausal status revealed that the protective role of diet was irrespective of menopausal status (i.e., premenopausal patients were 0.913, 95% CI 0.848–0.983 times less likely and postmenopausal patients were 0.911, 95% CI 0.851–0.975 times less likely to be adherent to the Mediterranean dietary pattern).
Conclusions: These findings highlight the protective effect of the adherence to the Mediterranean dietary pattern in relation to breast cancer, both for pre- and postmenopausal women.
No conflict of interest.

1479 POSTER

Prevalence & predisposing factors for tobacco chewing among secondary school students in Mukalla,Yemen (2012–2013)

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Objectives: To determine the prevalence & predisposing factors for tobacco chewing among secondary school students in Mukalla, Yemen (2012–2013).
Design: 530 randomly selected secondary school students from 10 schools were included in this cross-sectional study.
Results: The prevalence of tobacco chewing among secondary school students in Mukalla city was 28.7%. Majority of students were highly knowledgeable on relationship between tobacco chewing and occurrence of oral cancer and periodontal diseases (64%). 'Influence of friends' was the most common predisposing factor (66.5%). Appropriate guidance from parents and guardians, Knowing the detrimental health effects, and religious teachings were perceived as a. The tobacco smoking and Qat chewing were significantly higher among students chewed tobacco compared with non-chewed [(25% & 2.9%, P = 0.00) and (30.3% & 4.5%, P = 0.00) respectively.
Conclusions: Despite of the good level of knowledge on the detrimental effects of tobacco chewing on health, a high prevalence of chewers among secondary school students was discovered. Novel approaches involving the religious leaders, parents, school teachers are an urgent need in the country.
No conflict of interest.

1480 POSTER

New communication strategies of the Italian League against cancer to promote healthy behaviors in the province of Alessandria (Italy)

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Background: Primary cancer prevention efforts typically involve the development and distribution of persuasive and informative cancer education programs and materials, as well as the development of specific preventative behavioral interventions to adopt a healthy lifestyle. In the past the Italian League against Cancer, section of Alessandria (LILT Al), tried to persuade the greatest part of the local population to join programs of preventive diagnostic screening, whereas the current priority is to combat against selected behavioral factors, mainly poor diet and not being physically active, implicated in the onset of cancer. In the light of this shift in action, a working group has been recently set up by LILT Al with participants from the Group for Health Promotion and Education, Local Health Authority (PEAS-ASLAl), and the Institute of Sociology, University of Piemonte Orientale at Alessandria. The group is focused on building new strategies for encouraging healthy lifestyle choices by means of interventions capable of being appealing and effective especially among young population.
Material and Methods: At first, an analysis was carried out for the evaluation of previous health education campaigns with special reference to their contents, operating methods and results. Furthermore, the conditions of overweight and obesity have been used as a paradigm to improve our understanding of psychological and social mechanisms (the determiners of behavior) placing people at increased risk of health problems. Biographical interviews were conducted with patients (n = 22) suffering from first degree obesity and attending ambulatory care for dietary therapy. Finally, attention has also been given to the influence of socio-economic and cultural factors on local community health.
Results: Interviewed people appeared to consider themselves at health risk only when additional diseases overlap the condition of overweight or obesity. They did not agree that obesity is a disease and they never internalized the concept of 'obesity' as well as never thought of themselves as 'obese'. Finally, they never let themselves to be influenced by educational campaigns promoting healthy diet and emphasizing obesity as a health risk factor.
Conclusions: Although preliminary and still limited, these results could be useful to develop educational messages appropriate for the new emerging evidences related to the characteristics of the target population of our study. The study was funded in part by CSVA Alessandria through the call 'Bando a scadenza unica 2011'.
No conflict of interest.

1481 POSTER

Number needed to harm in prostate cancer screening with PSA

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Background: The United States Preventive Service Task Force (USPSTF) recently recommended against PSA testing for prostate cancer screening in asymptomatic men. Despite this recommendation, the use of PSA tests is still widespread as in France, 55% of men aged 50−60 have a PSA test every year and more than 75 % every 3 years.
Methods: We estimated the number of individuals needed to harm associated with PSA testing by applying different side effect estimates to a virtual population of 1,000 men aged 55−69 exposed to PSA testing and another 1,000 not exposed to PSA testing. Following a systematic literature review, we extracted results of PSA testing, biopsy rates and impact on prostate specific mortality from the European Randomized Study on Screening for Prostate Cancer (ERSPC) which is the study with the most favourable outcome to PSA screening. We also extracted, from reports with such information, data on mortality following prostatic biopsy, on mortality associated with radical prostatectomy as well as side effects of radical prostatectomy and hospitalisation rates following prostatic biopsy.
Results: In the group of 1,000 unscreened men, we estimated that 116 biopsies would be conducted and 60 prostate cancers would be diagnosed. Overall 193 deaths would occur in this group of which 5.17 would be from prostate cancer. In the population exposed to screening, 270 biopsies would be performed, with 96 prostate cancer diagnosed. The mortality would be similar with 191 deaths overall with 4.1 from prostate cancer. For 1 death from prostate cancer prevented among 1,000 men, this population would have to experience an additional 154 biopsies (among which 9 would require hospitalization for severe adverse effect and 0.2 deaths would occur due to biopsy). 35 additional prostate cancers would be diagnosed mainly from low risk men (32 cases). These additional cancers would be associated with 12 additional cases of impotence, 2 cases of incontinence and 1 case of faecal incontinence.
Conclusions: Overall, under the best scenario of screening efficiency, the prevention of 1 death from prostate cancer is associated with a significant additional adverse-effect burden from the biopsy and from the treatment of the additional prostate cancer diagnosed. These will severely impact the quality of life of patients and argues against using PSA testing for mass screening of prostate cancer.
No conflict of interest.

1482 POSTER

Changes in lifestyle in patients with previous diagnosis of colorectal or breast cancer

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Background: Colorectal and breast cancers are related with risk factors such as overweight, obesity and physical inactivity. Importantly during their follow-up patients should be motivated for adopting a healthy life style (maintain an ideal body weight, BMI 20−25, physical activity, at least 30 minutes five times a week, cessation of smoking, moderate alcohol use, healthy diet adoption). However patients usually are not really aware of its importance and medical oncologists don't insist enough in daily practice.
Material and Methods: We prospectively collected data from 109 patients who came to our consultation for follow-up since January to April 2013. We analyzed baseline comorbidity and changes in lifestyle and comorbidity between first visit in study and second visit (study is planned until July 2013). We also asked for intake of medications like aspirin, statins, beta blockers and ACE inhibitors.
Results: 68 patients had a previous diagnosis of breast cancer and 41 of colorectal cancer. In the group of breast cancer median age was 56 years (range 33−82), 30% had hypertension, 14% type 2 diabetes mellitus, 20% baseline dyslipidemia, 71 % were no smokers, 19 % were former smokers, and 10% active smokers, of whom 75 % reduced their consumption and 25% ceased after diagnosis; 82% were previously abstemious and 18% moderated their alcohol use after diagnosis; baseline BMI was 20−25 in 54%, 25−30 in 31%, and $\geqslant$30 in 15%; at first visit of present study 65 % of patients who were free of tumor recurrence had maintained their weight, 10% had lost weight, and 25% had put on weight; only 15% who had baseline BMI $\geqslant$25 had followed a weight loss diet even if 100% were aware of the importance of maintaining an ideal weight, 85% said exercise regularly and have an adequate intake of fruits and vegetables, only 13% had started smoking again, and most were abstemious or with very moderate intake of alcohol; 71% had screening for other tumors like colon and cervical cancer; 84% said to have been counseled by their medical oncologist on the importance of healthy lifestyle and wellness. Results for the second visit are still incomplete, and for the group of colon cancer the main differences were age (median age 64, range 35−81), baseline smoking status (42% current smokers) and BMI (20−25: 54%, 25−30: 35%, $\geqslant$30: 11%, and 85% had put on weight at first visit).
Conclusions: Medical oncologists should optimize counseling on healthy lifestyles during follow-up of patients treated for breast and colon cancer as important part of their treatment.
No conflict of interest.

1483 POSTER

HIV screening of patients with AIDS-defining cancers: A 10-year retrospective analysis of practices in a Swiss university hospital

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Background: Kaposi's sarcoma (KS), invasive cervical carcinoma (ICC) and non-Hodgkin lymphoma (NHL) have been listed by the Centers for Disease Control and Prevention (CDC) as AIDS-defining illnesses since 1993. The European Society of Medical Oncology (ESMO) recommendations mention HIV screening in the case of NHL but not ICC. However, patients with AIDS-defining cancers (ADC) who are HIV-positive

present better outcomes when their HIV infection is treated in parallel to cancer treatment. We examined HIV screening practices at a tertiary oncology centre where local HIV seroprevalence is 0.4%.
Methods: We included all patients with KS, ICC and NHL, and patients with Hodgkin lymphoma (HL), treated at Lausanne University Hospital, Switzerland, between January 2001 and January 2012. HIV testing was considered to be part of the oncology work-up if patients underwent testing at the time of oncological diagnosis, as documented in the central laboratory database or in patient notes. Patients of known HIV-positive status were included in our analysis but excluded from calculations of testing rates: (patients tested/patients treated) x 100.
Results: 880 patients were examined: 10 with KS, 58 with ICC, 672 with NHL and 140 with HL. For these cancer types, HIV testing rates were 100%, 19%, 75% and 74%, respectively. 37 patients (4.2%) were HIV-positive of whom 28/37 (76%) were Swiss and 6/37 (16%) were diagnosed as a result of screening related to the oncology work-up. HIV prevalence among patients with KS, ICC, NHL and HL was 60%, 1.7%, 3.4% and 5%, respectively.
Conclusion: In our study population, HIV prevalence among patients with non-KS cancers is low but higher than the population average. For non-KS cancers, HIV screening was performed in 19−75% of patients. As HIV-positive status impacts on the medical management of cancer patients, we propose that HIV screening should be mentioned in oncology treatment guidelines and that an opt-out approach should be adopted in patients with ADC and HL.
No conflict of interest.

1484 POSTER

The efficacy of MRI and mammography in screening BRCA1 and BRCA2 mutation carriers above 60 years

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Background: Screening guidelines advise breast cancer screening with yearly MRI and mammography to reduce mortality for *BRCA1* and *BRCA2* mutation carriers (*BRCA1/2*). The Dutch (NABON) and British (NICE) guidelines, recommend screening with only biennial mammography for mutation carriers from the age of 60 years on ($\geqslant$60). But less intensive screening may not be justified, since breast cancer incidence does not decrease in carriers $\geqslant$60. Furthermore, *BRCA1* tumours grow twice as fast as sporadic tumours, and no studies have been performed addressing screening in *BRCA1/2* $\geqslant$60. We assessed the proportion of *BRCA1/2* who did not have bilateral therapeutic or prophylactic mastectomy before the age of 60 to determine for how many screening above 60 years is relevant. Moreover, we compared efficacy of screening with; annual MRI and mammography, annual mammography, and biennial mammography in *BRCA1/2* $\geqslant$60.
Material and Methods: We assessed the proportion of *BRCA1/2* with breast tissue at risk at age 60 of the Rotterdam Family Cancer Clinic and the ongoing nationwide HEBON study. Furthermore, we compared tumour stage at detection between different screening methods in the 98 breast cancers detected in *BRCA1/2* $\geqslant$60 in these databases. Tumours larger than 2 cm, lymph node positive, and/or metastatic disease at detection were defined as 'unfavourable stage'.
Results: Of 413 *BRCA1,* 133 *BRCA2*, and 2 *BRCA1* and *BRCA2* mutation carriers $\geqslant$60 in 2012, 395 (72%) had one or both breasts at age 60. Of the women with breast tissue 20% had a history of invasive carcinoma other than breast or non-melanoma skin cancer. Screening method at detection of the 98 breast cancers was; 11 (11%) no screening, 28 (29%) biennial mammography, 48 (49%) annual mammography, and 11 (11%) annual mammography and MRI. With annual mammography 25% of tumours were detected in an unfavourable stage versus 64% with biennial mammography ($p = 0.001$). Tumour stage did not differ significantly between screening with annual MRI and mammography or mammography alone.
Conclusions: A large part of *BRCA1/2* still has breast tissue at risk at 60 years of age. Annual screening above age 60 detected tumours in a significantly more favourable stage than biennial screening. If life expectancy is good, continuation of annual screening of *BRCA1/2* mutation carriers above age 60 seems worthwhile. We will present updated results, also separately, for *BRCA1* and *BRCA2* mutation carriers.
No conflict of interest.

1485 POSTER

Level of awareness of cervical and breast cancer risk factors and safe practices among college teachers of different states in India: Do awareness programmes have an impact on adoption of safe practices?

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Background: Breast and cervical cancers are the most common causes of cancer mortality among women in India, but actually they are largely preventable diseases. In India, late presentation which is responsible for high mortality and morbidity is attributed to many factors and important being the lack of knowledge and awareness, lethargic attitude towards safe practices. Since, there is limited data from India on this issues, the purpose of this study is to know the impact of awareness program on change in adoption of safe practices in prevention and early detection.
Material and Methods: This assessment was part of pink chain campaign on cancer awareness. During the events in 2011 at various women colleges in India, Pre test related to knowledge, attitude and practices related to cervical and breast cancer was conducted by questionnaire. It was followed by awareness program consisting of lectures on preventive aspects of breast and cervical cancer, Pink Chain − a docu-drama on breast cancer and an interactive session. Post test using the same questionnaire was conducted at the end of interactive session. Literature related to cancer awareness was sent regularly for one year on email ids provided. After completion of 6 months and 1 year, same questionnaires were mailed to the participants to see the change in practice. Data was collected and analysed by using statistical software STATA 10.1. P values less than 0.05 were taken as significant.
Results: A total of 156 out of 182 teachers participated in the study (85.71%). Same questionnaire were responded by 109 and 95 teachers at the end of 6 months and 1 year respectively. Mean age of the study population was 42.46 years (28−59 yrs). For cervical cancer, the correct risk factors mostly indicated by teachers were smoking (53%), family H/O cervical cancer(45%) and genital hygiene(36%). Symptoms of cervical cancer were very less known to teachers (7.69% − 32.05%). Risk factors and symptoms of breast cancer were well known in more than 50% of teachers, except for early menarche (16.66%), late menopause (17.94%) and radiation treatment(14.10%). As for screening methods, BSE, CBE, and Mammography were known modalities for breast cancer in 70%, 45% and 54% of teachers respectively but pap's test was known to only 35%. Magazines and newspapers were source for knowledge regarding screening test for breast cancer in more than 60% of teachers where as more than 75% teachers were educated by doctors regarding pap's test. Post awareness at 6 months and 1 year, there was a significant change in alcohol and smoking habits. There was a significant increase in level of knowledge regarding risk factors, symptoms and screening test for cervical and breast cancer at 6 months and this was sustained at 1 year. There was a significant increase in adoption of BSE where as practice of CBE, mammography and pap's test were increased but not significant. For not doing screening test, major reasons came out to be ignorance (50%), lethargic attitude (44.87%) and lack of time (34.61%).
Conclusions: Level of knowledge of breast cancer risk factors, symptoms and screening methods was high as compared to cervical cancer. Though there was significant change in practices of BSE and pap's test, there was not much improvement in people undergoing screening such as mammography and pap's test. To inculcate safe practices in life style of people, awareness programmes such as pink chain campaign should be conducted more widely and frequently and knowledge attained through them should be reinforced by treating physicians who are at first point of contact with health system. So creating awareness among health care providers is another issue which has to be looked into.
No conflict of interest.

1486 POSTER

Primary efficacy of physical examination combined with ultragraphy and complemented with mammography for breast cancer screening in 280 thousand Chinese women

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Background: Seldom large randomized controlled trials of breast cancer screening had been conducted among Chinese women, and the efficacy of such screening had not been defined yet. Because the high expenses of mammography, we conducted a program to evaluate the efficacy of physical examination combined with ultragraphy and complemented with mammography for breast cancer screening in chinese women.

Methods: We conducted a project of women aged 35 to 59 years who, living in suburb of Guangzhou, were screened with a clinical breast physical examination and ultragraphy. Those whose ultrasound findings categorized as BI-RADS 4c and 5 were biopsied, and those which categorized as BI-RADS 0, 3, 4a and 4b accepted mammography additionally, and those as BI-RADS 1 and 2 were follow-up.
Results: From January 1st,2010 to January 31st, 2012, 284168 women were screened. We identified 151 breast cancers. The detective rate of breast cancer was 53.14/100,000 and had positive correlation with the rate of biopsy(P<0.05). Percentage of stage 0 and I breast cancer were 8.6% and 38.4%,and significantly more stage I patients were detected compared with those in-hospital(P<0.001). The sensitivity was 97.4% and specificity was 99.9%, and the sensitivity was much higher than that of procedures only including physical examination and ultragraphy. The detective rate of the groups aged 35−39, 40−50, 50−59 years was 29.7(1/ 3368),53.0 (1/1885) and 74.7(1/1339) per 100,000 sreening women, whereas the costs for each detective breast cancer was ¥202,000,113,000 and 80,000 respectively. The detective rate of early beast cancer in group aged 50−59 years was significantly much higher than that in other two groups (P<0.001) and the group had the best cost-effectiveness.
Conclusions: Physical examination combined with ultragraphy and complemented with mammography for breast cancer screening can improve the proportion of stage I tumor significantly. It obtained nice sensitivity and specificity. Women aged 50−59 years had the best cost-effectiveness.
No conflict of interest.

1487 POSTER

Regional experience of the mammographic screening implementation in Western Siberia

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Background: Breast cancer is the most common cancer in the female population, and one of the leading causes of cancer deaths in women. Almost 12 million new cancer cases were diagnosed in 2008 across the world and of these, 1.38 million women were diagnosed with breast cancer. In many areas, breast cancer mortality has decreased in recent decades due to improving treatment and implementation of mammography screening. The main aim of this study is to evaluate the results of the Breast Cancer Screening Program implemented in the Khanty-Mansiysky Autonomous Okrug − Ugra in 2007.
Methods: Mammography screening covers women over 40 years old, the screening interval is 2 years, and two-view mammography and single reading. Data number of screened are obtained annually from the reports for the State Healthcare Department. The information on the female population, all screen-detected and symptomatic detected breast cancer cases, deaths cases due to breast cancer has been obtained from the State Cancer Registry for years 2002–2012. The target population of women aged 40+ has increased from 273100 in 2002 to 323285 in 2012. We studied incidence of node positive breast cancer over the years 2002 to 2012, comparing observed incidence in 2007 to 2012 with that expected from the observed trend in 2002 to 2006. We also estimated the effect of screen detection on node positivity in the 3398 cancers diagnosed in the target age group in 2002–2012, using logistic regression and taking account of confounding factors.
Results: During 2007–2012 within the Program, 249106 women were screened in the region. The screening coverage rate is the approximately 67.5%. 9.7% of screened women were referred for further assessment. The prevalence was 2.7 per 1000 screened women. The test sensitivity for the first round was estimated as 80%. The number of node positive breast cancers in 2007 to 2012 was 985, significantly lower than the 1309 expected from the 2002−06 trend. Screen detected cancers were significantly less likely to be node positive after adjusting for district and year of diagnosis, and for tumour size (OR=0.49, 95% CI 0.39–0.62).
Conclusion: The quality evaluation of the Screening Program shows that the main criteria are within the international standards. Mammographic screening has contributed to a major reduction in node positive breast cancer and is likely to produce a corresponding breast cancer mortality reduction in the future.
No conflict of interest.

1488 POSTER

Neighbourhood deprivation and risk of morbidity and mortality in people with lung cancer: A multilevel analysis from Sweden

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Objectives: To analyze whether there is an association between neighbourhood deprivation and morbidity and mortality of lung cancer, beyond individual level characteristics.
Design: The entire Swedish population aged over 50, a total of 3.2 million individuals, was followed from January 1, 2000, until admission due to morbidity or mortality of lung cancer during the study period, or the end of the study on December 31, 2010. Multilevel logistic regression was used in the analysis with individual level characteristics (age, marital status, family income, education, immigration status, urban/rural status, mobility, and comorbidities) at the first level and level of neighbourhood deprivation at the second level. Neighbourhood deprivation was measured at small area market statistics level the use of Care Need Index, combining low educational status, low income, unemployment, and social welfare assistance.
Results: There was a strong association between level of neighbourhood deprivation and morbidity and mortality of lung cancer. In the full model, which took account of individual level characteristics, the risk of morbidity of lung cancer was 1.31 and 1.36 for mortality in the most deprived neighbourhood than in the most affluent neighbourhoods. The variance at neighbourhood level was over twice the standard error, indicating significant difference in morbidity and mortality of lung cancer risk between neighbourhoods.
Conclusions: This study is the largest to date of the influences of neighbourhood deprivation on morbidity and mortality of lung cancer. Results suggest that characteristics of neighbourhood affect risk of morbidity and mortality of lung cancer independently of individual level sociodemographic characteristics. Both individual and neighborhood level approaches are important in health care policies.
No conflict of interest.

1489 POSTER

Epidemiology of primary myelofibrosis (PMF), essential thrombocythemia (ET), and polycythemia vera (PV) in the European Union (EU)

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Background: PMF, ET and PV, three classic Philadelphia-chromosome-negative disorders, can cause substantial morbidity and mortality and have no therapeutic options addressing the underlying cause of disease. An evidence based synthesis of EU epidemiology data can inform population health care planning and economic decision for these disorders.
Material and Methods: Since information on MF, ET and PV is not routinely collected in disease registries in the EU, multiple sources are needed to understand the disease burden. Therefore, we conducted reviews of the literature, of disease registries and of online databases updated as of January 2013 to summarize recent data on incidence and prevalence of these disorders.
Results: Ten articles, four hematology or oncology registries and two web-based databases or reports were found to have information on epidemiological estimates for MF, PV and ET. The incidence rate of MF from the online registries or reports ranged from 0.1 per 100,000 per year to 1 per 100,000 per year while the literature estimated an incidence rate of around 0.3 per 100,000 per year. PV and ET incidence estimates were slightly higher. Among the online sources, the incidence of PV ranged from 0.4 per 100,000 per year to 2.8 per 100,000 per year with similar estimates in the literature (0.68 per 100,000 to 2.6 per 100,000 per year). The estimated incidence of ET was between 0.38 per 100,000 per year and 1.7 per 100,000 per year in the online sources and 0.52 to 2.00 per 100,000 in the literature. In contrast to MF and PV, the incidence of ET was higher among women than men. Few resources (n = 2 online resources, 1 registry and 3 articles) reported on the prevalence of MF, PV or ET. The prevalence of MF (range = 0.51 to 2.7 per 100,000) was lower than PV (range = 5 to 30 per 100,000) or ET (range = 1 to 24 per 100,000).
Conclusions: Few publications and registries report epidemiology data for MF, PV or ET and the variation in these estimates is wide across EU data sources limiting an informed application of these data. Additional research using standardized definitions/coding across appropriate real world databases and enhanced tumor registries are needed to add precision to or substantiate these results. Regardless, this review found

that the prevalence of ET/PV may be high enough to deserve resource allocation and attention towards development of national guidelines, development of novel agents, and healthcare planning.
Conflict of interest: *Other substantive relationships: JM,OM and UI work at Sanofi, UI owns sanofi stock*

1490 POSTER

The methodology and results of nosocomial infections surveillance at the Institute for Oncology and Radiology of Serbia

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Background: Epidemiological nosocomial infections surveillance imply the systematic gathering, analysis and interpretation of data on nosocomial infections, informing hospital staff and the Hospital Infection Control Committee of the surveillance results with the aim of prevention and control of infections.
Material and Methods: Hospital infections surveillance has been performed by the Department for Epidemiology and Prevention in collaboration with other departments. Monitoring of microbiology results of samples taken from patients, staff and environment is a component of surveillance since 1996; since 2005. all data are entered into the electronic database. Analysis of data for 2011 was performed.
Results: In 2011, 408 samples were taken from the work environment and 66 samples from employees (positive results in 18% and 24 % of samples, respectively). From clinical wards, 4729 samples from patients were sent to microbiological analysis, 26% being positive. The most frequently isolated microorganisms were Staphylococcus aureus, E. coli and Klebsiella Enterobacter. Share of gram-positive bacteria was 32.2%, gram negative 48.1%, and fungi 19.7%. Most frequent analyses were urinoculture, throught swab, hemoculture and nose swab. Urinocultures were positive in 30% of samples, most frequently isolated E.coli and Klebsiella. From hemocultures, postive in 10% of samples, most frequently were isolated KNS and Staph.aureus. Wound swabs were positive in more than 50% of samples, mostly with Staph.aureus, Klebsiella, Pseudomonas and E.coli.
Surveillance of antibiotic-resistance revealed that 7.7% infections were caused by resistant bacterial strains, most frequently VRE (58 samples), Pseudomonas resistant to piperacillin/ciprocinal (21) and MRSA (28 samples).
Conclusion: Regular surveillance of microbiological findings and antibiotic resistance enables efficient treatment and prevention of hospital infections in cancer patients.
No conflict of interest.

Poster Session (Sun, 29 Sep)
Public Health, Health Economics, Policy

1491 POSTER

Are the incremental costs of breast cancer clinical trials higher than standard of care?

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Background: Clinical trials (CT) are an essential element in the improvement of cancer prevention and treatment strategies. A widely held perception is that costs of care for CT patients are higher than standard of care (SOC). There is a paucity of data supporting this assertion.
Material and Methods: A retrospective cohort study was conducted to compare costs incurred by 97 breast cancer patients participating in industry and non-industry sponsored clinical trials with costs incurred by an equal number of eligible nonparticipants who received SOC over a year. Resource utilization was tracked and quantified to standardized price templates.
Results: On average, the costs were marginally higher for CT patients than SOC patients for all seven parameters, as were the mean total costs (Table 1, two-tailed t-test, p-value = 0.046) with pharmacy costs constituting the largest difference between trial and SOC patients (mean difference = $5157, p = 0.08). After excluding drugs that were provided by the pharmaceutical companies at no charge, the remaining average pharmacy costs became more similar between groups (mean difference = $990, p = 0.45). As a result, the mean difference between total costs was reduced by two-thirds, from $6396 to $2227 and significance was lost (p = 0.14).

Table 1. Cost by patient type (Canadian dollars)

Item	Trial patients Mean (SD)	SOC Patients Mean (SD)	Difference Mean (95% CI)	P-value
Tests and procedures	470 (640)	187 (439)	283 (128, 439)	<0.001
Diagnostics and Imaging	948 (945)	440 (626)	508 (281, 735)	<0.001
Physician	338 (303)	192 (238)	146 (69, 224)	<0.001
Nurse	434 (738)	232 (503)	202 (23, 380)	0.03
Pharmacy	10345 (25415)	5188 (14047)	5157 (−657, 10974)	0.08
Radiotherapy	3764 (2939)	3724 (3043)	40 (−807, 887)	0.93
Pathology	117 (168)	60 (132)	57 (15, 100)	0.009
Total	16418 (27186)	10022 (15480)	6396 (131, 12661)	0.046
Pharmacy − Drug-supplied	3846 (8417)	2855 (9611)	990 (−1469, 3549)	0.45
Total − Drug-supplied	9917 (10262)	7690 (10491)	2227 (−711, 5166)	0.14

Conclusions: This study revealed only marginal differences in the cost distribution of patients enrolled in clinical trials versus those receiving the standard-of-care. This is similar to previous results we have seen for prostate cancer patients and further questions the commonly held belief that clinical trials are a burden on a public-payer health-care system. Further research into this area is warranted.
No conflict of interest.

1492 POSTER

The landscape of medical oncology in Europe by 2020

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Background: The number of cancer patients is steadily increasing in most countries. In the US, there will be a shortage of medical oncologists (MO) by the year 2020. However, this information is not available in Europe. The aim of this study was to assess the current number of MO in the 27 European Union (27-EU) countries and to predict their availability by 2020.
Material and Methods: Between 06/2012 and 01/2013, a survey was submitted to health authorities or medical oncology societies in all 27-EU countries in order to gather data on the yearly number of MO since 2000. Contacts were made by e-mail, phone calls and research on official websites by two authors (EdA and MPr). Data regarding cancer incidence in 2008 and projections for 2015 and 2020 in all types of cancer for each country, were obtained through Globocan (http://globocan.iarc.fr). The mean annual increase in the number of MO was calculated for each country. The total number of MO by 2015 and 2020 was estimated as (MO in 2012)x(1+ (annual increase x 3)) and(MO in 2012)x(1+ (annual increase x 8)). A ratio of new cancer cases vs. number of MO was calculated for 2008, 2015 and 2020 in each country. A decrease in the ratio was considered a favourable evolution.
Results: Data from 11 countries were not obtained whereas 4 countries provided insufficient data. As a result, 12 countries were included in our analyses: Austria, Belgium, Bulgaria, Finland, France, Germany, Hungary, Italy, Netherlands, Portugal, Sweden and UK. The average mean annual increase in the total number of MO was 5.3% (range 1.8%-8.7%) with Belgium being the lowest and UK the highest. The 2008 ratio of cancer vs. MO was lowest in Hungary (113) and highest in UK (1067). With the exception of Belgium, which is estimated to show a similar ratio in 2015 and 2020 compared to 2008, a favourable decrease in this ratio was estimated in all other countries.
Conclusion: Though our estimates were based on incidence and not on prevalence, the results indicate that availability of MO will probably meet the projected need in most of the surveyed countries provided that (i) these countries maintain their rate of annual increase in MO, and (ii) no unforeseen changes in cancer incidence occur. Unfortunately, minimal information is available for Eastern Europe. Our data call for a prospective and standardised surveillance of cancer burden and MO availability to ensure adequate and equal care for cancer patients throughout Europe.
No conflict of interest.

Table 1 (abstract 1493). Descriptive statistics clinical information

	Hospitalized % (95% CI)	Cancer drug therapy % (95% CI)	Radiotherapy % (95% CI)	Cancer drug and/or radiotherapy % (95% CI)
All	68.5 (67.0–69.9)	14.5 (13.4–15.6)	7.7 (6.7–8.4)	20.3 (19.0–21.6)
Hospital supplementary insurance status				
None	63.0 (60.3–65.7)	11.0 (9.3–12.8)	6.5 (5.1–7.8)	16.3 (14.2–18.3)
Basic	69.3 (67.0–71.6)	13.2 (11.5–14.9)	7.6 (6.3–9.0)	19.3 (17.4–21.3)
Semi private and private (2 or single bed room)	73.6 (71.0–76.3)	20.5 (18.0–22.9)	8.7 (7.0–10.4)	26.3 (23.6–28.9)
Canton of residence				
BS/BL	74.1 (69.7–78.5)	13.2 (9.8–16.6)	8.5 (5.7–11.3)	20.1 (16.1–24.1)
TI	70.6 (67.7–73.6)	18.3 (15.8–20.7)	5.7 (4.2–7.2)	22.5 (19.8–25.2)
VS	58.4 (53.3–63.5)	8.5 (5.7–11.4)	5.8 (3.4–8.2)	13.2 (9.7–16.7)
ZH	68.3 (66.3–70.2)	14.1 (12.7–15.6)	8.5 (7.3–9.7)	20.6 (18.9–22.3)

1493 POSTER

Delivery of health care at the end of life in cancer patients from four Swiss cantons (SAKK 89/09)

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Background: Using claims databases, cancer registries and cancer patient records, it has been shown that the use of chemotherapy at the end of life has increased over time in the USA and European countries. Given a paucity of Swiss data, the objective of this study was to describe delivery of health care during the last month before death of cancer patients in terms of use of medical resources.
Material and Methods: In a retrospective cohort study claims data from a large health insurance company were linked with data from four cantonal cancer registries to identify patients with breast, colon, hematologic, lung, prostate and other cancers deceased in 2006 to 2008. Primary endpoints were hospitalization rates (acute hospitals), delivery of anti-cancer drugs (ACD) and/or of radiotherapy (RT). Multivariate logistic regression was used to assess associations between these endpoints and explanatory variables representing patient and geographic characteristics as well as supplementary hospital insurance (SHI) type.
Results: Of 3809 eligible cancer patients (Basel n = 378, Tessin n = 926, Valais n = 363, Zürich n = 2142) 2608 (68.5%) were hospitalized in their last month of life, 553 (14.5%) received ACD and 293 received RT (7.7%). Hospitalization and treatment frequencies strongly decreased with age. Patients with breast cancer and hematologic cancers had a significantly higher probability of receiving ACD (ORs 1.87, 95% CI 1.08–3.22 and 1.78, 95% CI 1.06–2.99, respectively, compared to lung cancer patients). ACD use was higher in patients with a semi private or private SHI (OR 1.83, 95% CI 1.40–2.38; reference: no SHI) or living in canton Tessin (OR 1.56, 95% CI 1.24–1.96; reference: canton Zürich). Hospitalization rate and receiving RT were also significantly associated with several patient and geographic characteristics and SHI type.
Conclusions: Hospitalization rate and cancer targeted therapies during the last month before death showed substantial variation unexplained by chance. Significant geographic and insurance status variations should be an issue for discussion within Swiss Oncology Centers and Oncologists. However, the interpretation of the data has to be cautious taking into account that there is no benchmark representing optimal treatment intensity.
No conflict of interest.

1494 POSTER

Improving cancer care in The Netherlands: Insight in hospital variation in quality of care leads to national actions

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Background: Quality of cancer care has become an important topic on a national as well as on an international level. The Signalling Committee Cancer of the Dutch Cancer Society commissioned a study to evaluate the quality of cancer care in The Netherlands and recommended strategies for improvement.
Material and Methods: A taskforce 'Quality of cancer care' comprising medical specialists from alle disciplines involved in the care for cancer patients was formed. An extensive review of the literature on infrastructure, volume and specialization on the one hand and outcome on the other was performed. In addition, a meta-analysis of the volume-outcome relationship for pancreatic, bladder, lung, colorectal and breast cancer resections was performed. Furthermore, variation in quality of cancer care between regions, groups of hospitals and individual hospitals in our country was investigated on data from the Netherlands Cancer Registry. For oesophageal and stomach cancer patterns of care and outcomes were compared at an international level with the United Kingdom, Sweden and Denmark. Also an overview of organisations and initiatives contributing to quality improvement in The Netherlands was made. The findings of the taskforce were published in a national report in 2010.
Results: In The Netherlands quality of care varies by hospital and region. These differences are not limited to surgical procedures and postoperative mortality, but are also demonstrated in other parts of the care process. Differences are only partly explained by differences in infrastructure, procedural volume and specialization between hospitals.
Importantly, the publication of the report and recommendations in 2010 has contributed significantly to quality improvement measures such as the development of national multidisciplinary quality standards for a wide range of cancer treatments, including minimal standards for hospital volume. Furthermore, outcome registries have been set up for a number of cancer treatments including surgery for colon, breast, lung and upper-GI cancers. The insight provided by these outcome registries has resulted in significant outcome improvements. Similarly, the minimal standards for hospital volume urged hospitals to either stop certain treatments or specialize in order to meet the volume requirements. The resulting concentration of care improved overall treatment outcome.
Conclusions: Giving insight into the actual quality of cancer care in the Netherlands has resulted in considerable awareness of the importance of quality improvement, underlined the need for action and endorsed the different stakeholders to team up and work on improving quality of cancer care in The Netherlands.
No conflict of interest.

1495 POSTER

Population-based evaluation of economic impact of trastuzumab prescription patterns in Piedmont, Italy

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Background: Health economic assessment based on cost-effectiveness analyses were only marginally used by decision makers. The main limitation of studies was their lack of budgetary impact in a real population setting. The main objective of the present study is to provide population based estimates of the treatment costs of HER2+ breast cancer patients in Piedmont that will help local decision makers for resource planning and health care management.
Methods: We estimated the number patients at early stage eligible for Trastuzumab treatment from the Piedmont Cancer Registry incidence data, while number of patients with metastatic breast cancer were estimated from prevalence data, using, as a proxy,those patients who were prone to fail in a mixture cure model. Treatment patterns (i.e. adjuvant, neoadjuvant or metastatic therapy, standard or shorter experimental protocol and average doses), disease stage and clinical characteristics were measured in five of the 24 breast reference centres (GIC) of Piedmont on a sample of 345 patients admitted in 2010 and 2011. From expenditure administrative data of the current and previous two years in Piedmont we measured costs by drug dose, associated cost and cost for other treatments. Model parameters and their distributions were then applied in a Bayesian empirical model for probabilistic sensitivity analysis (PSA) that allowed investigating the impact of different strategies and policies on total expenditures.
Results: Each year, in Piedmont about 685 women with a HER2+ breast cancer undergo chemo-treatment with Trastuzumab, mainly adjuvant or neoadjuvant (74%). Early stages represented about 28% of patients, while advanced stages and metastasis were 31%. 'Shorter' experimental protocol was administered in 16% cases, with an average 2223 mg of total dose: differences in the protocol adoption was found among the breast units. About 8% of patients suspended treatment because of toxicity. In Piedmont, total expenditure for Trastuzumab was about € 11.5 million in 2010.
Conclusions: Costs for HER2+ breast cancer was mostly influenced by the different adoption of treatment protocols. PSA showed that the duration of treatment, especially off-label prolongation of treatment in metastatic patients in the principal component of the increase in the total expenditure for Trastuzumab in a real setting using population-based data.
No conflict of interest.

1496 POSTER

A cost-minimization analysis of NCIC Clinical Trials Group LY.12: A phase III study of gemcitabine, dexamethasone, and cisplatin (GDP) compared to dexamethasone, cytarabine, and cisplatin (DHAP) for patients with relapsed or refractory aggressive histology non-Hodgkin's lymphoma

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Background: The NCIC CTG LY.12 study established that for patients with relapsed or refractory aggressive histology lymphoma prior to autologous stem cell transplantation (ASCT), the response rate with GDP (46%) was non-inferior to DHAP (45%). No important differences between these arms were detected for transplantation rate (OR=1.00), event-free (HR = 0.99) or overall (HR = 1.03) survival and GDP was associated with less toxicity (Crump et al. Blood 2012). We completed an economic evaluation from the Canadian societal perspective based directly on LY.12 trial data.
Material and Methods: The primary outcome of the study was a cost-minimization analysis comparing costs associated with GDP versus DHAP. Resource utilization data related to direct medical care, namely chemotherapy (including rituximab given for CD20+ disease), investigations, medications, hospitalizations, outpatient visits, home care visits, and emergency department care were derived from the Canadian subset of enrolled patients that proceeded to ASCT (n = 267). Direct medical costs and indirect costs (from a lost productivity questionnaire) were applied to the resource utilization data. The time horizon for the cost analysis included the time from randomization until the day before stem cell mobilization (or the last dose of salvage chemotherapy). Costs were descriptively presented in 2012 Canadian dollars ($1 CAD = 0.75 Euro) and were disaggregated to highlight the major cost drivers of care.
Results: Utilization data were collected from 267 Canadian patients (43% of the entire study population), 139 assigned to GDP and 128 assigned to DHAP. GDP therapy was associated with fewer total hospitalization days (680 vs. 1,658 days), hospitalization days for administration of chemotherapy (377 vs. 1,361 days), and hospitalization days for toxicity (120 vs. 267 days), compared to DHAP. The mean costs associated with GDP and DHAP-based therapy were $20,420 and $32,256, respectively, resulting in a cost savings associated with GDP of −$11,836 per patient (95% CI −$14,857 to −$8,890; p-value <0.0001). Mean chemotherapy and outpatient drug administration costs were similar for patients receiving GDP compared to DHAP ($12,237 vs. $11,161). However, mean hospitalization costs attributed to the GDP arm ($6,175) were significantly lower than those costs associated with the DHAP arm ($17,481; p < 0.0001). Patients who received GDP also incurred lower costs for transfusions ($285 versus $1,065; p < 0.0001) and concomitant medications ($1,622 versus $2,446; p < 0.0001) compared to DHAP patients. In the subset of patients (n = 211) with lost productivity and caregiver costs collected, no significant differences were detected between arms.
Conclusions: The LY.12 trial demonstrated that GDP was as efficacious as DHAP but provides these results at a much lower cost, predominantly due to lower hospitalization rates for inpatient chemotherapy administration and toxicity.
Conflict of interest: *Advisory board: Dr. Crump − membership on an advisory board for Roche Canada. Other substantive relationships: Dr. Meyer has received consultancy fees from Lilly Canada. The NCIC Clinical Trials Group has received research funding from Roche Canada and Lilly. Dr. Mittmann has received funding for provision of rituximab in patient care (Roche Canada).*

1497 POSTER

Budget impact analysis of a return-to-work intervention for cancer patients

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Background: Published literature shows that return-to-work interventions effectively support cancer survivors to resume work and potentially increase quality of life. However, return-to-work is currently not, or only partly (i.e. exercise test), reimbursed by health insurers. To ensure optimal support for cancer patients in resuming work, it is essential that hospitals can offer return-to-work in a financially viable way. The study 1) analyses the budget impact of a return-to-work intervention consisting of counselling by occupational physicians and a physical exercise programme; 2) explores how financing of a return-to-work intervention can be arranged.
Methods: A budget impact analysis was performed, comparing costs of return-to-work support for all patients able and willing to resume work versus no standardised support. All costs and financial benefits relevant from a societal perspective were considered, including intervention costs (based on the intervention protocol), productivity losses, social security, unemployment benefits, and patients' costs (based on literature data), and presented for a hypothetical hospital serving a population of 200,000 patients. We identified which stakeholders, including hospitals, employers, health insurances, social security, and patients accrue what costs; and which enjoy the financial benefits under different financing arrangements.
Results: Based on the return-to-work protocol, costs for the intervention are approx. €2,000 per patient. For a hypothetical hospital with 570 cancer patients a year of which 100 patients are eligible and willing to take part, this will result in yearly costs of €193,800. Physical exercise costs as part of the intervention, approx. €1,300 per patient, are in most cases covered by health insurance, leaving €67,800 to be financed by the hospital. Even small improvements in return-to-work and quality of life led to substantial reductions in productivity loss, need for social benefits, and future health care costs. These savings outweigh the costs of the intervention, rendering return-to-work cost-saving from a societal perspective. Several feasible options for distributing costs and benefits among stakeholders are identified.
Conclusion: From a societal perspective, return-to-work is expected to be cost-saving. Hospitals bear approx. €67,800 intervention costs annually (hypothetical hospital, assuming a population of 200,000 patients), while most financial benefits fall upon other stakeholders. Re-distributing costs and financial benefits among stakeholders would result in feasible financing of the intervention.
No conflict of interest.

1498 POSTER

Creating a platform for translational research in The Netherlands

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Background: In spite of an increased interest in translational research in The Netherlands, multiple roadblocks prevent smooth progression 'from bench to bedside'. The Dutch Cancer Society (DCS) has performed the project 'Translational Research' on behalf of the Dutch National Cancer Control Programme (2005–2010), a collaborative venture of the DCS, the Comprehensive Cancer Centres, the Ministry of Health, Welfare and Sports, the Dutch Federation of Cancer Patients' Organizations and the Dutch Association of Health and Social-Care insurance Companies. The project aims to facilitate translational research by identifying and overcoming hurdles in the translational process.
Objectives: To create a platform for translational research in The Netherlands.
Methods:
– Analysis of DCS research project files to register scientific discoveries with potential clinical application that were terminated during the development process.
– Analysis of roadblocks in 4 case-studies and exploration of solutions in practice.
– Analysis of the regulatory climate concerning cellular therapeutics and the execution of clinical studies.
Results: Various roadblocks in translational research were identified, including limited knowledge of the translation process, financial limitations, complex legislation and regulation, good manufacturing practice, patents and lack of small-scale production facilities. Especially for scientific findings that are not rapidly taken up by the pharmaceutical industry, suboptimal conditions for one or more of these factors stand in the way of obtaining proof-of-principle and further product development. The case-studies showed that roadblocks could be removed by the DCS with relatively small but highly specific tailor-made interventions and investments.
Conclusions: The project has shown that collaboration between research groups, the availability of shared knowledge, additional specifically targeted financial support and tailor-made guidance of research projects are important factors in promoting the translational process. At present, the infrastructure in The Netherlands is insufficiently equipped to offer these solutions on a structural basis. Based on the results of the this project, the DCS is currently innovating her activities regarding translational research.
No conflict of interest.

1499 POSTER

Multidisciplinary teams in cancer care: a systematic review of the evidence

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Background: Multidisciplinary teams (MDTs) are considered the best approach to organising care in a way that brings together all the medical specialists involved in cancer diagnosis and treatment, which has led to many cancer plans to incorporate MDTs. The aim of this study was assessing the impact of MDTs on physician practice patterns and patient outcomes in cancer care.
Material and Methods: We conducted a systematic review of the literature. Fifty-one papers were selected from the literature published from November 2005 to June 2012.
Results: MDTs have been shown to improve clinical and process outcomes in cancer-patient management, even though evidence of a causal relationship between this type of intervention and outcomes is still limited. A wide variation in the types of tumours studied has been reported, along with the fact that the scope of the MDTs' work extends to the entire process of care.
Conclusions: Different formats of MDT organisation were found, such as meetings, clinics and online conferences. These organisational patterns are nonetheless driven by the need to align the clinical dimension (effective access to multimodal treatments and palliative care) with the patient-management dimension (MDTs' working roles, and consistent communication between patient and team).
No conflict of interest.

1500 POSTER

Multidisciplinary oncology guidelines: Report of the ECCO guideline forum working group

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Background: Many European organizations are producing guidelines in the field of oncology. To improve European multidisciplinary oncology guideline development and stimulate cooperation among development groups, ECCO – the European CanCer Organisation organized a "Multidisciplinary Clinical Guidelines Forum Working Group" meeting to define quality criteria for the development group and quality measures to be recognized by ECCO as high quality multidisciplinary guidelines.
Methodology: Before the meeting, a questionnaire was sent to the different organizations belonging to ECCO and other organizations involved in cancer care. The questionnaire asked questions in relation to guideline development, specific procedures for guideline development; if multidisciplinary guidelines were produced; if they used specific templates and formats to publish guidelines; and how the quality of the guidelines was evaluated.
A meeting was organized in November 2012 with the aim to hear and learn about each others guideline development as well as to define quality criteria for ECCO-endorsed multidisciplinary guidelines and to define the role of ECCO in the guideline development and implementation process.
Results: *Quality criteria*: ECCO will endorse multidisciplinary guidelines if they fulfill the following quality criteria:
- Guidelines must be multidisciplinary and must involve representatives of the relevant disciplines.
- Validated methodologies must be used and must be explicit and transparent
- A conflict of interest policy must be in place and transparent
- Representatives of patient organizations must be involved.

Role of ECCO: It was concluded that ECCO will not develop clinical practice guidelines but will act as follows:
- ECCO will serve as a switchboard for its members and other European societies to inform each other of the development of new multidisciplinary cancer clinical guidelines so that all interested societies can be involved. This functionality is offered to ECCO members and other European societies as a way to facilitate collaboration between relevant disciplines and develop multidisciplinary guidelines. This will help avoiding redundancies.
- Upon submission by the development group, ECCO will review and endorse multidisciplinary guidelines that fulfill the quality criteria.
- ECCO will disseminate the European multidisciplinary guidelines that have been endorsed. ECCO will create a dedicated webpage for the dissemination and promotion of endorsed guidelines (with links).
- ECCO will represent the voice of oncology on European oncology guidelines at the EU policy level.

Conclusion: Oncology is a multidisciplinary discipline and this should be reflected in multidisciplinary guideline development. In future, ECCO will serve as a switch board for multidisciplinary oncology guidelines and will promote European oncology guidelines fulfilling the ECCO quality criteria.
No conflict of interest.

1501 POSTER

Homecare utilization and costs in stage IV lung cancer: a Canadian public payer experience

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Background: Lung cancer is a leading cause of morbidity and mortality. Individuals may require homecare at some point during the management of their disease. There is limited information on the type, quantity and cost of homecare services in lung cancer. The objective was to determine the utilization and costs of homecare services for a population of individuals with Stage IV lung cancer.
Methods: New cases of Stage IV lung cancer were extracted from a provincial cancer registry (Ontario Cancer Registry, 2005–2009) and linked to the homecare services administrative datasets from the health system payer perspective. The type and proportions of homecare services used were determined by phase of disease (initial⩾6 months after diagnosis;

terminal⩽6 months prior to death; continuation=terminal minus initial). Homecare utilization and costs for cases were determined ($CAN 2012, $1 CAD = 0.75 Euro).
Results: There were 18,187 cases of lung cancer in the cohort. 11,929 were staged. 6,115 (51.3%) were Stage IV lung cancer cases. 75.5% of the Stage IV cases used homecare. Of those using homecare services, there were 66.3 homecare visits per person per annum. The mean cost per person per annum was $6,076. There were 243,236 homecare visits in the cohort, 57.3% of which were nursing visits and 32.8% were homemaking and personal support care visits. There were 5,255 Stage IV cases in the terminal care phase (⩽6 months prior to death), of which 75.8% used homecare services. The mean (95% CI; median) number of homecare visits per 30-day period was 7.7 (7.4−8.0; 4). The homecare cost per 30 days was $798 ($766-$830; $472).
Conclusion: End of life lung cancer patients utilized a number of homecare services resulting in high 30 day and annual costs. Attributable costs and costs for other stages of the disease will be determined.
No conflict of interest.

1502 POSTER

Survival modeling in UK oncology technology appraisals since the publication of good practice guidelines

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Background: To assess the methods used, their implications and the effect of the 2011 guidance published by the National Institute of Health and Care Excellence (NICE) Decision Support Unit (DSU) in the extrapolation of overall survival in oncology in the UK.
Materials and Methods: Though overall survival is one of the most important outcomes used in the assessment of clinical effectiveness and cost-effectiveness in oncology for reimbursement decisions, its evaluation is rarely straightforward with the different methods leading to different conclusions. Although according to NICE methodological guidelines, a lifetime horizon if survival benefit is expected, in oncology, overall survival data from clinical trials are often incomplete (i.e. at the time of trial not all patients experience an event). Thus long term projection of data is required. Although this can have a significant impact, the evidence used prior 2011 was often not fully explored, leading to a DSU guidance.
To assess the currently used methods and the effect of the guidance, a review of oncology technology appraisals published after June 2011 was carried out. A data extraction table was designed to capture the main aspects of the disease and patient population; the technologies assessed and methods used for the extrapolation. The latter included the use of parametric modeling, distributions tested, the basis for final selection including tests for goodness of fit, including graphical and statistical tests; assessment of clinical face validity of findings and external validation. Data was assessed qualitatively and compared to a review conducted prior the guidance.
Results: 21 oncology assessments were identified, including 19 single technology appraisals and two multiple technology assessments (MTAs) covering 6 treatments. While the majority of the assessment incorporated some form of parametric modeling and extrapolation of survival data, the implementation of the full set of recommended steps for the extrapolation were rare. Although the proportion of studies testing all commonly used survival models for fit to the data increased, the majority of them depended mainly of the statistical goodness of fit criteria and testing for clinical face validity and external validation remained rare.
Conclusions: Since the publication of methods guidelines on survival extrapolation, the quality of extrapolations have improved within the oncology technology appraisals in the UK, contributing to more transparent decisions-making. However treating the extrapolation of OS as a statistical exercise without appropriate clinical and external validation requires further improvement.
No conflict of interest.

1503 POSTER

Survival and lifetime costs associated with first-line bevacizumab in older patients with metastatic colorectal cancer

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Background: The relative costs and benefits of newer agents such as bevacizumab (Bev) in older patients with metastatic colorectal cancer (mCRC) are not well understood. The objective of this study was to investigate clinical effectiveness and incremental lifetime costs associated with first-line bevacizumab in older mCRC treated in community settings, from the United States government healthcare payer (Medicare) perspective.
Material and Methods: Patients diagnosed with mCRC in 2004–2007 were identified from SEER-Medicare, a database which links Medicare claims with a population-based cancer registry representing ~25% of the United States population (SEER). Patients were stratified by first-line treatment strategy (no chemotherapy (CTx), CTx alone, CTx + Bev). Median and mean survival times were determined for each cohort by Kaplan–Meier method. A Cox proportional hazards model was used to determine the relative benefit of Bev, controlling for important demographic and treatment characteristics. Mean lifetime costs were calculated for each cohort using Medicare claims for all services rendered between diagnosis and end of follow up, adjusting for death and censoring.
Results: 4,414 patients (mean age 77.3) were identified, of whom 15% received first-line Bev. Mean duration of first-line Bev was 6.9 months. Receipt of CTx + Bev was associated with an improved survival compared with CTx alone in the Cox model (HR 0.80, 95% 0.71–0.89). Median and mean survival were greatest in patients treated with CTx + Bev relative to CTx alone or no CTx (19.4 (28.0) vs. 15.1 (22.9) vs. 5.7 (14.1) months, $p < 0.001$). Mean lifetime costs were also greatest in the CTx + Bev group compared with CTx or no CTx (mean per patient cost $143,284, $111,280, and $55,504 respectively). Compared with CTx alone, CTx + Bev was associated with a 5.1 month increase in mean survival and $32,004 increase in mean lifetime treatment costs; the relative cost of Bev treatment was $75,303 per life year gained.
Conclusions: The relative benefit of Bev in older Medicare enrollees treated in real world clinical settings in the United States is comparable to the benefit observed in randomized clinical trials but is associated with an incremental cost of $75,303 per life year gained.
Conflict of interest: *Ownership: Elaine Yu has stock ownership in Roche. Corporate-sponsored research: Veena Shankaran, David Mummy, Lisel Koepl, Dana Mirick and Scott Ramsey all received research funding from Genentech, Inc. Other substantive relationships: Robert Morlock is a health economist employed by Genentech, Inc. and Elaine Yu is associated director of the health outcomes program at Genentech, Inc.*

1504 POSTER

Measuring process quality in oncology practices in Germany

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Background: In 2013, WINHO started its first collection of data for process quality indicators in oncology practices. The WINHO indicators − altogether 46 quality measures − were developed as a tool for self-monitoring, for benchmarking and to enhance quality reporting in the context of outpatient care in medical oncology. In Germany, this is the first analysis of process quality indicators in office-based oncology. While the indicators were developed with regards to treatment processes within oncology practices, they could also be applied in a clinical setting. This presentation provides results from the first two rounds of data collection.
Material and Methods: In the first round of data collection, six quality indicators were examined that address basic documentation (i.e. anamnesis), tumour boards and planning of chemo therapy for breast cancer patients. Information was collected via an online questionnaire from nearly 1900 patient records in 20 oncology practices. The second round of data collection takes place in the second quarter of 2013 and includes 15 indicators that cover basic documentation, therapy planning and psycho-social wellbeing. Further office-based haematologists and oncologists registered for participation in this round.
Results: The results indicate thus far high levels of compliance with regards to indicators of basic documentation. For example, tumour specific anamnesis was documented in 99% of the analysed patient records within the first two doctor's visits, pre-existing illnesses and comorbidities in 85% of the cases. Data for quality indicators for basic documentation could often be collected faster than information about therapy planning. In addition, the results for the indicators for therapy planning are more diverse among the office-based cancer specialists.
Conclusions: This pilot study proves the feasibility of applying process quality indicators in oncology practices and examines differences between office-based haematologists and oncologists in Germany. First results indicate some variance among oncology practices and point to areas where outpatient cancer care could be improved. However, data extraction from patient records is time-consuming as much information is saved in continuous text. In order to use the rich information documented by office-based cancer specialists for the purpose of quality assurance, IT systems in

oncology practices should be optimised to allow more data to be retrieved electronically.
No conflict of interest.

1505 POSTER

Motivations and perceived added value of European cancer centers from participating in an accreditation programme

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Background: The study aimed to understand the motivations, benefits & added value of the OECI (Organization of European Cancer Institutes) accreditation & designation programme as perceived by stakeholders from cancer centres. This can help understand the immediate effects of the accreditation programme & how it might be improved.
Material and Methods: Semi-structured individual interviews of 30 stakeholders: basic research, management, clinicians & nursing from 9 European cancer centres, categorized according to the participating stage: self-assessment, final reporting & accredited for at least one year. Thematic analysis & adapted grounded theory were used for data analysis.
Results: Similarities in the motivation & perceived benefits of cancer centers exist irrespective of accreditation stage e.g. benchmarking against other European Centres judged by a common European standard, becoming a renowned European/International Centre, attracting new opportunities for collaboration/funding; continuous quality improvement in research, education & care. In the 'self-assessment' phase, implementing quality standards & data-integration were important. In the final reporting & accredited stages, achieved benefits were: stimulating critical thinking based on issues identified by peer reviewers; clearer organizational structure & clarification of staff roles; funded collaborative opportunities with research teams both within and outside the centre. Added value from accreditation is achieved in expected (e.g. better communication between researchers & clinicians within/outside the Centre) & unexpected ways (e.g. staff from different disciplines participating in quality improvement programmes despite initial doubts; interest of the Centre to participate in other accreditation programs). For some basic researchers the benefits of accreditation were hard to define. They are seen as mainly issues for managers & clinicians as comprehensiveness is seen as focussing more on the coherence of translational research rather than its individual content.
Conclusion: Participation in accreditation seems to deliver real benefits e.g. better funding opportunities, data integration, standard implementation, multi-disciplinary teams reconstitution, staff engagement etc. But, it is hard to confirm if these are solely attributable to the accreditation programme. Further longitudinal research on the effects of accreditation programmes especially on patient benefits is needed.
No conflict of interest.

1506 POSTER

Oral vinorelbine (NVBo) plus cisplatin (CDDP) versus pemetrexed (PEM) plus CDDP followed by maintenance with single agent NVBo or PEM as first-line treatment of patients (pts) with advanced non-squamous non small cell lung cancer (NS-NSCLC): A cost minimization analysis from the Italian National Health System (NHS) perspective

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Background: Vinorelbine and CDDP are a standard treatment in NSCLC; NVBo is registered in 45 countries. PEM plus CDDP is recommended in front-line chemotherapy of NS-NSCLC. An economic evaluation of NVBo/CDDP versus PEM/CDDP was implemented in NS-NSCLC pts adopting specific costs and clinical settings reflecting the Italian practice.
Materials and Methods: A cost minimisation analysis was conducted from the perspective of the Italian NHS, based on a randomised phase II study in NS-NSCLC (NAVoTRIAL01), randomizing 100 NVBo/CDDP pts (arm A) and 51 PEM/CDDP pts (arm B). Overall, Arm A/Arm B reported respectively: Disease Control Rate including combination (4 cycles) and maintenance periods (%) of 75.0/76.5, and median Progression-Free or Overall Survival of 4.2/4.3 or 10.2/10.8 months.
Costs considered in the analysis were for Anti-Cancer drugs (AC), administration settings (AS, i.e. out-patient/in-patient/at home), and serious adverse events (SAE, defined as involving hospitalization and suspected to be due to AC).
Unit costs used for AC were official ex-factory prices, with further percent deductions enforced by law. The distribution of AS was re-modelled according to the respective frequencies found for the subset of Italian pts participating in NAVoTRIAL01; for out/in-pt settings, DRG and other tariffs (day-hospital or one day admission) were used (no cost was charged when administration was at home). Hospitalization costs were assessed for SAE on the basis of appropriate DRG tariffs.
Results: See the table.

	Average cost per patient (€)		
	Arm A	Arm B	A − B
AC	1,763	13,615	−11,852
AS	1,703	344	1,359
SAE	611	569	42
Total	4,077	14,528	−10,451

In detail, the cost for AC in arm A was € 572 in the four-cycle combination period and € 1,191 in the maintenance period; the analogous cost in arm B was € 6,738 and € 6,877 respectively.
Conclusions: Given the reported efficacy outcomes with both regimens, NVBo/CDDP followed by maintenance with NVBo provides substantial savings (€ 10,451 per patient on average), appearing a cost-effective treatment option in advanced NS-NSCLC. Such results should be confirmed by a phase III trial.
No conflict of interest.

1507 POSTER

Developing patient reported outcome measures (PROM) for implementation in the Swedish National Breast Cancer Quality Register

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Background: The local authorities for health and welfare support the introduction of Patient Reported Outcome Measures (PROM) in the quality registers in Sweden. Valid and reliable instruments measuring PROM do not exist that could be used throughout the whole breast cancer process. We sought to develop and implement PROM for breast cancer at different stages in the disease course in different Swedish geographic regions for later use in the Swedish National Quality Register for breast cancer.
The aim was to develop appropriate PROM to assess symptoms and problems among patients with breast cancer about one year after diagnosis.
Materials and Methods: A scoping review and focus group discussions were conducted with women invited by the breast cancer association Amazona (Stockholm). The symptoms that emerged from the scoping review and focus group discussions formed the basis for the development of a web based questionnaire consisting of validated instruments (EORTC QLQ-C30, BR 23, MSAS) for measuring PROM. The women who participated in the focus group discussions were invited to respond to a pilot version of the web based questionnaire. The results were used to revise the web based questionnaire. An invitation was sent to a national random sample from the Swedish National Breast Cancer Quality Register diagnosed one year earlier to respond to the revised version of the web based questionnaire.
Results: The results will present the work process of the development of the PROM as well as plans for further work on the implementation of the PROM in the Swedish National Quality Register for breast cancer. Preliminary data shows that about 70% responded to the revised version of the web based questionnaire. However, some women requested a paper version of the questionnaire mostly because they did not have access to a computer.
Conclusion: In the development of PROM in quality registers it is important to include patients experiences in order to develop relevant outcome measures to influence the quality of the health care delivery.
No conflict of interest.

1508 POSTER

The Belgian cancer plan: A balanced governmental support of comprehensive cancer care

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The Belgian cancer plan was launched on 10/03/2008 by the Minister of Social Affairs and Public Health to improve the fight against cancer in Belgium. It is a long-term plan covering all aspects of the fight against the disease and integrates the support of both physicians and patients and their families. The Belgian government policy was already focused on cancer issues by implementing standards in 2003 that specify the legal requirements of basic cancer care and an oncological care programme. In 2007, the White Paper 'Action against cancer in Belgium: Facing up to the challenges of tomorrow' was published. This document was prepared by a work group consisting of Belgian specialists in oncology and haematology and listed recommendations for improving cancer treatment.
Belgium being a federal country wherein health care is the shared responsibility of the Federal State and the communities/regions opted for an intense consultation with all stakeholders prior to launching the cancer plan. For this, the Minister of Social Affairs and Public Health organized round-table discussions with a variety of stakeholders. A range of priorities was identified as a result of these round-table discussions with experts.
The Belgian cancer plan contains to date 32 actions in 3 domains: 1º) prevention and screening, 2º) care and treatment, and 3º) innovation and research. A specific budget was allocated to each action of the cancer plan and responsibilities for implementation were clearly defined. A regular evaluation of the progress and results of the plan is made by the Belgian Cancer Centre. A first evaluation report was prepared in 2012. Here, we report the main steps in the development of the Belgian cancer plan and describe the first results of its implementation.
No conflict of interest.

1509 POSTER

Quality of the end of life − utility values in advanced solid tumors in technology appraisals in the UK

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Background: To assess the utility values used in advanced solid tumours in technology appraisals conducted by the National Institute of Health and Care Excellence (NICE) in the UK and to compare them to those of the general population.
Materials and Methods: Through the use of quality-adjusted life-years (QALYs) the importance of quality of life, established using generic instruments resulting in utility values, increased and it became the center of various studies and debates in advanced oncology. The debate eventually led to a differential treatment of technologies aiming to extend life in the last two years by NICE, by placing a higher utility value at the end of life. However issues concerning the magnitude of cancer patients' utilities pre- and post-progression still surface in many appraisals: the measured utility values are often considered high. To assess the magnitude of the issue a literature review of advanced oncology technology appraisals published in the last two years was carried out. A data extraction table was designed to capture the main aspects of the disease and patient population; the technologies assessed; the methods used for the elicitation of utilities, and the values and their evaluation by NICE. Data were assessed both qualitatively and quantitatively.
Results: Thirteen oncology assessments were identified in advanced solid tumours, including 11 single technology appraisals and two multiple technology assessments (MTAs). Four assessments did not report final utility data. The mean utility was 0.77 (standard deviation (SD): 0.056, range: 0.66–0.88) and 0.57 (SD: 0.103, range: 0.47–0.76) for pre- and post-progression respectively. Among the pre-progression utilities 46% was equivalent to the general UK population aged 75 or more, 15% to population 65−74, 30% to 55−64, and 8% to 45−54. EQ-5D, as requested by NICE was the main method of elicitation in 5 assessments, and standard gamble based on the general population was still more common (6 assessments).
Conclusions: The assessment of utilities in advanced oncology indications is although crucial in terms of cost-effectiveness, is in many cases not give emphasis in the design of the phase II clinical trials. Methods of elicitation often does not conform to the NICE reference case and the values reported are very close to those of the general population raising concerns in individual cases indicating the need for additional research and guadance.
No conflict of interest.

1510 POSTER

Obstacles to delivering optimal care for early breast cancer in Croatia

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Introduction: Unlike decreasing trends in breast cancer (BC) mortality in other high income countries, mortality in Croatia (CRO) is not declining. We conducted a web-based survey among Croatian oncologists to better understand current patterns of care and to identify key obstacles to delivering optimal management.
Methods: A web-based survey was sent from the MGH-AVON International Breast Cancer Center in Boston to 121 members of the Croatian Oncology Society. The survey covered questions on demographics, availability of BC resources and patterns of clinical care. Survey data were anonymised and collected using our Red Cap on-line survey tool. To describe the results we calculated frequencies, percentages and/or mean values for each response on our questionnaire.
Results: 28 of 121 participants responded (23.1%). 75% of respondents practice in public hospitals or academic medical centers, representing a cross-section of oncologists providing cancer care in CRO. Results show 68% of newly diagnosed BC patients present with stage I, II disease and 22% and 10% with stage III or IV respectively. Surgically, 66% are treated by lumpectomy, 22% by mastectomy without reconstruction and 12% by mastectomy with breast reconstruction (12 %). In the absence of palpable lymph nodes 25% undergo sentinel lymph node biopsy while 75% do not. All physicians report having tumour ER, PR and Her2/neu results reported within routine pathology reports. More than 60% of high risk, ER+ patients receive anthracycline/non-taxane regimens due to limited availability of taxanes in CRO. Both tamoxifen and AI's are generally available for ER+ pts. The average wait time for radiotherapy for the majority of patients is longer than 6 weeks (34.3% 6−12 weeks, 25% >12 weeks). 42% of respondents report that they deliver sub-optimal therapy to their patients mainly due to restrictions in available chemotherapies and radiation therapy. Detailed results on adjuvant treatment patterns will be presented.
Conclusions: Despite stage at presentation of BC in CRO being comparable to Western Europe, it is worrisome that mortality rates are not declining comparably. Restrictions in prescribing taxane − containing regimens and long waiting lists for radiation therapy were identified as major obstacles for providing optimal care. These issues require further analysis and action to help improve outcomes of patients with BC in CRO.
Conflict of interest: *Other substantive relationships: Goss PE: speakers honoraria for Novartis and GSK in the past 3 years*

1511 POSTER

Diagnostic efficacy of the two week wait referral system for suspected head and neck cancer in the United Kingdom

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Background: The two week wait referral system was introduced by the UK Department of Health in 2000 to help general practitioners identify and urgently refer patients with suspected head and neck cancer. The effectiveness of these guidelines, consisting of 8 symptoms and signs warranting urgent referral, has only been assessed in a few small studies.
Material and Methods: We retrospectively analysed the medical records of 50 patients referred to our department via the 2 week wait pathway from January − December 2012 and collected data on investigations, diagnoses and management plans. We further looked at all head and neck cancer diagnoses between October − December 2012 and identified method of referral for each patient. We made comparisons between stage of cancer for patients referred urgently and those referred routinely.
Results: 98% (49 cases) of patients referred urgently were seen by an otolaryngology specialist within the expected 2 week target wait. The average wait to be seen was 9.8 days. The commonest referral reason was for persistent hoarseness (22%) and unresolving neck mass (22%). 26% (13 cases) of urgent referrals did not meet the referral criteria and of these the most common referral reason was persistent epistaxis (10%). 6 cases of head and neck cancer were identified in 2 week wait referrals equating to a 12% yield. An additional 10 cases of head and neck cancer were identified via routine referral for the corresponding time period. There was

no significant difference in stage of cancer between 2 week wait referrals and routine referrals (Mann Whitney, $p < 0.05$).
Conclusion: Significant numbers of patients with head and neck cancer are being diagnosed via routine referral, whilst those diagnosed via the 2 week wait pathway are not being identified at an earlier stage of disease. Further audit and research is needed to improve the referral criteria and develop a more efficient system.
No conflict of interest.

1512 POSTER

Measuring the financial burden on cancer patients: A randomised study

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Background: It is increasingly recognised that cancer and its treatment incurs notable expense to patients, however there is little evidence guiding best methods for the collection of data on patient out-of-pocket expenses. This study compared patient-reported expenses recorded using a recall-questionnaire with those recorded using a daily diary.
Material and Methods: After gaining ethical approval, patients with a diagnosis of cancer were recruited during attendance for chemotherapy or radiotherapy at a single UK Cancer Centre. Consenting patients completed a baseline questionnaire assessing quality of life (EuroQoL EQ-5D) and out-of-pocket healthcare-related expenses (covering seven financial domains) incurred during the preceding month. Patients were then randomised to Arm A: a single repeat questionnaire after 28 days, or Arm B: a daily diary of similar format for 28 days. The primary endpoint was the proportion of questionnaire/diary returns after 28 days (Chi squared test).
Results: In total, 93 patients were recruited. After 28 days, 48% of questionnaires (Arm A) were returned compared with 59% of diaries There was no statistically significant difference in return rates ($p = 0.49$). Mean per-patient expenses over the 28 days were £289 and £290 for Arms A and B respectively. Increasing age, male sex and treatment with radiotherapy were associated with higher expenses.
Conclusions: In this study there is no evidence of a difference in data return when using diaries or questionnaires. Given the relative ease for patients completing a single questionnaire compared to a daily diary, this may be the preferred method.
No conflict of interest.

1513 POSTER

How expensive is a gene signature test for patients with cancer of unknown primary origin (CUP)? An audit of the referral pathway for CUP Multidisciplinary Team

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Background: Specialised multidisciplinary teams (MDT) for the CUP are a new establishment in the UK. They aim to facilitate the process of referral and improve the time interval from symptom to treatment, which is universally long for CUP patients. The CUP MDT at Musgrove Park Hospital (MPH) started in March 2012. We audited the referral process to explore the time needed for CUP patients from the onset of symptoms to first investigation through to the MDT meeting; and the number and type of investigations these patients went through.
Method: All patients referred to the CUP MDT at MPH over one year were included. We retrieved information from the online pathology database, clinic and referral letters and scan requests and results. For each patient we recorded the date of first symptom, number of blood tests and imaging investigations after the onset of symptoms, date and number of biopsies, number of immunohistochemical markers (IHC) tested, number of other tests performed including endoscopies, the MDT discussions and the overall outcome.
Results: A total of 35 patients were included in the audit, 14 males and 21 females. The median age was 70 years (range 47−91 years). The median number of imaging tests was 5 (range 1−20). The time between the first symptom and the first imaging investigation was 24.35 days (range 0–629 days). The average referral process time, from symptom onset to first CUP MDT discussion, was 58.80 days (range 4–770 days). Of the 35 patients, 21/35 had a referral process of greater than 28 days and 6/35 greater than 100 days. Seven patients had endoscopies and 3/7 had more than 1 endoscopic procedure. Twenty seven patients had a biopsy and for 14/27 it led to a definitive diagnosis, with 11/27 patients having more than 1 biopsy. Three patients' histology samples were sent away for genetic testing. The number of IHC markers tested ranged from 0 to 20 per patient.
Conclusion: The investigation and management of CUP is empirical and the delay in diagnosis is still present. Patients can be faced with a long period of multiple investigations to identify the primary source prior to referring to the CUP MDT. There is a need to identify an alternative way of diagnosing these patients. The gene signature tests available, although validated in literature are not currently funded outside a clinical trial. This audit proves that their cost may be comparable to the actual investigation process. The impact in the patient's life expectancy is invaluable.
No conflict of interest.

1514 POSTER

Growing workload for Dutch medical oncologists caused by increased prescription of systemic therapies

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Background: The burden of cancer is rising in the Netherlands as a result of ageing and growth of the population. Concerns are increasing that the number of medical oncologists is insufficient to meet the rising demand. Therefore, the aim of this Dutch population-based study is to evaluate trends in systemic treatment of newly diagnosed cancer patients and illustrate the workload of Dutch medical oncologists.
Material and Methods: All patients with newly diagnosed cancer between 1990 and 2010 were included. To illustrate the workload of medical oncologists, the number of patients receiving systemic treatment within the first six months after diagnosis was calculated. Systemic treatment included chemotherapy and targeted therapy; hormonal therapy was not taken into account.
Results: The number of newly diagnosed cancer patients increased in the southern Netherlands from 8.000 in 1990 to 17.500 in 2010. The rate of prescription of systemic therapy for these patients doubled from 12% to 24% in the above-mentioned period. Consequently, a four fold increase in the absolute number of systemic treated patients was seen. The increased rate of prescriptions was especially large for patients with breast cancer, gastrointestinal cancer and lung cancer. In contrast, the rate of prescriptions decreased in patients with hematologic or gynecologic malignancies. Especially for patients with metastatic disease the administration of systemic therapy increased, from 17% of the newly diagnosed patients with metastatic cancer receiving chemotherapy in 1990, to 45% in 2010. With an increase from 42% to 61%, the increase in percentages of systemically treated was most marked for patients with metastatic colorectal cancer. The percentage of patients with non-metastatic forms of cancer receiving (neo) adjuvant treatment increased from 8% to 17%. The increase was most pronounced among patients with non-metastatic breast cancer, from 12% in 1990 to 41% in 2010. After introduction of targeted therapies around the year 2000, the prescription rates increased rapidly. Nowadays, 23% of the systemically treated patients receives a targeted agent.
Conclusion: The workload of Dutch medical oncologists increased drastically the last two decades. As ageing of the Dutch population will endure, concerns are growing that the number of future medical oncologists is insufficient to meet the future demands. An estimated 70 FTE medical oncologists will be extra needed by 2020 in the Netherlands.
No conflict of interest.

1515 POSTER

Cancer patients and mass media

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Background: Nowadays cancer patients tend to be more involved in medical decision process. Active participation improves health outcomes and patient satisfaction. To participate effectively patients require huge amount of information, but time limits make it impossible to satisfy all of information needs at clinics. We explored which kind of media and how often cancer patients use them in information seeking process. We also tried to evaluate how popular is Internet to reach medical information among cancer patients.
Materials and Methods: In this research we invited cancer patients, who had regular clinic examinations at Oncology Institute during 21st and 25th May in 2012 to answer to the anonymous questionnaires. Questionnaire contained questions about which media and how often did

cancer patients use them for disease related information. We analyzed results with descriptive statistics, χ^2-test and t- test.
Results: Patients returned 478 of 919 questionnaires distributed. Mean age was 59.9 (20−88) years. 61% of responders were female, and most common was high school education (33 %). Most common was breast cancer (33 %), followed by gastrointestinal and lung cancer. Television was the most used media for information seeking (84.1% of patients) followed by specialized brochures (78%) and Internet (70.8%). 67.6% of patients searched for disease related information in newspapers, 66.8% in specialized health magazines and 57.5% on radio. Patients most often searched for information regarding treatment options and alternative therapies. Patients who use Internet, most often looked for information on health related sites (60.5%), sites regarding alternative medicine (59.2%) and sites of newspapers and televisions (58.8%). 23.2% of patients responded they do not use media for disease related questions and as reason they specified that this was mainly because they get necessary information from their doctors. Patients who do not use media are older compared to all responders (62.5 mean age, $p < 0.001$).
Conclusions: According to our results, television, printed brochures and Internet are the most used media for information seeking by cancer patients. Information about treatment options is most often needed. Elderly patients search for information less often so they need to get as many as possible information at clinics.
No conflict of interest.

1516 POSTER

Coordination of the outpatient oncology care in Germany

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Background: Continuity of care is a core value in modern medicine. Coordination in cancer care becomes increasingly important. Because of the complexity of the disease and the specialization of different care providers, it is necessary to ensure the flow of information between physicians. Coordination problems are easily sensed by patients and can therefore be used as a patient related quality measure. In addition to coordination, the survey addressed other issues of the long-term care.
Methods: The study based on Part 4 of the NCQ − questionnaire by Uijen et al. 'coordination of care'. In addition, we examined quality aspects of pratices, supportive care, doctor-patient communication, the level of stress and socio-demographic data of patients. All physicians in the WINHO network (more than 400) were invited to participate in the survey. The survey was conducted in-house with a paper-based questionnaire and the data were analyzed by using SPSS.
Results: A total of 35 oncology pratices, 73 doctors and 3411 patients participated in the survey (response rate 78%). The patients were on average treated 3 years and 4 months. 76% of the patients with a solid tumor who were referred to an office-based oncologist by a certified centre (n = 769) strongly agree/agree that the care providers pass on information to each other very well. Further 65% strongly agree/agree that the care providers always know very well what the other care providers have done. With concern to the course of treatment, 41% of patients reported that their case had been presented to a tumor board meeting. 30% have participated in an rehabilitation programm.
Conclusions: The results show the importance of continuity and some coordination issues in the course of care. With an average of more than 3 years of treatment, many cancer patients experience treatment as a long-time partnership with a single oncologist. The data show that these patients overly perceive a very good coordination of care. The results need to be analysed with regard to comparable studies and the oncologist's role.
No conflict of interest.

1517 POSTER

Tailoring treatment based on risk of relapse in advanced laryngeal squamous cell carcinoma

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Background: The aim of this study was to quantify potential health gain and cost consequences by comparing concurrent administration of chemotherapy and radiotherapy (RT) with RT alone in the treatment paradigm of laryngeal squamous cell cancer patients with high-risk of developing relapse.
Materials and Methods: A Markov model was designed for patients with stage III/IV cancer of the supraglottic or glottic larynx, curable with surgery and post-operative RT. Model inputs were derived from the long-term published results of the Radiation Therapy Oncology Group (RTOG) 91−11 trial (Forastiere et al., 2013), literature and publicly available sources. The compared model treatment strategies were concurrent cisplatin/RT and RT alone. Effectiveness measures were locoregional control (LRC), defined as absence of persistent or recurrent disease, and preservation of larynx (LP). The perspective of the Dutch healthcare sector was used. Costs were expressed in 2012 euros. A time horizon of ten years with discounting was applied. Incremental cost-effectiveness ratios (ICERs) were calculated. Sensitivity analyses were performed.
Results: For the LRC end-point of our study, concurrent cisplatin/RT group yielded cost-savings compared with RT alone; in the range of €594-€2,479 per patient. Discounted cost-savings were €465–2,224. The improvement in effects of the concurrent cisplatin/RT group was 1.35 (1.24 discounted) per rate of absence of recurrent disease. For the LP end-point of the study, base-case and discounted results were comparable. The calculated ICERs were dominant and in favor of the concurrent cisplatin/RT group. Sensitivity analyses confirmed the robustness of these findings. The most influential variable was the proportion of patients that underwent salvage surgery. Probability of patients eligible for concurrent cisplatin/RT and management of recurrent disease were other key components which affected per group differences.
Conclusion: Treatment of stage III/IV laryngeal squamous cell cancer patients with concurrent cisplatin/RT is not only clinically favorable but also cost-saving for maintaining LRC and preserving function at the primary site. Intensity-modulated radiation therapy techniques and novel imaging tools for staging and assessment of response would likely improve both therapeutic and cost-effectiveness ratios in future studies.
No conflict of interest.

1518 POSTER

Combining 18F-FDG PET/CT and MRI in monitoring neoadjuvant chemotherapy in breast cancer: Scenarios and decision modeling to inform development decisions in an early stage

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Background: Neoadjuvant chemotherapy (NACT) reduces tumor volume before surgery. Scientists are developing monitoring techniques to assess its potential clinical impact. Early health technology assessment (HTA) can support the translation of these technologies to the clinic by providing data on its expected clinical, economic and other impact, from the first development stages. Objectives of this study are to 1) Combine scenario drafting and decision modeling to describe development and adoption scenarios for FDG-PET/CT and MRI in monitoring NACT in breast cancer, and 2) Identify the scenario with the highest expected cost-effectiveness.
Methods: A basic scenario and several 'what-if scenarios' were drafted with principal investigators and breast cancer experts, based on the technology's expected accuracy, competing technologies, regulatory issues and user satisfaction. The likelihood of each scenario was estimated and the most likely scenarios were quantitatively incorporated in a health-economic model. The expected Incremental Cost-Effectiveness of each scenario was estimated.
Results: The basic scenario described increased adoption of FDG-PET/CT+MRI in the hormone positive group. This was influenced by the likelihood of FDG-PET/CT+MRI being more accurate than MRI in 2014 (75%). The resulting ICER of € 111968/quality-adjusted-life-year (QALY)) indicates that PET/CT-MRI is not yet cost-effective compared to MRI alone. Accuracy changes were also the main drivers for the 'what if scenario' of: 'differential adoption in breast cancer subtypes'. The likelihoods of a higher accuracy of FDG-PET/CT − MRI vs MRI of 25% in the HER2 amplified and 50% triple-negative led to ICERs of €11865/QALY and €80560/QALY respectively. Accuracy was seen to affect key opinion leader's attitude, the degree of MRI substitution, and its uptake in clinical guidelines. Another key 'what if scenario' was the role of competing technologies. If technologies such as circulating tumor cells or new imaging discoveries would emerge, they could affect adoption over time.
Conclusions: The combined used of scenario drafting and decision modeling permits estimating the expected ICER of various likely development/adoption scenarios of a technology during translational research. It shows that accuracy of FDG-PET/CT strongly influences its expected cost-effectiveness and herewith its likely adoption in the clinic.
No conflict of interest.

1519 POSTER

Establishing patient and public involvement in cancer research: An integrated approach

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Background: Patient and public involvement (PPI) incorporates and integrates patients' or users' perspectives into research, throughout different stages of research so that cancer research reflects issues that are important and relevant to those whom the research potentially affects.
Methods: A process mapping exercise of how PPI is integrated into all types of research was undertaken with the aim of describing the development of an integrated approach to establishing and developing Patient and Public Involvement (PPI) in Research in the UK's first Biomedical Research Centre (BRC) for Cancer, comprising a large cancer hospital and an academic cancer research institute. This mapping exercise entailed reviewing all PPI activity and processes within the two organisations and was undertaken in conjunction with, and reviewed by, members from the Patient and Carer Research Review Panel. This exercise was then used to develop a PPI strategy which informs the Biomedical Research Centre's research strategy, with patient and public input for the enhancement of research that is truly in the public interest.
Results: The mapping exercise has yielded how several stands of PPI are interwoven to create a culture of patient and public involvement in cancer research. PPI has extended across the research spectrum and included imaging, translational, drug development and health services research. The strands to achieve this include: establishment of a panel to review research; development of open web-resources to engage and involve patients and the pubic, priority setting processes that rank patient and public suggestions for what kinds of cancer research should be undertaken and increasing awareness of how patients and the public can get involved in ground-breaking cancer research. It also extends to advocacy representation in trial steering groups, education events, awareness training and the establishment of a culture that seeks PPI at the early ideas stage. The mapping showed how at present the BRC is at the 'Creative' end of the PPI continuum representing collaboration and co-production of research, where research is shaped by PPI and PPI partner input and insight has made a difference to planned research design. Ultimately, this impacts on what will become the outcomes of future cancer research.
Conclusion: Involving patients and the public in cancer research requires a culture shift across organisations, but the imperative for PPI is compelling and results in research with clinically important and meaningful patient outcomes.
No conflict of interest.

1520 POSTER

An investigation into the delayed presentation of breast cancer in Lahore, Pakistan

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Background: Due to the inadequacy of screening programmes for early detection of breast cancer in Pakistan and the predominance of advanced cases, a study was conducted to assess the factors responsible for the delayed presentation of breast cancer.
Material and Methods: All consecutive patients with a diagnosis of advanced breast cancer, whether locally advanced or distant metastases, presenting to a university hospital for the first time over a period of twelve month were prospectively included in this study. Factors including age, socio-economic status, education, marital status and lack of access to health care services were assessed.

	Socio-economic category	Patients	
		Number	Percentage
Upper class	A	11	5
Middle class	B	27	12
	C	47	20
Lower class	D	57	25
	E	88	38
Total		230	100

Results: 230 patients were diagnosed with advanced breast cancer during this study period. They were all women. Ninety percent (207/230) were over the age of 35 years. A statistically significant proportion ($p < 0.05$; 63%) belonged to the below poverty socioeconomic group (table). Eighty percent (184/230) of patients were completely illiterate, while 46 patients (20%) had some formal education. 138 patients (60%) associated their late presentation to the lack of access to health care services. Other reasons given for delayed presentation included shyness, little support from family, lack of knowledge of breast cancer symptoms and not familiar with the importance of breast self-examination.
Conclusion: This study found that illiteracy, poverty, shyness and lack of health care facilities in distant areas are mainly responsible for the late presentation of breast cancer in women of Pakistan. Development of a screening programme, public education, school seminars and comprehensive awareness programmes focused on encouraging women to see a doctor promptly for the evaluation of breast symptoms can prevent the delay and improve patient outcome.
No conflict of interest.

1521 POSTER

Therapeutic benefit as a criterion for a prioritization in oncology

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Background: In oncology therapeutic benefit is of high importance. Despite the enormous progress in medical cures leading to an increasing life expectancy, some treatments often improve the health status only marginally or cause strong adverse effects. Sometimes they even harm the patient seriously. This study examines preferences of different stakeholder groups with respect to their criteria concerning the allocation of medical resources.
Methods: A questionnaire study with standardized questions including typical questionnaire items, rankings and scenarios was conducted. To date, 123 interviews were carried out with cancer patients and different staff members including medical practitioners, nurses and administrative officers of one of the largest centers for oncological care in Northern Germany. Sociodemographic variables were elicited to serve as covariates in regression models and as variables in contingency analyses to test specific hypotheses and to account for the variability in the data.
Results: Allocating resources according to different criteria gave the following importance ranking: Treatments leading to a full recovery; quality of life; life extension; proved effectiveness of a treatment; patient's commitment and engagement for a treatment (e.g. hospital stay or journeys); age of a patient; and treatment costs. This clearly points out the importance of therapeutic benefit. A ranking evaluating the *degree* of treatment benefits gave the following: Treatments leading to a full recovery; quality of life; fast recovery; life extension; period until next cancer breakout; adverse effects; and psychological well-being. Furthermore, the respondents were asked whether treatments should only be financed by the public health care system, if their effectiveness is positively proven (evidence based medicine). The majority supported this idea but many changed their opinion when effectiveness was embedded in more complex scenarios. One scenario was concerned with an ongoing scientific study accumulating evidence for the treatment. In the second scenario a practitioner believes that the treatment is effective.
Conclusions: The study indicates the importance of therapeutic benefit for allocating health care resources. It shows the difficult situation of evidence based medicine within a discussion of prioritization.
No conflict of interest.

1522 POSTER

Advanced stage presentation of cancer in Eastern India- how is the alternative medicine responsible?

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Background: A majority of Indian cancer patients are often presented with incurable diseases at the latest phase of disease progression. The use of TCAM has been identified by Indian oncologists as a potential factor for the delay in seeking health from medical practitioners but no research has been conducted to verify such claims. The aim of this study is to identify socio-demographic and disease status differences between TCAM and non-TCAM users among cancer patients in India and associated patterns of seeking professional medical help.
Materials and Method: A random survey of 825 cancer patients in one public and one private hospital was conducted in Delhi, India where a list sampling technique was used to interview every patient over a four month period, of response rate 80% where 10,200 cases were registered with age distribution of 1 month to 91 years, mean age 44.2 years. Male (54%)

cancer patients were little predominating compared to the female (46%) patients where in males ca lung (14%), followed by ca oral cavity (11%) ca colon (6%). The most frequent reported malignancy in female was breast (30%), uterine cervix (21%), gallbladder (11%) ovary (10%). In paediatric age group ALL (32.4%), Ewings Sarcoma (21.2%), Rhabdomyosarcoma (16.1%) and Brain tumour (13.6%).
Results: The results showed that 34.3% of cancer patients had used TCAM and demonstrating statistically significant relationship between the use and reported delay in seeking help from clinical medicine ($p < 0.001$). On the other hand, 35.2% users reported seeking help immediately after onset of symptoms, whereas 50% of non-users sought help from conventional medicine and 11.5% of users reported waiting for six months or more after noticing symptoms, while only 2.1% of non-users waited this long.
Conclusion: Overall, early diagnosis and intervention is critical for effective treatment of many malignancies. Delays in presentation related to the use of TCAM may be an important factor relating to the high rates of advanced disease on presentation and low survival rates in the care of Indian cancer patients. Further research is needed to explore the reasons for using TCAM and to ensure existing issues of delays in help seeking are addressed.
No conflict of interest.

1523 POSTER

Cost-effectiveness of denosumab versus zoledronic acid in patients with bone metastases from solid tumours in Spain

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Background: Denosumab was superior to zoledronic acid (ZA) in the prevention of skeletal-related events (SRE) in patients with bone metastasis (BM) from solid tumours in 3 large clinical trials. This study assessed cost-effectiveness of subcutaneous denosumab vs intravenous (IV) ZA in patients with BM from breast cancer (BC), prostate cancer (PC) or other solid tumours (OST) in Spain.
Methods: A Markov model (4-week-cycle duration) was used to estimate lifetime costs, SRE incidence (pathologic fracture, spinal cord compression, bone radiation and surgery) and quality adjusted life years (QALYs) from the Spanish Health System's perspective. Health states considered were 'on treatment', 'off treatment' and 'death'. Transition probabilities (discontinuation and death rates), adverse event (AE) rates and rate ratio (RR) of SRE (denosumab vs ZA) (RR_{BC}=0.77; RR_{PC}=0.82; RR_{OST}=0.85) were obtained from clinical trials. Base case did not consider discontinuation or AE as the overall incidence was similar between the drugs. The analysis included drug, administration, monitoring and SRE management costs. To reflect the potential availability of generic ZA, a 40% discount in ZA branded price was applied. Drug, administration and monitoring costs were based on annual administrations [13 (denosumab); 14.47 used in clinical practice (ZA)]. Denosumab and ZA administration and monitoring costs applied only to doses not synchronised with IV chemotherapy (64.2% [BC]; 68.4% [PC]; 52.6% [OST]). Unit costs (2013 €), utilities and synchronisation were procured from literature and local databases. A 3% annual discount was used in costs and outcomes. Sensitivity analyses (SA) were performed for SRE management costs (±20%), administration and monitoring costs (±50%), using SRE rates from clinical practice and including discontinuation and AE rates in the analysis.
Results: Denosumab yielded 0.044, 0.041 and 0.026 additional QALY; avoided 0.48, 0.35 and 0.22 SRE and was associated with savings of €704 and €606 in patients with BC and PC. Greater variations in SA were related to SRE rates and administration costs. Denosumab was dominant (more efficacious and less costly) in 69% of scenarios and remained cost-effective in 97% (using €30,000/QALY threshold). Denosumab was cost-effective in 100% of the BC and PC scenarios.
Conclusions: Denosumab is cost-effective vs generic ZA in the prevention of SRE in patients with BM from solid tumours and is cost-saving in most scenarios.
Conflict of interest: *Ownership: ML, GH, LG, JAG − own Amgen stock. Advisory board: ID − Amgen. Corporate-sponsored research: DI − Amgen, Lilly, Roche IO,CR, MAC − Amgen. Other substantive relationships: ML, GH, LG, JAG − employed by Amgen*

1524 POSTER

Cost-benefit analysis for gastric and cervical cancers: Public health oncology in Japan

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Background: Our study objectives were to evaluate medical economy for gastric and cervical cancer prevention in Japan and thereby contribute to cancer care policy decisions. In addition to medical cost, those associated with cancer incidence should include overhead due to income loss, hospital visits, and psychological and social costs. We created presence/absence models for prevention by setting primary prevention for gastric and cervical cancers as *Helicobacter pylori* (Hp) eradication and human papillomavirus (HPV) vaccination, respectively, and performed cost-benefit analyses.
Methods: *1. Model creation*:
Gastric cancer model A: A person was found to be Hp-positive at age 20 and had no gastric cancer onset after eradication.
Gastric cancer model B: A person without eradication or examination had onset of progressive gastric cancer at age 50, received anticancer drug therapy, but died one year later.
Cervical cancer model C: A person received HPV vaccination at age 14, stage 0 cervical cancer was diagnosed at age 40, and cured by conization.
Cervical cancer model D: A person who did not receive HPV vaccination was diagnosed with stage IIIb cervical cancer, underwent radical hysterectomy + irradiation + anticancer drug treatment, but died 3 years later.
2. Cost classification and cost estimate:
We divided the costs of cancer care into seven categories and estimated costs for each model.
3. We performed cost-benefit analyses for Japan as a whole.
Results: 1. Table 1 presents costs for each model.
2. Gastric cancer: Cost was estimated as follows: Hp examination $2{,}926 \times 10^6$ JPY, Hp eradication 708×10^6 JPY; loss due to death $131{,}415 \times 10^6$ JPY; net benefit $127{,}781 \times 10^6$ JPY.
3. Cervical cancer: HPV vaccination $29{,}150 \times 10^6$ JPY; cervical cancer examination $5{,}830 \times 10^6$ JPY; loss decrease due to death $15{,}916 \times 10^6$ JPY. Thus, the estimated net benefit is negative $19{,}064 \times 10^6$ JPY.
Discussion: Prasad et al. conducted cost-benefit analyses of HPV vaccination in Kentucky, USA, and reported it to be cost effective (J KY Med Assoc 2008). We estimated that net benefit will be generated if the HPV vaccination cost decreases to 17,000 JPY. While few cost-benefit analyses have been reported for cancer care, they would be essential for policy determination. Therefore, we hope there will be many reports in the future.
No conflict of interest.

Table 1. Costs for each model (unit:JPY)

Cost classification	model A	model B	model C	model D
Prevention	4,600	0	50,000	0
Mass-screening	2,400	0	55,000	0
Curative treatment	0	0	270,000	0
Palliative care	0	2,760,000	0	1,480,000
Indirect cost	0	70,000,000	365,000	44,070,000
Non-medical cost	0	106,000	25,000	490,000
Psychosocial cost	0	18,840,000	0	46,490,000
Total cost	7,000	91,706,000	765,000	92,530,000

1525 POSTER

Multidisciplinary meetings in the management of patients suffering from cancer

M. Grima[1], R. Grech[1], J. Debono[1]. *[1]Mater Dei Hospital, General Surgery, Msida, Malta*

Background: Cancer multidisciplinary meetings (MDTs) are part of the philosophy of multidisciplinary care. Effective MDTs have positive outcomes for patients receiving the care and for the health professionals involved in providing the care and health services.
An audit was carried out to focus on the management of patients discussed at the general surgery oncology meeting (excluding breast cancer) held at Mater Dei Hospital, Malta every 2 weeks. These meetings are held between the general surgeons, pathologists, oncologists and radiologists taking care of their respective patients.
The audit looked into:
1. The management plan decided during the MDT

2. Whether the treatment was adhered to and if not, the reason behind such a decision.
3. The time between the decision to offer treatment and the initiation of treatment
4. The guidelines used in each decision plan and if none was mentioned the management plan was compared with the European and international guidelines

Material and Methods: The first MDT was organised in early 2010 and since then it has taken place on a fortnightly basis. Data about all patients who were discussed during 2011 and 2012 were collected and processed. About 700 patients were included in the audit. The medical records of each patient were looked into to obtain the data required for this audit. Data was also collected using PACS and iCM software available in Mater Dei Hospital.

Results: The management plan discussed in the MDT was documented in the medical records and in the majority of cases the treatment adhered to European and/or International guidelines. In most of the cases there was written evidence that the patient was informed about the treatment decided in the MDT however most of the time the decision on treatment options was doctor led rather than patient led. In a minority of cases there was a difference between the management decided during the MDT and the treatment provided and this was secondary to patient choice.

During data collection it transpired that there is a need for proper documentation of MDTs. Currently there is no proforma on the documentation submitted prior to and during the MDT. Each surgical firm has his own way of submitting the patient's data and this may lead to lack of information needed for discussion during MDTs. In the medical records, there was a lack of documentation on the discussion that took place and the reasoning behind each particular decision taken even though the management decided upon agreed with the guidelines available.

Conclusions: The MDTs are useful as treatment planning is better coordinated and expedited. There is greater continuity of care and less duplication of services. Communication between care providers improves, and as a result time and resources are used more efficiently for the benefit of the patient.

This audit also highlighted some lacunae which if taken into consideration will improve the multidisciplinary care of the patient suffering from cancer.

No conflict of interest.

1526 POSTER

Content analysis of social media traffic related to the 2012 EORTC-NCI-AACR Symposium on molecular targets and cancer therapeutics

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Background: Social media has become a major mode of communication, and sites such as Twitter are growing exponentially in both user base and breadth of applications. Medical conference participants and sponsors interact in real time, enriching the conference environment. We explored social media's function as a medium for information exchange associated with the EORTC-NCI-AACR sponsored Symposium on Molecular Targets and Cancer Therapeutics held November 6−9, 2012.

Materials and Method: We used Tweet Archivist (http://www.tweetarchivist.com/), an online analytic tool, to conduct a Boolean search for '#ENA2012' tagged posts on Twitter from 4/11/12 to 10/11/12. Data was gathered on tweet content, attitude, subject, platform, and authorship and analyzed through simple descriptive statistics. #ENA2012 was designated as the official meeting tag prior to the meeting by ECCO (EuropeanCancer).

Results: 258 posts were captured (0−78/day). 34% of posts involved logistics/scheduling, 29% disseminated information, 11% contained commercial content, 9% related personal experience, 7% were press releases, 4% were miscellaneous and 3% were queries. The subject discussed was networking in 34%, general oncology in 14%, miscellaneous in 12%, personal opinions in 9%, clinical trials in 9%, molecular targets in 8%, cancer biology in 7%, conveying expert information in 6% and technology or products in 2%. 10% of all posts were positive, 90% were neutral and none were negative in tone. 43% of tweets contained a hyperlink. 9 of 258 posts referenced specific cancer types, of which 11% referred to leukemia, 67% to prostate cancer, and 22% to miscellaneous cancers. The most common tweeting platform was TweetDeck with 38% of tweets. PC web browsers accounted for 26%, iPhones for 20%, iPads for 6%, BlackBerries for 4%, and Android for 1%. Individual users were the most frequent author type, producing 45% of all posts. The meeting organizer contributed 39% of posts, companies contributed 12%, and professional societies 4%.

Conclusions: Our analysis shows that Twitter is an active communication platform for professional conferences. It is a relatively underutilized sphere for influence and information exchange by stakeholders and professional organizations during these events as individual users and the meeting organizer presently dominate tweet authorship, with an emphasis on networking and conference logistics, respectively. The analysis provided here represents a tool for acquiring instantaneous feedback, mapping information movement, and monitoring the evolution of public opinion, complete with the potential to harness such information to guide and influence the marketplace.

No conflict of interest.

1527 POSTER

Management of medical information between general practitioners and onco-hematologists regarding patients undergoing chemotherapy: Perceptions and realities

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Background: The exchange of information is crucial in the multidisciplinary management of patients. Our aim was to identify communication effectiveness between onco-hematologists and General Practitioners (GPs) who were treating patients with outpatient chemotherapy in Lille (northern France).

Material and Methods: Onco-hematologists of Saint Vincent de Paul Hospital were surveyed after the initial consultation of new patients. For each included patient, GPs were interviewed by phone about 2 weeks after the first chemotherapy session. Mail from GPs and from onco-hematologists regarding first consultation and first chemotherapy were also examined. About ten informations were explored to compare the returns with the reality of exchanges from hospital to GPs, including cancer diagnosis, prognosis, degree of patient information, treatment protocol and timetable, terms of future exams, potential side effects and their management. From GPs to hospital, 14 informations were explored, including medical history, usual treatments, results of previous tests, degree of patient information, degree of autonomy, psychological state and social environment.

Results: From 04/2011 to 02/2012, GPs response rate was 85.2% (n = 69 for 81 new patients). Each GP had a small number of patients being treated by chemotherapy in his patient base: 0.6% (0.1 to 3). Patient was referred for chemotherapy by another physician in 88% of cases (n = 37/42). Communication from all 9 oncologists was deemed adequate by GPs (69.6 to 100%), with exception that prognosis was poorly communicated (37.7%) and difficult to interpret. In comparison with mail, GPs underestimated the level of communication for every informations (from 31.9% to 91.3%), in particular for patient information and side effects. Moreover, mail following the first session of chemotherapy was given to GPs by the patient in only 52.2% of cases (n = 36/69).

According to onco-hematologists, only 0 to 17.4% of the 14 informations were transmitted by GPs. It was confirmed by our analysis of 10 mail sent by GPs. Only 21.7% of initial consultation were accompanied by mail from GPs. Furthermore, 44.9% ignored the identity of their patient's onco-hematologist but 79.7% were in favour to complete a record of medical and social information before initial consultation.

Conclusions: There is a difference between informations provided by the onco-hematologist and their reception by the GP. The difficulty of communication could be due to many patient referred for by another physician. The use of a record of medical and social information, a therapeutic tracking sheet and encrypted messaging system could improve reception of information by GPs during outpatient treatment. Communication devices could secondarily be integrated into the future computer shared patient file.

No conflict of interest.

1528 POSTER

Early integration of palliative care into standard oncologic care: The development of a network for integrated oncology and palliative care in a rural European region

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Background: The early integration of palliative care in the course of cancer treatment was discussed recently in the US (1). There is a discussion ongoing in Germany strongly demanding the participation of palliative care teams early in the course of oncological treatment. However, oncological and palliative services differ significantly between the US and the EU and

also within the EU. Furthermore, there are considerable disparities between the rural and urban situation within one health system. Organisational structures cannot easily been transferred or compared. Simple calling for a palliative care physician or palliative care team who cares for the patient in addition to the oncologist does not take into account the different needs in varying tumour entities and disease courses, differences of specialisations of oncologists and health care systems as well as financial aspects. Comprehensive Cancer Centres might be able to provide the whole spectrum of the proposed services, but most of cancer patients in Europe are not treated at these centres. The key elements of early palliative care in the setting of cancer treatment can be realized in different ways.
Results: We report the successful development of an ESMO accredited Designated Centre of Integrated Oncology and Palliative Care (Onkologisches und Palliativmedizinisches Netzwerk Landshut) under limited resources in a rural region of Bavaria. From this experience we conclude the following points to be essential: palliative care should be included in the oncology training, and there should be regular scientific updates for palliative treatments of different cancer types. Important is the principle of continuous care (e.g. the oncologist follows the patient until his death, even when end-of-life care is provided by a palliative care team, and the patient can stay in contact with the doctor seen at time of cancer diagnosis). As part of a network of all required services for palliative care (e.g. ambulatory and inpatient palliative care team, hospice) the oncologist must be able to manage patients' needs, the personal communication between the health care professionals within the network is elementary. Counselling and support for the patients' relatives must be offered. The degree of palliative care versus oncological care should be balanced depending on patients' wish and the stage of the disease.
No conflict of interest.

1529 POSTER

Central unit of cytostatics' preparation in hospitals: Luxury or necessity?

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Background: University Hospital of Crete (UHC) is the largest general hospital in Crete and among the 5 largest hospitals in Greece. With the implementation of the memorandum in Greece, all operators were asked to reduce their costs, while special emphasis was placed on decreasing healthcare costs. In 2012, in this context, UHC made various attempts to reduce its budget.
Material and Method: Until January of 2012, every oncologic clinic was preparing the drugs for the therapies of its patients at its amenities. One of the actions taken by the UHC was the foundation of a Central Unit for the Cytostatics Drugs' Preparation (CUCDP) where the dilution of all the oncologic drugs for all the therapies in the hospital is taking place. The CUCDP is part of the hospital's pharmacy and it's recruited by a pharmacist, as the scientific supervisor, plus four nurses and a medical laboratory technologist, who cope with the 115 preparations per day for the about 62 daily patients of the 11 associated clinics. The CUCDP personnel has developed a great know-how in dissolving these drugs that enables the quick and safe preparation of the solutions and offers the best quality for the patients' treatment.
Results: In the first year of its operation, over 15.500 therapies were prepared in the CUCDP that correspond to 28.000 different dilutions. 120 different brand-names of cytostatics drugs are used for the injectables oncologic treatments. The good management of the medicines according to their SPC instructions and the economy of scale due to cumulative drugs' preparation succeeded in quantity saving of drugs that were re-entered in pharmacy's stock for use. More than 100.000 units were used and from them 6.000 units were saved and returned at the pharmacy. In a total of 10 million euro that these treatments cost (calculated in hospital price), a cost saving of 850 thousands euro was achieved.
Conclusions: Taking into pharmacoeconomic consideration that the value of these used cytostatic medicines equals to the 1/3 of the total hospital's pharmaceutical expenditure, even if only this CUCDP was the only action taken, a 3% budget decrease would have been accomplished.
No conflict of interest.

1530 POSTER

Cancer pattern in West Bengal, India: Data from hospital based cancer registry

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Background: The first Population Based Cancer Registry (PBCR) in India was organized in Mumbai in 1963. Subsequently under National Cancer Registry Programme (NCRP) of Indian Council of Medical research a few more registries was started in different cities of India like Bangalore, Chennai and New Delhi. The 1st PBCR was organized in Kolkata in Chittaranjan National Cancer Institute in 1997. We started our hospital based cancer registry from 2002, Kolkata. The PBCR from different cities has shown the distributions of different cancers are different in different cities because of ethnic and dietary differences. The aim of our study was to show the prevailing cancer pattern from eastern part of India.
Materials and Methods: From our hospital based cancer registry we analyzed all the cancer patients, who attended the out patients and in patients departments of Netaji Subhash Chandra Bose Cancer Research Institute during period from August 2004 to December 2012.
Results: A total of 20,400 cases were registered. The age distribution was 1 month to 91 years, with mean age of 44.2 years. The male (54%) cancer patients were little predominating compared to the female (46%) patients. The most frequent malignancies in males were carcinoma lung (14%), followed by cancer of the oral cavity (11%) and carcinoma colon (6%). The most frequent reported malignancy in female was breast (30%), followed by uterine cervix (21%), gallbladder (11%) and ovary (10%). In paediatric age group the most frequent malignancies were ALL (32.4%), followed by Ewings Sarcoma (21.2%), Rhabdomyosarcoma (16.1%) and Brain tumour (13.6%).
Conclusion: The cancer pattern in eastern India is little different from other parts of India & World cancer registry, because of life style and diet habit of this part of the country.
No conflict of interest.

1531 POSTER

High incidence of gall bladder cancer in Gangetic West Bengal: A study from a hospital based cancer registry

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Background: Gall bladder cancer accounts for about 1% of all cancer deaths. Incidence varies geographically with higher rates in certain areas and among women is approximately double than that of men. As the incidence of this disease is increasing, a systematic trend analysis may help to understand alterations in incidence with regard to time, place and person distribution, and changing cancer risk. The present communication makes an attempt to analyze the time trends of gallbladder cancer for people of Gangetic West Bengal.
Materials and Methods: From our hospital based cancer registry we analyzed all cancer patients, who attended outpatient and inpatient department of Netaji Subhash Chandra Bose Cancer Research Institute during period from August 2004 to December 2012. A total of 20, 400 cases were registered. We then analyzed the total cancer cases and gall bladder cases belonging to gangetic West Bengal. The Gangetic West Bengal consisted of Malda, Murshidabad, Nadia, Burdwan, Hooghly, Howrah and 24 Pgs(S) through which districts the river Ganga flows. A detailed dietary, water consumption and lifestyle history were noted for those patients.
Result: A total of 20, 400 cases were registered out of which overall gall bladder cancer was 11%. Among all cancer patients residing in Gangetic belt (8,000), gall bladder cancer ranked third and was 16%. The probable reason we noticed a particular dietary habit of Bengalis. They kept fasting for some particular religious reasons till noon and then were habituated to take rice with ghee (full fat dairy product) or fatty diet. They followed fasting for 2 or 3 times a week. Muslim people tend to relish on spicy and fatty foods. Second history we noticed was repeated *Salmonella typhi* infection because of contaminated water supply leading to chronic cholecystitis which led to cancer. Third reason was arsenic contamination of drinking water which was concentrated in gall bladder producing carcinoma. The fourth and one of the most important factors in Gangetic West Bengal

was consumption of polluted drinking water of the river Ganga which the Indians spiritually drink as pure water. The heavy metals deposited, were Molybdenum, Mercury and Lead because of industrial pollution along the river bank.
Conclusion: Statistically, the gall bladder cancer in Gangetic West Bengal was the highest incidence in India and second highest in the World after Japan. This cancer is mostly related to diet and drinking habit. We intend to take preventive measures of gall bladder cancer by proper awareness and changing diet and drinking habit of Bengalis of Gangetic West Bengal.
No conflict of interest.

1532 POSTER

Patients' preferences for bone metastases treatments in France, Germany and the United Kingdom

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Background: Patients with bone metastases from solid tumors often experience skeletal complications (skeletal-related events [SREs]; commonly defined as pathologic fracture, radiation to bone, surgery to bone and spinal cord compression). Several bone-targeted agents are approved to prevent SREs, but patients' preferences among available options has not been evaluated. The aim of this study was to assess patients' preferences for efficacy, safety, and mode of administration in relation to currently available treatment options in Europe.
Material and Methods: Adults in France, Germany, and the United Kingdom (UK) with a self-reported physician diagnosis of bone metastases secondary to a solid tumor completed a web-enabled discrete-choice experiment survey consisting of a series of 10 choices between pairs of hypothetical medication profiles. Each profile included five attributes with 3 or 4 levels each (primarily based on product prescribing information): months until first SRE (10, 18 and 28 months); months until worsening of pain (3, 6 and 10 months); annual risk of osteonecrosis of the jaw (ONJ; 0, 1 and 5%); annual risk of renal impairment (0, 4 and 10%); and mode of administration (oral tablet, subcutaneous injection, 15-minutes infusion and 120-minute infusion). Choice questions were based on an experimental design with known statistical properties. The survey was pretested with 26 patients using open-ended interviews. A separate main-effects random parameters logit model was estimated for each country.
Results: A total of 159 patients in France, 166 patients in Germany, and 159 patients in the UK completed the survey. Among the attributes included in the survey, months until first SRE, annual risk of renal impairment and time until worsening of pain were the three most important attributes for patients in all countries. For all these attributes better levels of outcomes were significantly preferred to worse levels ($p < 0.05$). In all three countries, a 120-minute infusion every 4 weeks was the least preferred mode of administration. The annual risk of ONJ was judged by patients to be the least important attribute in the UK and Germany and second to least important in France.
Conclusions: When considering treatment choices for preventing skeletal complications associated with bone metastases, patients focused mainly on delaying SRE, avoiding renal impairment as well as delaying pain worsening.
Conflict of interest: *Ownership: GH, JA, YQ, FG, IA − own Amgen stock. Advisory board: AB − Amgen, Sanofi, Pfizer, janssen, Roche, Bayer, Teva, Astellas. Corporate-sponsored research: AM, BH − Amgen AB − Sanofi. Other substantive relationships: GH, JA, YQ, FG, IA − employed by Amgen*

1533 POSTER

A study of the support and information needs of men using the 'your prostate' service

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Background: The purpose of the study was to find out what motivated men to use the 'Your Prostate' service.
Prostate cancer incidence is now the main cause of cancer deaths among men in Europe. European Men's Health Forum (EMHF) developed an e-service for men to ask questions about any aspect of their prostate health with the intention of identifying the main concerns men have, the gaps in information and support available to them, and to make an analysis of the language used and to compare this across countries.
Material and Methods: A bespoke database was designed to enable questions and answers to be automatically entered exactly as they had been written into the database and to be analysed.
- Quantitative analysis included how many:
  - Questions were asked and to rank the question by type and the age of the user
  - Users were male/female
  - Users previously sought medication attention and/or received any treatment
  - Users accessed the service from different countries
- Qualitative analysis included textual analysis:
  - categorization of questions by topic
  - language used by men from different countries

Secondary analysis of a review of European (National) Cancer Plans was carried out.
Results: 710 questions were asked between December 2010 and March 2012 by a total of 424 unique users. 391 male, 33 female. 241 had previously sought medical attention; 172 had received treatment; questions received from 17 European countries. Most questions were asked by men aged 50 and over.
The largest group of questions numbered 147, categorized as relating to 'urination' and including: having to rush to the toilet to pass urine; difficulty in passing urine; increased frequency of passing urine, especially at night; pain on passing urine; blood in urine or semen. These symptoms are similar for both prostate cancer and benign prostatic hyperplasia. The next largest group of questions related to treatment being considered (126) followed by erectile dysfunction (87), prostate cancer (80) and then other categories including treatment received previously and potential adverse drug reactions. Difficulties in making a judgement about seeking diagnosis, agreeing to a medical intervention and making a choice among different treatments were commonly expressed. Fear was expressed about making decisions with the potential to make matters worse as well as better and about maintaining personal and sexual relationships.
Conclusions: It is evident from this study that men accessed an online website to gain information regarding their prostate health. The findings indicate that men have unanswered questions and require systems in place to meet this growing need. There is considerable scope for improving information aimed at men who face choices about their prostate health, the support available to them to make choices, and to assist them to recover following treatment. Further research is required to expand this area of practice.
No conflict of interest.

Proffered Papers Session (Mon, 30 Sep)
Cancer in the Older Patient

1550 ORAL

Predicting outcome in onco-geriatric surgical patients: screening tools versus the comprehensive geriatric assessment

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Background: In the onco-geriatric surgical population, patients at risk of postoperative complications need to be identified preoperatively to allow for the implementation of preventive measures and to minimize the risk of over- and under-treatment. The comprehensive geriatric assessment (CGA) is useful for the purpose of identifying frail elderly, however it is too time consuming. There is a need for screening tools to identify frail patients, who are at risk of adverse outcome. The aim of this study was to compare the predictive ability of several screening tools to the CGA.
Materials and Methods: In an international prospective cohort, 345 patients $\geqslant$70 years undergoing elective surgery for solid tumors were included. Primary endpoint was the incidence of major complications 30 days post-operatively. Pre-operatively three screening tools were administered and compared to theCGA, which was administered simultaneously. 'Timed Up & Go' (TUG) quantifies functional mobility by means of a walking test, 'Vulnerable Elders Survey' (VES) addresses self-reported health issues to identify vulnerable older people and 'Groningen Frailty Index' (GFI) identifies frail patients by a 15-item questionnaire. Data were analyzed using multivariate logistic regression analyses to estimate odds ratios (OR)

and 95% confidence intervals (95%-CI). Positive Predictive Values (PPV) were calculated.
Results: The median age was 76 years (70−96). The majority of patients underwent major surgery (n = 240; 69.6%). Postoperatively 64 patients (18.9%) experienced major complications. GFI and VES were not associated to 30-day morbidity in a univariate logistic regression analysis (GFI: OR 1.52; 95% CI=0.81–2.87; p = 0.20. VES: OR 1.63; 95% CI=0.85–3.11; p = 0.14). In a multivariate logistic regression analysis, adjusted for center, gender and minor or major surgery, TUG and CGA were predictive of 30-day morbidity (table 1).

Table 1. Results

	OR (95% CI; p-value)	Major complications in patients with	
		Good test results	Poor test results
TUG	3.16 (1.20–8.31; 0.020)	13.6%	45.7%
CGA	3.25 (1.52–6.94; 0.002)	11.9%	36.5%

Conclusions: In onco-geriatric surgical patients the time-saving TUG is an appropriate screening tool with a similar predictive ability as the CGA. TUG identifies even more patients at risk of adverse outcome.
No conflict of interest.

1551 ORAL

Performance of two geriatric screening tools in older cancer patients

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Background: To compare the diagnostic characteristics of two geriatric screening tools (G8 and Flemish version of the Triage Risk Screening Tool (fTRST)) to identify patients with a geriatric risk profile and to evaluate their predictive value for functional decline and their prognostic value for Overall Survival (OS).
Patients and Methods: Patients ⩾70 years with a malignant tumor (breast, colorectal, ovarian, lung, prostate cancer and hematologic malignancies) were prospectively included if a new cancer therapy was considered. At baseline, geriatric screening with G8 (cut-off ⩽14) and fTRST (cut-off ⩾1 (= fTRST(1)) and ⩾2 (= fTRST(2)) evaluated) was performed in all patients, as well as a Geriatric Assessment (GA). The GA was used as gold standard and based on the presence of at least 2 of the following 7 criteria: 1/ living alone, 2/ ADL score >6, 3/ IADL score <5(male)/8(female), 4/ MMSE score <24, 5/ GDS-15 score ⩾5, 6/ MNA score <24 and 7/ presence of at least one comorbidity on the CCI. Functionality was reevaluated 2 to 3 months after cancer treatment decision. Functional decline (increase of ⩾2 points for ADL; decrease of ⩾1 point for IADL) and OS were assessed by logistic regression and by Kaplan–Meier method and Cox' regression, respectively.
Results: 937 patients have been included in this study (10/2009−07/2011). A geriatric risk profile according to the gold standard was present in 73.5% of the patients. G8 and fTRST(1) showed high sensitivity (86.5%-91.3%) and moderate NPV (61.3%-63.4%) and specificity (59.3%-41.9%) to detect patients at risk for geriatric profile while fTRST(2) performed worse.
Functional decline for ADL was observed in 17.3%, for IADL in 35.9% of the patients. For prediction of functional decline on ADL and IADL, G8 and fTRST(1) also had higher sensitivity than fTRST(2).
For evaluating OS, the median follow-up is 18.95 months (range: 0–39.7). G8 and fTRST(1;2) all showed a strong prognostic value for OS (logrank p-value <0.0001). However, G8 had higher discriminatory power than fTRST(2) as suggested by Hazard Ratios (HR) for OS: HR G8 negative versus positive 0.38 (95% CI: 0.27–0.52), HR fTRST(2) negative versus positive 0.67 (95% CI: 0.53–0.85), while fTRST(1) was not retained in the stepwise regression.
Conclusion: Both geriatric screening tools, G8 and fTRST, are simple and fast screening tools with great potential for identifying patients with a geriatric risk profile, strongly predict functional decline and have a strong prognostic value for OS.
Note: Cindy Kenis and Lore Decoster have equal contribution for this abstract.
No conflict of interest.

1552 ORAL

Decreasing resection rates over time among patients with gastrointestinal cancer

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Background: We evaluated surgical resection rates over time among patients with oesophageal, gastric, colon, rectal, or pancreatic cancer, according to age.
Material and Methods: 41.671 patients diagnosed between 1995–2011 in the Eindhoven Cancer Registry area were included: 3.385 patients with oesophageal cancer, 5.560 with gastric cancer, 18.613 with colon cancer, 10.224 with rectal cancer, and 3.889 with pancreatic cancer.
Age was categorized as <55, 55−64, 65−74, 75−84, and ⩾85 years, period of diagnosis as 1995–1998, 1999–2002, 2003–2006, and 2007–2011. Multivariate logistic regression analysis determined the independent influence of period of diagnosis on the chance of undergoing resection, adjusted for age, gender, tumour penetration depth (cT), lymph node stage (cN), metastatic disease (cM), comorbidity, and socioeconomic status.
Results: Resection rates decreased with increasing age from 40% for patients with oesophageal cancer <55 years to 0% for patients ⩾85 years. For patients with gastric cancer, resection rates decreased with increasing age from 48% to 24%, for colon cancer from 88% to 73%, for rectal cancer from 83% to 44%, and for pancreatic cancer from 15% to 1%, respectively. Resection rates decreased between 1995–1998 and 2007–2011 for gastric, colon, and rectal cancer, most notably for patients with rectal cancer 75−84 years (76% 1995–1998 to 64% 2007–2011), and ⩾85 years (54% to 36%), and for patients with gastric cancer ⩾85 years (33% to 13%). The adjusted odds of undergoing a resection decreased over time for oesophageal (odds ratio (OR) = 0.9, 95% confidence interval (95% CI)=0.7−1.2), gastric (OR=0.6 95% CI=0.5−0.7), colon (OR=0.6, 95% CI=0.6−0.7) and rectal cancer (OR=0.4, 95% CI=0.4−0.5), but increased for pancreatic cancer (OR=3.2, 95% CI=2.1−5.0).
Conclusion: Resection rates decreased over time, especially for elderly patients, except an increase for pancreatic cancer. It should be evaluated to what degree decreased resection rates reflect unjust withholdment of potentially curative treatment, or whether it reflects availability of other treatment options (e.g. chemoradiation) and results in a more adequate selection of patients that might benefit of surgical resection. It should be ascertained that not the increased attention by public, audits, health inspectorate, insurance companies, etc. for mortality rates at individual hospital level, but the improved selection for surgical treatment is the reason for this reduction.
No conflict of interest.

1553 ORAL

Analysis of docetaxel therapy in elderly (⩾70 yrs) castration resistant prostate cancer (CRPC) patients enrolled in the Netherlands Prostate Study (NePro)

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Background: Prostate cancer truly is an age-associated disease, approximately half of prostate cancer patients in the Netherlands are aged 70 years or older at the time of diagnosis. Due to the increased life expectancy and more sensitive diagnostic techniques in the Western world, prostate cancer, like most other malignancies, is diagnosed more frequently and with rapidly increasing incidence and prevalence rates. However, age above 70 years has been an exclusion criterion in many clinical trials. Hence the knowledge about chemotherapy tolerance and toxicity in patients aged 70 years and above is limited. This possibly results in mistreatment of cancer patients of advanced age. The aim of this study was to evaluate the influence of age on docetaxel chemotherapy in elderly (⩾70 yrs) castration resistant prostate cancer (CRPC) patients.
Material and Methods: We performed a retrospective analysis of data acquired from the recently published Netherlands Prostate Study (NePro) to evaluate the influence of advanced age on docetaxel therapy (75 mg/m^2) in men with CRPC and bone metastases (mCRPC). For statistical analyses the data was stratified into four categories: <70, 70−74, 75−79, and ⩾80 years of age. Docetaxel tolerance was quantified by assessment of completion of the first three cycles at the intended dose. Common

Terminology Criteria for Adverse Events (CTCAE) version 2.0 was used to grade toxicity. Time to progression (TTP) was assessed as previously described.
Results: We analysed 568 patients (median age 68.1 yrs, range 46−89 yrs, 44.5% aged ⩾70 yrs). There was no relation between dosage and age (p = 0.60). We found no significant differences between the number of dose reductions, TTP, overall survival, chemotherapy tolerance and toxicity up to the age of 80 years. However, when compared to younger men, men aged 80 years or above more frequently experienced grade 3/4 toxicity, were five times less likely to complete the first three treatment cycles at the intended dose (OR 5.34, p = 0.0052) and showed decreased overall survival (15.3 mos versus 24.5 mos in <80 yrs group, p = 0.020).
Conclusions: In mCRPC, and possibly other cancer patients, up to the age of 80 years docetaxel chemotherapy is well tolerated with toxicity levels, tolerance and TTP comparable to that of younger patients. However, for chemotherapeutic treatment of patients aged 80 years and above an individual assessment should be made.
No conflict of interest.

1554 ORAL

Hormone receptor positive breast cancer in patients aged 75 years and older: Limited external validity of clinical trial results

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Background: Despite comprising a large proportion of all breast cancer patients, elderly are underrepresented in clinical trials. Moreover, inclusion is likely to be selective. This may hamper the generalizability of trial results to the general elderly breast cancer patient. The aim of this study was to evaluate the external validity of a randomized clinical trial which included elderly patients, by comparing characteristics and outcomes of trial patients with patients in a population-based cohort.
Material and Methods: A trial cohort (Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial) and a population-based cohort of elderly breast cancer patients (FOCUS cohort) were included. Inclusion was restricted to Dutch patients aged ⩾65 years at diagnosis, who had non-metastasized breast cancer with positive hormone-receptor status, who completed local therapy with curative intent. Analyses were stratified by age (65−75 years; ⩾75 years). Endpoints were overall mortality, and relative mortality as an approximation of disease specific mortality.
Results: Overall, 2,738 patients were included (TEAM cohort n = 1,325; FOCUS cohort n = 1,413). Irrespective of age, trial patients had fewer comorbid diseases and a higher socio-economic status as compared to patients in the population-based cohort. Trial patients had more often nodal involvement (all p values <0.001). In patients aged 65−75 years, overall mortality was similar for both cohorts (Table 1). Contrary, patients aged ⩾75 years in the population based cohort had an increased risk of death as compared to trial patients of similar age. Irrespective of age, relative mortality was similar for both cohorts.
Conclusions: With increasing age, inclusion in a clinical trial is more selected for general health. Therefore, results obtained in a trial may not necessarily be valid for the general elderly breast cancer patient aged ⩾75 years.
No conflict of interest.

Table: Overall mortality by cohort, stratified by age at diagnosis

	65−75 years			⩾75 years		
	5 years death (%)	HR (95% CI)	p	5 years death (%)	HR (95% CI)	p
Univariate			0.7			**<0.001**
Trial	14	1 (reference)		28	1 (reference)	
Population	14	1.05 (0.80–1.37)		38	1.54 (1.24–1.91)	
Multivariable*			0.9			**0.038**
Trial	14	1 (reference)		28	1 (reference)	
Population	14	1.03 (0.71–1.51)		38	1.34 (1.02–1.76)	

*Adjusted for tumor (histological grade, T stage, nodal stage), treatment (most extensive surgery, radiotherapy, endocrine therapy, chemotherapy), and patient characteristics (age, socio-economic status, comorbidity).

1555 ORAL

Low grade toxicities can have significant impact on chemotherapy completion in older patients

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Background: In clinical trials, clinically meaningful toxicity is usually defined as grade 3/4. In clinical practice, however, multiple lower grade toxicities are often considered meaningful. We hypothesise that multiple low grade toxicities may be a common reason for treatment modification/discontinuation in older people. The purpose of this observational cohort study was to identify which level of toxicity (and how many) trigger a) treatment modification (defined as dose reductions, delays or drug omissions) and b) early discontinuation of treatment.
Material and Methods: Patients aged 65+ were recruited via oncology clinics and the chemotherapy day unit in a tertiary referral hospital in central London. The overall study aimed at identifying the comprehensive geriatric assessment needs of older people with cancer (LREC 09H71865). We present a subgroup of 108 patients aged 65+ who were recruited just prior to commencing chemotherapy treatment between October 2010 and July 2012.
Results: Mean age 72.1 ±5 years (range 65−86). 50.9% (55) male with colorectal (33), gynaecological (18), upper GI (16), lung (15) and other cancers (26). Chemotherapy was palliative in 59.3% (64/108) and curative/adjuvant/neoadjuvant in 40.7% (44/108). Mean chemotherapy cycles completed 4.2 ±3. Treatment modifications due to toxicity occurred in 60 patients, 35% (21/60) of whom had no greater than grade 2 toxicity. Of these 21, the mean number of grade 2 toxicities resulting in treatment modification was 2.19+/−1.33, 7 patients had only one grade 2 toxicity. Early treatment discontinuation due to toxicity occurred in 23 patients, 39.1% (9/23) of whom had no greater than grade 2 toxicity. Of these 9, the mean number of grade 2 toxicities resulting in treatment discontinuation was 1.78+/−1.20, 3 had only one grade 2 toxicity, 1 patient only grade 1 toxicities.
Conclusions: In this cohort, many older patients did not complete treatment as planned. Treatment was modified/discontinued even for one or two low grade toxicities. Low grade toxicity resulted in treatment modification for 19.4% (21/108) and treatment discontinuation for 8.3% (9/108) of the whole cohort. Further work is required to clarify whether low grade toxicity has a greater clinical impact in older people, or whether clinicians have a lower threshold for modifying/discontinuing treatment in older people.
No conflict of interest.

Poster Session (Mon, 30 Sep)
Cancer in the Older Patient

1556 POSTER

Association between age at diagnosis and breast cancer outcome among elderly breast cancer patients − a FOCUS population-based study

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Background: Almost half of all breast cancers occur among the elderly population (65 years and older). Although tumor biology is often considered more favorable in the elderly, it was recently shown that breast cancer specific mortality was higher and recurrence rate was worse among the oldest elderly in a trial population. However, it is unknown whether this association persists in breast cancer patients in the general population. Therefore, the aim of this study was to explore the association between age and breast cancer outcome in a detailed population-based cohort of elderly breast cancer patients.
Methods: Patients were selected from the FOCUS cohort study, a population-based study of all consecutive elderly breast cancer patients diagnosed between 1997 and 2004 in the South Western part of The Netherlands. All patients with non-metastasized breast cancer who

received at least breast surgery were included in the current study. Primary endpoint was relative mortality (as the ratio between observed mortality in the cohort and expected mortality in the general population). Secondary endpoints were locoregional recurrence, distant recurrence and contralateral breast cancer. The endpoints were compared between the younger elderly (65−74 years) and the older elderly (75 years and older), using multivariable Cox models and Fine and Gray analyses to account for competing risks.
Results: Overall, 3,124 patients with a median age of 74.6 years were included. The oldest age group presented with more comorbidity, more hormone receptor positive cancer and higher disease stage, and they were treated less extensively. Relative mortality was higher for the oldest patients, as compared to patients aged 65−74 (multivariable RER 1.72, 95% CI 1.21–2.44; p = 0.003). The difference in relative mortality was most pronounced among patients with early stage disease. Recurrence free period for the development of locoregional recurrences, distant recurrences or contralateral breast cancer was similar for both age groups.
Conclusions: In the present study, we found an age-specific increase in relative mortality among elderly breast cancer patients. The age-specific increased mortality was not accompanied by a decreased recurrence free period. This may be due to under-registration or under-diagnosis of recurrent disease among elderly.
No conflict of interest.

1557 POSTER

Patient-reported information on diagnosis and cancer treatments in elderly: A cross-sectional analysis of the ELCAPA cohort study

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Background: Little is known about how the medical information regarding diagnosis and treatment is delivered and reported in elderly cancer patients. The objective was to assess the level and the factors associated with patient-reported information regarding cancer diagnosis and treatment proposal in elderly cancer patients.
Methods: From 2007 to 2012, all consecutive cancer patients aged 70 years or older referred to the geriatric oncology clinic were included in the prospective ELderly CAncer PAtients cohort survey (ELCAPA). Patients were systematically asked about the information received regarding diagnosis and treatment proposal. The interest variable was the level of patient-reported information: fully, partially or not reported. Analysis was done using ordered logistic regression.
Results: From 1103 included patients 691 had available data: mean age 80 (±5.6), 51.4% of men, metastatic 40.8%, colorectal cancer 23.1%, upper gastro-intestinal or liver 17.9%, breast 16.8%, urologic 23.6%. 306 (48.5%) had an anti-cancer treatment proposal with curative intent, 179 (28.4%) with palliative intent, and 146 (23.1%) had exclusive supportive care. 600 (86.8%; 95% CI: 84.3–89.3) reported a complete information, 35 (5.1%; 3.4−6.7) a partial and 56 (8.1%, 6.0–10.1) no information. In multivariate analysis, factors associated with a poorer level of patient-reported information were increasing age (1-year increase: adjusted OR (aOR), 1.07; 95% CI: 1.01–1.13, p = 0.01), type of treatment proposal (palliative vs curative treatment: aOR, 2.83; 95% CI:1.29–6.22, exclusive supportive care versus curative aOR 3.51, 1.57–7.84, p = 0.01), depressive symptoms (mini-Geriatric Depression Scale (⩾1vs<1) aOR, 2.07, 1.12–3.84, p = 0.02), cognitive impairment (MMSE (⩽24vs>24/30), aOR, 2.07, 1.12–3.84, p = 0.02), increasing nb drugs (1-drug increase aOR, 1.09, 0.99–1.22, p = 0.06). Functional status assessed by performance status and Activity Daily Living score was not independently associated with the level of patient-reported information due to a high correlation with the treatment type.
Conclusion: Level of patient-reported information is high in elderly cancer patients. But those with a palliative anti-cancer treatment or exclusive supportive care are less able to report the diagnosis or treatment information than those with a curative intent. Increasing age, depressive symptoms, cognitive impairment and polymedication were independently associated with a poorer patient-reported information.
No conflict of interest.

1558 POSTER

Clinical benefit of a one-day multidisciplinary work-up for risk assessment in unfit cancer patients

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Background: Unfit cancer patients are exposed to excessive drug toxicity or suboptimal treatment. The rapidly growing elderly cancer population makes urgent treatment guidelines for patients with comorbidities, polypharmacy or psycho-social frailty.
An early pre-therapeutic multidisciplinary assessment might improve the unfit patient management. We developed an experimental multidimensional program of integrated medicine called ARIANE, and evaluated its impact on treatment decision-making and patient trajectory.
Material and Methods: Unfit patients with an existing defined cancer treatment strategy entered into the program. A one-day multidisciplinary evaluation in outpatient setting combined consultations of cardiologist, geriatrician, diabetologist, anesthetist, pharmacist, pain specialist, dietician, psychologist and social worker. Staff meeting was conducted on a weekly basis. The day ended with a multidisciplinary meeting to decide either no change, or reinforced supportive measures follow-up, or upgrading of the treatment strategy, or less aggressive treatment option.
Results: Between March 2012 and February 2013, 41 patients, median age 76 years (range 25−88), 85% male, 59% PS 0−1, 90% grade 3 or 4 comorbidity in CIRS-G scale, were included. Genito-urinary, lung cancers and sarcoma represented 76% of pts. Eighty-three percent of pts were assessed by at least ⩾7 participants. Identified factors of vulnerability were polypharmacy (n = 34; 83%; >3 drugs), social distress (n = 12; 29%), depression based on GDS-scale or cognitive impairment (both n = 8; 19.5%) and severe malnutrition (n = 7; 17%). We identified drug interaction in 11 pts (27%). Amongst 30 elderly patients, only 9 were frail. The risk assessment resulted in anticancer treatment changes in 27/41 patients (66%): protocol adaptation (n = 10/41; 24%), less aggressive treatment (n = 8/41; 19.5%), or more intensive therapy (n = 9/41; 22%).
Conclusion: A one-day multidisciplinary risk assessment is feasible in the outpatient setting and results in changes in treatment strategy in the majority of unfit cancer patients.
Conflict of interest: *Ownership: none. Advisory board: Nutricia, Frésénius. Board of directors: none. Corporate-sponsored research: none. Other substantive relationships: none.*

1559 POSTER

Correlation of comprehensive geriatric assessment (CGA) with mortality in elderly patients with lung cancer: A single institution cohort analysis

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Background: In the last 60 years, >65 y population in Brazil has increased more than eigth-fold, from 1.6 million to more than 13 million people. This shift in demographics has a huge impact in healthcare, specially in oncology. Nevertheless, so far there is no national innitiative focusing oncologic geriatric patients. This study is part of an innitiative to improve oncologic care in geriatric patients in a single institution in São Paulo, Brazil.
Material and Methods: Since March/12, all patients >70 y admitted at AC Camargo Cancer Center have been submitted to CGA tools: Katz, Lawton, Nutritional Status (Mini nutritional assessment), Depression scales (GDS), comorbidities and polypharmacy analysis. The aims of the study were to assess if CGA could be feasible in daily practice and if it could be useful as a tool in treatment decision making. Statistical analysis used chi-square or Fisher exact tests, when indicated. Survival analysis was performed by Kapplan-Meier curve and group's comparison by the log-rank test and Mantel-Cox test. The results here presented refer only to lung cancer patients.
Results: From Mar/12 to Feb/13, 73 lung cancer pts were analyzed. Median age at admission was 75 y, 53% male, 47% female. Histology distribution was 57% adenocarcinoma, 22% squamous cell, 12% other non small cell and 9% small cell. Staging distribution was I (10%), II (8%), III (24%), IV (58%). There was an association between mortality and Katz (A

vs B/C; p = 0.004), Lawton (27 vs <27; p = 0.047), nutrition status (nutrition vs undernutrition/risk for undernutrition; p = 0.004) and performance status (0/1 vs ⩾2; p = 0.013). There was no association between mortality and the other parameters analyzed: number of comorbidities (⩽2 vs >2; p = 0.44), polypharmacy (<5 vs ⩾5; p = 0.73), age (<79 vs ⩾80; p = 0.95) and sex (male vs female; p = 0.52).
Conclusion: In this cohort, the incorporation of CGA tools in daily practice was feasible, able to predict mortality and could be useful in the treatment planning in elderly patients with lung cancer.
No conflict of interest.

Categories	Mean survival (months)	Statistical analysis (p, x^2)
PS 0/1 vs ⩾2	65.5 vs 20.8	p = 0.013, x^2 = 6.16
Katz A vs B/C	72.15 vs 29.42	p = 0.004, x^2 = 8.38
Lawton 27 vs <27	77.84 vs 37.23	p = 0.047, x^2 = 3.94

PS: performance status.

1560 POSTER

Concurrent chemoradiotherapy for elderly (over 75 years of age) patients with esophageal cancer

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Background: Evidence of concurrent chemoradiotherapy (CRT) has been established in younger patients with esophageal cancer (EC), but there is little data on the efficacy and safety of concurrent CRT for elderly patients. Conventional standard dose cisplatin plus 5-FU in CRT is generally not feasible for elders, and optimal chemo-regimens are unknown.
Patients and Methods: Betweeen 2007 and 2012, thirty consecutive elderly (⩾75 years) patients with EC underwent concurrent CRT in our institute. These patients were not considered surgical candidates due to age, comorbidity, patient refusal, or stage IVb. We retrospectively reviewed the efficacy and safety of CRT in the patients. Patients were sorted into two major groups: 5-FU- and taxane-based regimens. Comparison between these chemo-regimens was performed.
Results: Median age was 79 years (range, 75−88). Patient clinical stages were stage I:3; II:5; III:5; IVa:5; and IVb:8. Fourteen 5-FU-based regimens (10 cisplatin plus 5-FU, 3 S-1, and 1 5-FU) or 16 taxane (12 carboplatin plus paclitaxel, 2 paclitaxel, 1 docetaxel, and 1 cisplatin plus docetaxel) were administered as chemotherapies. Median total dose of radiotherapy was 60 Gy (range, 30−66 Gy). Twelve complete response (CR) and 8 partial response were confirmed, and overall response rate was 67%. Median progression-free (PFS) survival was 13.7 months (95% confidence interval, 6.3–32.3 months). Median overall survival was not reached. Regarding grade 3/4 adverse events, 8 (27%) neutropenia, 2 (7%) anemia, 2 (7%) febrile neutropenia, 1 (3%) esophagitis, and 1 (3%) dermatitis cases were observed. Treatment-related death due to broncho-esophageal fistula was suspected in one (3%) patient. Median PFS with taxane-based regimens was 19.1 months, and that of 5-FU-based was 8.4 months (p = 0.2837). Response rates and safety profiles were similar between taxane- and 5-FU-based regimens. Six (50%) of 12 patients who had received carboplatin plus paclitaxel achieved CR.
Conclusions: Our data suggest the efficacy and safety of concurrent CRT in elderly patients with EC. Carboplatin plus paclitaxel may be a potentially optimal regimen for elderly patients in CRT, and warrants future studies.
No conflict of interest.

1561 POSTER

Comprehensive Geriatric Assesment (CGA) based risk factors for caregiver burden amongst elderly asian cancer patients

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Background: The vital role played by caregivers in supporting elderly cancer patients is well recognized. While a number of caregiver burden analysis tools have been developed, none are based on clinical factors in the elderly cancer patient setting. This study aims to identify CGA based risk factors to help predict caregiver burden among elderly cancer patients.
Materials and Method: 249 newly diagnosed cancer patients aged 70 years and above, who attended the geriatric oncology clinic at the National Cancer Centre Singapore between 2007 and 2010 were evaluated.
Categorical characteristics were compared using Chi-square test or Fisher's exact test. Mann-Whitney U test was used to compare the continuous characteristics. Logistic regression models were fitted to assess the association of the variables with mild to severe caregiver burden. Multivariate analyses were performed on variables significant on univariate analysis.
Results: 244 of 249 patients had available information on caregiver burden. The median age of the patients was 77 and they were mainly males (61.1%).
Factors that were significantly associated with mild to severe caregiver burden on univariate analysis were ADL dependence (odds ratio [OR], 2.60; 95% CI, 1.29–5.24;), cognitive impairment (OR, 2.44; 95% CI, 0.71–8.41;), ECOG performance status 3−4 (OR, 5.14; 95% CI, 2.69–9.83;) higher fall risk (OR, 3.91; 95% CI, 1.52–10.04;), lower scores in dominant hand grip strength test (OR, 0.96; 95% CI, 0.94–0.98;), abbreviated mental test (OR, 0.80; 95% CI, 0.69–0.94;) and mini mental state examination (OR, 1.91; 95% CI, 1.01–3.59;), polypharmacy (OR, 2.22; 95% CI, 1.13–4.34;), higher nutritional risk (OR, 3.99; 95% CI, 1.58–10.05;), lower haemoglobin levels (OR, 3.25; 95% CI, 1.61–6.56;) and geriatric syndromes (OR, 4.60; 95% CI, 2.13–9.91;).
On multivariate analysis, only ECOG performance status of 3−4 (OR, 4.47; 95% CI, 2.27–8.80;) and abnormal haemoglobin levels (OR, 2.38; 95% CI, 1.14–4.99;) were associated with an increased probability of mild to severe caregiver burden.
Conclusion: ECOG performance status and haemoglobin were associated with mild to severe caregiver burden among elderly cancer patients. Using these factors may help clinicians identify caregivers at risk and take preventive action to mitigate that.
No conflict of interest.

1562 POSTER

Determinants of wellbeing in elderly non-small cell lung cancer patients: Are we asking the right questions? An explorative study

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Purpose: Chemotherapy is used to improve quality of life and median survival. The established quality of life questionnaires focus almost exclusively on parameters of negative wellbeing. The current study is an explorative study into determinants of wellbeing in elderly patients suffering from advanced non-small cell lung cancer (NVALT-3 study).
Patients and Methods: A total of 990 geriatric assessments (MGA) completed by 119 patients within 24 weeks of randomization were included. The analysis consisted of two stages. Items from the repeated MGAs at baseline, during and after chemotherapy, were divided into those with positive and negative wellbeing. Hierarchical cluster analysis was used to determine which items formed wellbeing clusters. During the second stage of analysis, these wellbeing clusters were used to assess patterns of patient wellbeing throughout time, based on similarity in wellbeing domain scores.
Results: Four independent (one positive and three negative) wellbeing clusters were distinguished, which included ninety per cent of all patients. Subsequently, four patterns of patient wellbeing throughout time were observed. The first patient cluster did not benefit from chemotherapy. The second and fourth cluster benefits from chemotherapy. The estimates for cluster 3 are less straightforward: although physical symptoms worsen during treatment, the negative affect improves temporarily.
Conclusion: Four different patient patterns of wellbeing were found throughout chemotherapy. Positive wellbeing is inadequately reflected in quality of life questionnaires.
No conflict of interest.

1563 POSTER

Persistence to aromatase inhibitor therapy among older women with breast cancer

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Purpose Aromatase inhibitor therapy (AI) significantly improves survival in breast cancer patients. Little is known about adherence and persistence to aromatase inhibitors and about the causes of treatment discontinuation among older women. Our objective was to combine multiple sources of data in order to describe adherence and persistence to AI − using prescription refills and patients' questionnaires − in a cohort of post-menopausal women with BC.
Methods: The ELIPPSE 65 cohort was constituted in order to document the medium and long-term psychosocial impact of BC on women over 65. Between 2006 and 2008, 382 women over 65 receiving a first AI therapy for breast cancer were included and followed until June 2011. Women were selected from the French National Health Insurance databases. We used survival analysis methods to study time to treatment discontinuation.
Results: Overall, using pharmacy refills, non-persistence to treatment decreased over time: from 8.7% (95% CI: 6.2–12.1) at 1 year, to 15.6% (95% CI: 12.2–19.8) at 2 years, 20.8% (95% CI: 16.7–25.6) at 3 years, and 24.7% (95% CI: 19.5–31.0) at 4 years. In addition, 13% of the women with positive hormonal receptor status at cohort entry did not fill any prescription for anti-hormonal therapy. During patients' follow-up, 35 of the 382 women switched from AIs to tamoxifen. Among continuous users of AI treatment, 93.5% (n = 357) had more than 80% of days covered by medication.
Using questionnaires, 292 of the 382 women reported taking their medication without outside help. Among them, 10.7% reported having forgotten to take their hormonal treatment at least once. The most frequent reason mentioned (29.7%) was not being at home when supposed to take the treatment. Self report of non-adherence by women was not associated with decreased persistence to treatment measured by pharmacy refills.
Conclusion: In our cohort of older women with BC, AI therapy is discontinued prematurely in a substantial portion of patients,using pharmacy refill data. Combining this information with patient questionnaire will enable us to identify determinants of persistence to AI therapy among the 292 women reporting taking their medication without help. Results will be discussed.
No conflict of interest.

1564 POSTER

Information needs of older women considering breast screening attendance: A mixed methods study

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Background: Disease specific survival for older women with breast cancer are reduced compared to younger women. Older women (>70 years) have an increased risk of breast cancer yet have reduced breast symptom awareness and are no longer routinely invited for routine screening. Voluntary uptake rates are poor. There is ongoing debate about the relative risks and benefits of screening in older women and little randomised trial data to inform debate. This study has used mixed qualitative and quantitative methods to explore the information needs and preferences of older women (and health professionals) to aid informed screening decision making.
Methods: Semi structured qualitative interviews with specialist health professionals (breast surgery, radiology, specialist nurse, breast oncology) and women over 70 years were undertaken. These were analysed using framework analysis to identify themes and issues relevant to screening decision making. A bespoke questionnaire was then designed to quantify the importance of each issue in a larger cohort of women.
Results: Interviews were conducted with 23 health professionals and 19 older women (age range 71−84 years, recruited from hospital clinics). These suggested a range of information needs and preferences. A bespoke questionnaire was designed using a mixture of Likert or other quantification techniques and distributed to 177 older women attending a range of hospital clinics. The response rate was 51% (91 of 177). Only 22% (20/91) were aware that breast cancer risk increases with age with 63% (57/91) aware of self-referral service for screening. Women felt screening decision making required information about breast cancer age-specific incidence (71%; 65/91), treatment options following a breast cancer diagnosis (57%; 52/91) and local contact details for the screening unit (73%; 66/91). Screening risks were felt to be less important, and if mentioned, older women preferred risk levels to be quantified as a proportion (34%; 31/91) or statement, e.g. rare/common (34%; 31/91) rather than a percentage. The preferred format for information varied but leaflets were most popular (68%; 62/91). Web-based information was unpopular (12%; 11/91).
Conclusions: Older women have low levels of breast cancer and screening knowledge which may contribute to inferior cancer outcomes. Education may enhance informed screening uptake. This research has identified key informational needs and preferences for older women.
No conflict of interest.

1565 POSTER

Safety and efficacy of bevacizumab (Bv) in elderly patients with NSCLC adenocarcinoma

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Background: Bv is a novel anti-angiogenic agent used in many advanced solid tumours, including non-squamous NSCLC. In contrast to clinical studies where enrolled pts are fit, many elderly NSCLC pts suffer from co-morbidities and often have history of a CVD.
Methods: Medical records of 2672 pts diagnosed with NSCLC between 2001–2012 were screened. We identified and examined pts ⩾75 yrs old treated with bev, for their demographics, clinical data and treatment (Tx) details. We focused on those elderly pts with stable pre-existing cardiovascular disease.
Results: 356/2672 NSCLC pts received Bv at any Tx line. 33/382 (8.6%) were ⩾75 yrs old. Of those, 29 had various co-morbidities including 19 pts with stable CVD on medical Tx. In the 19 pts with CVD the male:female ratio was 17:2 and mean age 77 yrs (range 75−86). 8/19 pts had impaired renal function. All pts were of Performance Status ECOG 0/1. Median number of Bv cycles was 5 (range 2−11). 17/19 pts experienced ⩾1 side effects (11 epistaxis and haemoptysis, 5 proteinuria, 4 hypertension) which led to treatment discontinuation in 5 pts. No major/fatal adverse events were noted. 8/19 pts (42%) showed radiological partial response and 5 (19%) stable disease (total disease control rate 61%). Median survival from initiation of Bv till death/last follow up was 7 months (range 2−28, 95% CI 5.14–12.55).
Conclusion: Treatment with Bevacizumab seems to be safe and effective in elderly NSCLC patients with controlled pre-existing cardiovascular disease and good PS. These patients might benefit from participation in clinical trials similarly to younger NSCLC patients.
No conflict of interest.

1566 POSTER

Safety and efficacy of erlotinib (E) in elderly patients with NSCLC adenocarcinoma

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Background: Besides chemotherapy, E is another option in NSCLC pts especially in those with EGFR mutations. Elderly pts enrolled in trials are fit without cM, but in clinical practice most suffer from cM.
Methods: Medical records of 1221 pts diagnosed with NSCLC between 2008–2012 were screened. We examined pts ⩾75 yrs for demographics, clinical data and Tx details.
Results: 233/1221 NSCLC pts received E at any line. 53/233 (23%) were ⩾75 yrs old. Male:female ratio was 34:19 and median age 79 yrs (range 75−88). NSCLC subtypes included 31 adenoca, 8 squamous cell, 9 NOS and 5 others. 50/53 pts had cM (⩾2 in 46 pts, 1 in 4pt). Main cM were cardiovascular disease (n = 41), COPD (n = 14), other cancer (n = 10) and diabetes (n = 8). 8 pts were tested for EGFR mutations (5 -ve, 3 +ve). Performance Status was satisfactory (ECOG 0−1) in 8 pts and poor (2−3) in 45pts. 8pts were treated with E 100 mg and 45 pts with E 150 mg (12 pts needed dose reduction). Complete follow up data were found in 46pts. Mean duration of treatment was 79 days (range 9–662). 35/46 pts experienced side effects (s.e) [rash n = 29, diarrhea n = 17] which led to treatment discontinuation in 12pts. Pts with abnormal creatinine clearance (n = 13) were more likely to stop treatment due to s.e (6/13 versus 6/33). 17/46 pts (37%) achieved disease control (5 PR, 12 SD) and a time to progression (TTP) of 157 days (range 106–662, 95% CI 132.79–270.74) while 22/46 pts had PD as best response (TTP 49d, range 19−88, CI 44.67−64.97). 7pts were not evaluable (stopped Tx due to s.e). All EGFR+ve pts had disease control (2PR, 1SD).

Conclusion: E is a valuable option in elderly NSCLC patients with co-morbidities, especially if they harbor EGFR mutations. Impaired renal function might be associated with propensity to side effects and earlyTx discontinuation.
No conflict of interest.

1567 POSTER

Rectal cancer management in elderly patients: Experience of a single Portuguese institution

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Background: Cancer is the leading cause of death between ages of 60 to 79 years in developed countries. More than a half of all cancer deaths happen in patients with more than 75 years. Colorectal cancer is the second most common neoplasia and a third of cases have origin in the rectum. We aim to evaluate the influence of age and comorbidities in rectal cancer (RC) management in a Cancer Centre in Portugal.
Material and Methods: Retrospective analyses of patients (pts) with rectal cancer aged 75 or more treated in our institution from January 2007 to March 2010. Epidemiological and clinical data were recorded. Charlson Comorbidity Index (CCI) was calculated, along with 1 and 3-year survival.
Results: 82 pts (24.6% of the total RC treated in the institution in that period), 64.6% men, mean age 79.7±3.8 years (75−91). Tumor location: lower rectum-43.9%, midrectum-42.7%, upper rectum-13.4%. TNM Stages: 39%, IIIB, 28% IIA. 74.4% had neoadjuvant treatment: 51.2% chemoradiotherapy (CHRT; protracted 5-FU) and 22% (20 pts) only radiotherapy (9 had short course). Dose reduction was needed in 26.2%. Surgery was performed in 79.3%, 65 pts (of these 73.8% had a low anterior resection). 23.2% had adjuvant chemotherapy (de Gramont regimen 14.6%). Colostomy closure was achieved in 62.5% of suited pts. Grade III/IV toxicities occurred in 17.1%. Survival was 74.4% at 1 year and 40.2% at 3 years. 56.1% are dead, median follow up (40 months). CCI was low (0−1) in 68.3% and high (⩾2) in 31.7%. Age was well balanced between both groups (mean 79.88 *vs.* 79.18 years; P = 0.459). Most frequent comorbidities were: diabetes (18.3%), myocardial infarction (15.9%), congestive heart failure (14.6%) and chronic pulmonary disease (8.5%). Pts with lower CCI scores were treated more aggressively (64.7% *vs.* 36% did CHRT; p = 0.083) and colostomy closed more frequently (81.8% *vs.* 33.3%; p = 0.04). Survival was not affected by comorbidities at 1 year (76.8% with low CCI *vs*. 69.2% with high CCI; p = 0.319) but was a trend toward decreased survival at 3 years (46.4% *vs.* 26.9%; p = 0.075). Pts with survival over 3 years tended to have CHRT more often (71% *vs.* 45.5%; P = 0.073).
Conclusions: Rectal cancer management should always include comorbidities assessment to guide the treatment choice. Our data suggests that low comorbidity elderly patients could be managed with standard treatment. Only high comorbidity patients should be managed with less intense treatment, as there is a trend for shorter survival. In those patients surgery could be simplified if colostomy closure is thought to be unlikely. These results should be viewed with caution, as they need to be tested in prospective randomized trials.
No conflict of interest.

1568 POSTER

Cardio toxicity for older breast cancer patients treated with trastuzumab

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Background: Trastuzumab is used in adjuvant setting and metastatic setting of breast cancer who over-expressed Her. The reduction of mortality and recurrence are obtained when used. The incidence of complications, especially cardio toxicity is unknown, especially in older patients. In this study, we evaluated the rates associated with Trastuzumab regimens in older breast cancer patients.
Methods: Breast cancer patient's ⩾65 years old with diagnosed stage III−IV breast cancer, with over expression of HER, in patients between 2010–2012, treated with chemotherapy and Trastuzumab were identified and enrolled in this study.
Results: A total of 28 patients were included. 100% of them received Trastuzumab; 20 patients (71.4%) in adjuvant setting and 8 (28.5%) in metastatic setting. After adjusting for chemotherapy used, patients developed congestive heart failure in 39.2% (11 patients). 21.4% (6 patients) was observed in adjuvant setting and 17.8% (5 patients) in metastatic setting. A comparison was done with younger patients who received Trastuzumab; in adjuvant and metastatic settings. Older age increase the risk of developing congestive heart failure (39.2% Versus 20% in younger patient's). However, there was an increased risk of congestive heart failure associated with anthracycline regimens in older and younger age.
Conclusions: In this study, the risk of cardio toxicity in older breast cancer patients is higher than in younger population. Cardiac comorbidities and other clinical characteristics may identify high-risk patients. More studies and comparison in younger population are needed.
No conflict of interest.

1569 POSTER

Dynamic MRI assessment of response to a new radiosensitization treatment (KORTUC II) in patients with stage I/II breast cancer with advanced age or who refuse surgery

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Background: We developed a new tumor-injectable radiosensitizer agent that contains hydrogen peroxide and sodium hyaluronate, which can convert radioresistant tumors into radiosensitive ones. The method was named Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, Type II(KORTUC II). The advent of this agent has allowed us to perform breast-conserving treatment (BCT) without surgery for patient with stage I/II breast cancer with advanced age or who refuse surgery. Since surgery was not performed, histological confirmation of the primary tumor region following KORTUC II treatment was not possible. Dynamic magnetic resonance imaging (MRI) is highly useful for precise evaluation of the therapeutic response to neo-adjuvant chemotherapy (NAC) and/or induction chemotherapy for patients with breast cancer. Therefore, the purpose of this study was to evaluate the therapeutic response to KORTUC II treatment in patients with stage I/II breast cancer using annual dynamic MRI.
Material and Methods: The study was performed at Kochi Medical School Hospital from 2006 to 2013. Nineteen patients with stage I/II breast cancer and advanced age or who refused surgery were enrolled. Full informed consent was obtained from all patients. Hypofractionated radiation therapy (RT) was administered using a tangential field approach: energy level was 4 MV, the total dose was 44 Gy administered as 2.75 Gy/fraction. RT was performed five times per week for each patient. The new radiosensitizer was injected into the breast tumor tissue twice a week under ultrasonographic guidance, just prior to each administration of RT from the 6th fraction onwards. Chemotherapy was not administered before or after Prior to KORTUC II treatment, either due to advanced age or patient refusal. Following KORTUC II treatment, patients with estrogen receptor-positive tumors were started on endocrine therapy with an aromatase inhibitor. All patients underwent dynamic MRI prior to and every year after KORTUC II treatment. Findings from MRI were compared with those from other diagnostic modalities performed during the same time period.
Results: In all cases, dynamic MRI performed at approximately 1 year following KORTUC II treatment showed disappearance of tumors. The marked therapeutic effects of treatment were also confirmed through other diagnostic modalities performed during the same time period. None of the 19 patients had distant metastasis, and only one patient experienced local recurrence (at 34 months after KORTUC II). The mean follow-up period for patients at the end of February 2013 was 42.6 months.
Conclusions: Dynamic MRI showed that KORTUC II had a marked therapeutic effect in patients with stage I/II breast cancer. These results confirm that BCT without surgery procedure can be safely performed using this new radiosensitization treatment.
No conflict of interest.

1570 POSTER

Impaired pre-operative nutritional status is a risk factor of adverse outcome in onco-geriatric surgical patients

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Background: In the growing onco-geriatric surgical population identifying frail patients is crucial as they are at an increased risk of adverse outcome.

Ageing is characterized by an increased incidence of malnutrition and also cancer patients frequently present in a malnourished state. Our aim was to investigate the incidence of impaired nutritional status and the impact of an impaired nutritional status on short term outcome in onco-geriatric surgical patients.
Methods: In an international cohort, patients ⩾70 years undergoing elective surgery for solid tumors were prospectively recruited. Primary endpoint was the incidence of major complications during the first 30 days after surgery, secondary endpoint was post-operative length of stay (LOS). Patients were classified as having a normal nutritional status, a mildly impaired nutritional status or a moderately or severely impaired nutritional status. This was defined by the decrease of food intake compared to their previous amount of ingestion and the rate and amount of weight loss. Data were analyzed using multivariate logistic regression analyses to estimate odds ratios (OR) and 95% confidence intervals (95%-CI).
Results: Data of 345 patients, with a median age of 76 years (range 70−96), were analyzed. A total of 240 patients (69.6%) underwent major surgery and 64 patients (18.9%) experienced major complications. LOS was more than 7 days in 176 patients (51.3%). Nutritional status was mildly impaired in 87 (26.2%) and moderately or severely impaired in 26 (7.8%) patients. Multivariate logistic regression analyses showed that nutritional status is an independent predictor of the occurrence of major complications and prolonged LOS (table 1).

Table 1. Results

Nutritional status	Major complications OR (95% CI; p-value)[a]	LOS >7 days OR (95% CI; p-value)[b]
Mildly impaired	3.80 (1.76–8.22; 0.001)	2.07 (1.17–3.68; 0.013)
Moderately or severely impaired	3.43 (1.16–10.11; 0.026)	4.16 (1.39–12.43; 0.011)

[a]Corrected for center, gender, age and minor/major surgery.
[b]Corrected for center and age.

Conclusions: Results indicate that impaired nutritional status is a risk factor of adverse postoperative outcome, but more research on the influence of preoperative optimization of nutritional status on postoperative outcome in onco-geriatric patients is needed.
No conflict of interest.

1571 POSTER

Influence of preoperative nutritional screening on treatment planning, and short-term outcome in elderly patients with gastric cancer

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Background: About 30% of all patients in hospital are undernourished. A large part of these patients are undernourished when admitted to hospital and in the majority of these, undernutrition develops further while in hospital. Particularly undernourished patients undergoing surgery treatment due to gastric cancer are exposed to increased risk of severe complications. In Poland in 2011 an obligatory nutritional screening was implemented according to the binding statute. Over 70 years after Hiram Studley's research, do we pay our attention enough to nutritional screening in our everyday practice?
Material and Methods: Retrospective study of 148 cases of gastric cancer patients underwent surgical treatment in the years 2005–2013. Patients treated before 2011 were not screened, and those treated after 2011 were obligatorily examined according to NRS 2002 or SGA scale on admission to hospital.
Results: During the last 8 years 148 patients with gastric cancer underwent surgical treatment. Patients were retrospectively divided into two groups: − before 2011 (121 cases), and without nutritional screening, and − after 2011 (27 cases) examined due to NRS 2002, or SGA scale. The percentage of patients over 65 year (55.6% vs. 57.8%), and average hospital stay (17.8 vs. 17.4 days) were similar in both groups. The percentage of total resections was higher in second group (46.3% vs. 59.3%). 11 patients in second group were estimated 3 or more points in NRS 2002. In 7 cases among screened patients the operative treatment was delayed because of malnutrition (average 7 days after admission to hospital). The most common nutritional support implemented was preoperative oral nutrition with ready-made nutrients. There were no severe complications (perioperative death, anastomotic leakage) noted in second group, and a severe postoperative respiratory failure was sparser (17.6% vs. 12.5%).
Conclusions: Implementation of the obligatory nutritional screening resulted in modification of perioperative planning, and in some cases delayed surgical procedure. However, there was no influence on an average hospital stay. In group of screened patients there were no severe complications (perioperative death, anastomotic leakage) noted until end of this study. However, watchful screening, and monitoring of complications have to be continued.
No conflict of interest.

1572 POSTER

Surgical treatment of patients aged 85 years and over with special consideration to neoplastic disease

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Background: The growing number of elderly and aged people is noted in the general structure of contemporary societies. At the same time an increase in the risk of the incidence of chronic disease including oncologic ones is observed in elderly and aged patients requiring surgical treatment.
Aim of work/research: The aim of this work/research was an analysis of indications for surgical treatment, results of treatment as well as complications and mortality of patients aged 85 years or older.
Materials and Methods: The study group consisted of patients aged 85 years and older treated on at General, Oncological and Endocrine Surgery Department of the Provincial Polyclinic Hospital in Kielce between 2009 and 2011. All patients underwent analysis of retrospective medical documentation. The research concerned the analysis of indications for surgical treatment, a procedure for surgical intervention, a kind of possible complications and mortality. The results of the research were compared with the ones of a randomly selected control group of patients (n = 98) aged 40−75 years who underwent surgical treatment in the same place and time.
Results: The most frequent indication, urgent for surgical intervention in patients aged 85 years and older was *ileus*/*intestinal occlusion ileus* (34%) caused by colorectal carcinoma, and both abdominal hernias (24%) and cutaneous neoplasms and tumors of subcutaneous tissue (24%) were the planned ones. Surgical interventions most often concerned the large intestine in the age group which was analysed. Postoperative complications occurred *more*/*in larger numbers* in patients who had undergone *surgical intervention*/*surgery* as a matter of urgency, had general character and took the form of circulatory and respiratory insufficiency (7%). Postoperative *mortality*/*death rate* in the group of patients aged 85 years and older was 13%. As a general rule, postoperative complications were of local character in the control group and concerned mainly the course of healing of postoperative wound (4%). *Mortality*/*Death rate* in the postoperative period in this group *constituted*/*was* 1%.
Conclusions: Early diagnostics of neoplastic diseases, especially concerning the large intestine at the stage which do not give symptoms of ileus and enable to perform surgical intervention in a planned procedure is significant in the *surgical oncology care*/*surgical cancer care* of patients aged 85 years and older. Performing surgical intervention as a matter of urgency in aged people significantly increases the risk of postoperative complications, including death.
No conflict of interest.

1573 POSTER

The course of health related quality of life in postmenopausal women with breast cancer from breast surgery and up to five years post-treatment

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Background: Cancer treatment of the elderly patients is an increasingly important concern since the risk for developing breast cancer increases with age. The effects of adjuvant chemotherapy on the breast cancer disease seem to be as good for pre and postmenopausal patients, at least for hormone receptor negative patients. However, very few patients older than 65 years are included in randomised studies. In clinical practice, it is common that elderly women are offered less chemotherapy, because of the unsubstantiated belief that they will experience a larger number and more severe adverse effects as well as poor functional outcomes and significant decrements in health related quality of life (HRQOL).
The aim of this study was to follow HRQOL in postmenopausal women (55−80 years) with breast cancer receiving adjuvant treatment after surgery, until five years post-treatment, and compare with a general population.
Patients and Methods: The patient sample included 150 women (adjuvant CT n = 75 and RT n = 75) and two reference samples from the Swedish SF-36 norm database.
Results: The results showed that at baseline the women in the patient sample experienced significantly higher levels of physical functioning and general health compared to the general population. They also experienced

significantly less bodily pain, lower emotional role functioning and mental health. Five years after completion of treatment, the patient sample experienced better HRQOL than the reference sample in all domains, supporting our hypothesis that the impact on HRQOL would have been resolved over time for these patients.
Conclusion: Postmenopausal women (55−80 years) seem to successfully manage the effects of adjuvant treatment on HRQOL.
No conflict of interest.

1574 POSTER

Epoetin biosimilars in the management of chemotherapy-induced anemia in elderly patients: A subanalysis of the ORHEO study

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Background: Chemotherapy-induced anemia (CIA) treatment requires transfusion, or epoietin administration. Elderly patients (pts) may experience severe complications from CIA, with fatigue and cardiovascular events.
Methods: ORHEO (place of biOsimilaRs in the therapeutic management of anemia secondary to chemotherapy in HaEmatology and Oncology) was a post-marketing, observational, prospective, multicentric study. Adult CIA (Hb<110 g/l) pts with solid tumors, lymphomas or myelomas and eligible for epoetin alpha biosimilar (EAB) treatment were included to receive EAB according to drugs approval recommendations. Recorded data included demographics, performance status, blood count and iron load profile. Safety (NCI-CTC V2.0) and efficacy were also assessed. The primary study endpoint was the rate of responders (defined as increase in Hb levels to 100 g/l or at least 10 g/l since inclusion visit, or reaching target Hb set at start of study, without any blood transfusions in the 3 weeks prior to measurement) at +3 months (M+3). Other endpoints included safety, patterns of treatment interruption and rate of responders at +6 months (M+6). Here we present data for the elderly (>= 70 years old) pts.
Results: 1,009 pts (54.3% male, 45.7% female) >= 70 y.o. were included in this analysis. Median age was 77 y, range [70−93]. At baseline, 36.3, 57.8 and 3.4% of pts had respectively grade 1, 2 and 3 anemia. Iron supplementation was given in 9.9 (oral) and 16.0% (IV) of pts. At M+3, 84.0% of pts were responders (IC95% 81.4–86.3). Moreover, respectively 241 pts (23.8%) and 139 pts (13.7%) had stopped EAB permanently or temporarily, mainly because of efficacy (45.2 and 79.1% respectively); other reasons were side-effects (2.9 and 0.7% respectively), lack of efficacy (7.0 and 4.3%), and unspecified reason (44.8 and 15.8%). Similar results were observed at M+6 with 86.8% of responders. 17.0% of pts reported side effects (all grades); the most frequent were thromboembolic events (4.5%). No EAB-related death was reported. 94.6% of pts reported being satisfied with EAB therapy at M+3 and M+6 and willing to restart if needed.
Conclusion: EAB therapy is efficacious on CIA management in elderly pts with low toxicity.
No conflict of interest.

1575 POSTER

Current approaches in the treatment of malignant ascites in Germany and Austria

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Background: Malignant Ascites (MA) is a common manifestation of advanced cancer associated with a poor prognosis and decreased quality of life. Currently there are no evidence based guidelines for the management of MA and only one agent is approved for its treatment. We conducted a survey with physicians throughout Germany and Austria, to get an overview of current approaches and opinions in the treatment of MA.
Methods: 128 medical oncologists (MO), gastroenterologists (GE) and gynecologists (GYN) completed an electronic questionnaire consisting of 33 questions. Answers were evaluated with descriptive statistics.
Results: 90% of the physicians were from Germany, 10% from Austria. 48% of those were MO, 30% were GYN and 14% were GE. Most physicians treated an average of 34 pts/year with MA. 26% of these pts suffered from ovarian, 20% from pancreatic, 17% from gastric and 14% from colorectal cancer. The majority of the physicians associated MA with poor prognosis (92%) and significant reduction in quality of life (87%). One third felt MA was a contraindication for full dosing of systemic chemotherapy. Paracentesis (P) was performed in 70% of pts with with symptom relieve and quality of life being the main reasons. Almost half of the pts required 3−5 P, 50% even more than 5 P during the course of their disease. Only 15% of pts needed multiple P per week, the majority (79%) needed the procedure either once a week or every 14 days. In 61% of pts 3−5 l ascites fluid was drained. Only in 8%, 5 l and more were removed. Volume substitution with IV albumin was performed in 40% of pts. Most pts (55%) had to stay 1−3 h in a healthcare facility for the procedure. However 21% had to stay >1 day. While almost all physicians (89%) performed a P at some point in the treatment of MA, 75% felt that a systemic chemotherapy and 55% thought a concomitant diuretic therapy were a necessary adjunct. 7% of the pts received a targeted treatment with catumaxomab.
Conclusions: Even though repeated P is the main pillar of treatment of MA, its effect is only temporary, must be performed multiple times, requiring hospital resources. Further treatment strategies have to be evaluated in prospective studies. Targeted therapies like catumaxomab should be integrated into these.
No conflict of interest.

1576 POSTER

Phase I trials in patients (pts) >65 years with advanced solid cancers: Do they fare worse than younger patients?

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Background: Individuals ⩾65 years (yr) represent ≈60% of the total cancer population and 80% of the cancer related deaths in Europe and the US. However, pts ⩾65 yrs are generally a small proportion of those enrolled in clinical trials due to the un-proven bias that their tolerability levels are less than that of those <65 yrs. This study aims to compare the experience of pts ⩾65 years (G1) treated in a dedicated Phase I unit with those <65 years (G2) to test the hypothesis that G1 pts have lower level of tolerability and clinical benefit compared to G2.
Methods: Clinical characteristics and outcomes of all the pts treated consecutively in the Drug Development Unit, Royal Marsden Hospital, 2005–2009 were recorded. The outcomes including progression free survival (PFS), overall survival (OS), response rate (RR), clinical benefit rate (CR+PR+SD=CBR) at 6 months (m) along with the detailed toxicity data were compared between G1 and G2.
Results: One thousand and four pts were treated in the phase I unit in 30 Phase I trials, with 315 (31%) pts ⩾65 years. Both groups were balanced with most common tumour types for respective age group, except prostate cancer. Prostate cancer constituted 83 of the 315 cases in G1; excluding these from the analysis, the CR/PR and CBR ⩾6 months rates were 3.6% and 11.2m respectively and PFS/OS were 3.0m and 7.9m. The clinical benefit achieved with and without prostate cancer patients is summarised in table 1. Grade 3/4 toxicities were observed in 24% in G1 (22% in G2) and led to trial discontinuation in 6% (8% in G2); no toxicity-related deaths were recorded in either groups. In G1 9.5% pts had un-planned hospital admissions and 15.6% had serious adverse events (SAE). In a separate multivariate analysis, the previously validated Marsden prognostic index (Arkenau JCO 2009) was examined in G1. This confirmed that as in G2 the serum albumin, number (no.) of metastatic sites, lactate dehydrogenase (LDH) were predictive of PFS and OS and in addition no of previous lines of chemotherapy in both groups and ECOG performance status (PS ⩾2) at inclusion were prognostic of OS; in G1.
Conclusion: Phase I clinical trials should be considered in advanced cancer pts regardless of their age. Acknowledging the impact of pt selection, there is no evidence that the older pts do worse as regards either efficacy or safety compared to the younger counterparts.
No conflict of interest.

	G1 (all tumour types) (Median 69 yrs, range 65−85) n = 315	G1 (without prostate) n = 232	G2 (Median 52 yrs, range 12−64) n = 689	G2 (without prostate) n = 640
CR, % (95% CI)	0.6	0.6	0	0
PR, % (95% CI)	3.5 (1.9−6.3)	3.0 (1.3−6.3)	5.1 (3.5−7.3)	4.5 (3.3−6.8)
CBR ⩾6 months, % (95% CI)	14.3 (10.9–18.8)	11.6 (8.18–16.6)	15.3 (13.4−19)	11.3 (11.9–17.7)
1 Year Survival, %	42	31	31	29.2
mPFS, months (95% CI)	3.5 (2.9−4.1)	3.0 (2.5−3.5)	1.8 (1.7−2.0)	1.8 (1.7−1.9)
mOS, months (95% CI)	9.7 (8.6–10.9)	7.9(6.5−9.3)	7.7(6.6−8.6)	6.9 (6.2−7.7)

1577 POSTER

Reduced risk of distant recurrence after adjuvant chemotherapy in patients with stage III colon cancer aged 75 years or older

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Background: Little is known about effects of adjuvant chemotherapy (CT_{adj}) on risk of distant recurrence in elderly with colon cancer, treated in daily practice.
Patients and Methods: All patients who underwent resection for stage III ($T_{any}N_{1-2}M_0$) colon cancer diagnosed in the southern Netherlands in 2003–2008 were included. Distant recurrence was defined as a distant metastasis of primary colon cancer in other organs, regional lymph nodes not included, after a primary diagnosis of M0 disease. Propensity score matching (PSM) was applied to create a subsample to reduce bias caused by differences between age groups. For both the total study population and the PSM sample, crude 5-year percentages for distant recurrence were calculated based on Kaplan–Meier curves and Cox regression analyses were used to discriminate independent risk factors for distant recurrence.
Results: 1189 patients were included in the study of whom 60% received adjuvant chemotherapy and 33% developed a distant recurrence. 35% of the study population was aged $\geqslant$75 years. Median follow-up time was 35.2 months. In the PSM sample, 698 patients (59%) of the original study population could be included, with an equal proportion of patients being <75 years and $\geqslant$75 years. 50% received adjuvant chemotherapy and 37% developed a distant recurrence. Adjuvant chemotherapy was correlated with a reduced risk of distant recurrence in both the total study population (hazard ratio (HR) CT_{adj} vs. nCT_{adj} 0.59, 95% CI 0.45–0.76) and in the PSM sample (HR CT_{adj} vs. nCT_{adj} 0.69, 95% CI 0.50–0.96). In separate analyses for patients aged <75 years and $\geqslant$75 years, the effect of adjuvant chemotherapy on the risk of distant recurrence remained comparable for both age groups (HR CT_{adj} vs. nCT_{adj} 0.55, 95% CI 0.40–0.76 and 0.57, 95% CI 0.36–0.90 respectively).
Conclusion: The results of the present study underline that consideration of adjuvant chemotherapy is definitely warranted for all patients aged $\geqslant$75 years with resected stage III colon cancer, as they derive comparable benefit from adjuvant chemotherapy as their younger counterparts with regard to risk of recurrence. However, it remains important to realize that in certain circumstances, withholding adjuvant chemotherapy from elderly may be appropriate, for example in case of short life expectancy or increased risk of serious side-effects.
No conflict of interest.

1578 POSTER

Sorafenib's safety and efficacy are similar in elderly and younger patients treated for hepatocellular carcinoma

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Background: Sorafenib is the standard of care for advanced hepatocellular carcinoma (HCC). The peak incidence of HCC is around 70 years in western countries; however, data are scarce regarding safety and efficacy of sorafenib in the elderly population.
Material and Methods: We retrospectively reviewed data from patients treated with sorafenib for HCC at our institution. We compared baseline characteristics, safety and efficacy data across different age groups. Proportions were compared with a Chi-2 test, survival were compared with the Kaplan–Meier method with a log-rank test.
Results: Since 2008, 129 patients were treated. 78 (60.5%) were <70 years-old (YO), 27 (20.9%) were between 70 and 74, 18 (14.0%) were between 75 and 79 and 6 (4.7%) were $\geqslant$80 YO. Comparisons were primarily done between the 105 (81.4%) <75 YO and the 24 (18.6%) $\geqslant$75 YO patients. Both groups had similar baseline characteristics, except for a trend toward more patients with Child B cirrhosis in the younger group (22.5% vs 5.3%, p = 0.09). The frequency of dose reduction was similar between the 2 groups (52.4% vs 54.2%, p = 0.87), as was the occurrence of severe toxicities (43.8% vs 50.0%, p = 0.58) and the need for hospitalization due to toxicity (10.5% vs 12.5%, p = 0.77). There was a trend toward less frequent interruption of treatment in the younger group (27.6% vs 45.8%, p = 0.08), and less frequent definitive discontinuation of treatment due to toxicity (29.5% vs 45.8%, p = 0.12). Response rates by mRECIST were similar (27.4% vs 35.3%, p = 0.55). Median progression-free survival was 5.4 months in the younger age group vs 7.8 months in the older age group (p = 0.30), while median overall survival were 11.4 months and 9.9 months, respectively (p = 0.17). Results were similar if the thresholds chosen were 70 or 80 YO, except for discontinuation of sorafenib due to toxicity that was significantly less frequent in the <70 YO age group compared with the $\geqslant$70 YO age group (24.4% vs 45.1%, p = 0.01).
Conclusion: In this single-center retrospective study, sorafenib shows similar results in terms of safety and efficacy in the elderly and younger populations. Careful baseline evaluation is needed for patient's selection in the elderly population, as well as active management of toxicity. Elderly patients in our series have been considered fit for sorafenib therapy. Such selection could be improved by implementing geriatric evaluation, which could also prevent complications from other comorbidities.
No conflict of interest.

1579 POSTER

Overall treatment utility: A novel outcome measure reflecting the balance of benefits and harms from cancer therapy

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Introduction: Established clinical trial endpoints fail to individually capture the balance of benefits and harms from cancer treatments. 'Overall Treatment Utility' (OTU) is a novel composite outcome measure that was developed within the FOCUS2 trial in elderly patients treated with chemotherapy for advanced colorectal cancer. It combines clinical and radiological response, toxicity, adverse events and patient-reported acceptability of treatment. OTU needs further development and validation. This study aimed to test the feasibility and value of measuring OTU in an alternative frail/elderly population with advanced gastric or oesophageal (GO) cancer.
Methods: Patients were randomised between three treatment arms containing triplet, doublet or single agent chemotherapy. Details of the trial and conventional outcomes are reported elsewhere. OTU was scored according to the algorithm used in the FOCUS2 trial which categorises outcome into a three-point ordered categorical scale (good/intermediate/poor). Data return and compliance with the patient-reported component was recorded. Survival analysis was used to correlate OTU with overall survival (OS) and progression free survival (PFS).
Results: The study included 55 patients with a median age of 75 (range 50−87). OTU provided useful information enabling discrimination between treatment arms. OTU was prognostic for OS in patients alive at Week 12 (logrank test for trend p = 0.0001), PFS in patients alive and progression free at week 12 (logrank test for trend p = 0.0003). Radiological response (RECIST) was less prognostic for OS (logrank test for trend p = 0.40). Alternative formulations of OTU were also investigated. The distribution between good, intermediate and poor OTU varied depending on the cut-point in patient question responses.
Conclusion: OTU is a feasible and useful outcome measure that combines objective and subjective information regarding the balance of benefit and harm of treatment in a frail/elderly population with GO cancer. It correlates more strongly with overall survival than radiological response. Further research should focus on establishing the optimal definition and combination of patient reported outcomes.
No conflict of interest.

1580 POSTER

Evaulation of geriatric aged (>65) early stage colorectal carcinoma patients' comorbidity scale

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Background: Approximately 60% of newly diagnosed carcinoma patients are older than 65 years age. Many clinicians consider the toxic effects of drugs in elderly population and avoid administering standard dosage chemotherapy. In practice, Eastern Cooperative Oncology Group (ECOG) performance scale is one of cornerstone of chemotherapy planning. Since chronological age and performance scale are insufficient during chemotherapy planning, different comorbidity scales have been developed. Comprehensive Geriatric Assessment (CGA), analyses multiple factors and can detect possible benefits.
Material and Methods: We evaluated the Charlson Comorbidite (CS) Index and Cummulative Illness Rating Scala (CIRS) at colorectal caner patients older than 65 years. We retrospectively examined 527 patients file, older than 65 years age, among 1320 patients who were admitted to

Medical Oncology Department of Ankara Numune Education and Research Hospital with diagnosis of colorectal cancer from March 2003 to December 2012. Two hundred and ten (n = 210) non metastatic operated patients data were recorded, CS and CIRS scores were calculated. At Charlson and CIRS scales, according to comorbide illnesses and stage of comorbide illness and organ dysfunctions, patients get scores between 0−31 and 0−56.

Results: The median age at diagnoses of our study population (n = 210) was 71(65−87) years. One hundred-fifteen (55 %) of the patients were men and 95 (45%) of them were women. Stage I, II, III of colorectal cancer was; 25 (12%), 102 (49%) and 83 (39%), respectively. Hundred-forty (67%) patients were treated with adjuvant chemotherapy and 77 (36.8%) patients were treated with chemoradiotherapy. According to CS and CIRS system minimum and maximum score was as follows, 0 and 5 points, 0 and 12 points. According to CS system the number of patients who had score 0, 1 and 2, 3 or more were, 80 (%39), 107 (%51) and 21 (%10), respectively. According to CIRS system the number of patients who had score 2 or less and 3 or more were, 51(%25) and 158 (%75), respectively. According to comorbidity scales, patients overall survival analysis were done. Although in CS system patients whose score 0 did not reached the median overall survival, score 1 and 2 was 59 months and score 3 or more was 28 months (p = 0.035). According to CIRS system, while median overall survival of patients whose score 2 or less did not reached, score 3 or more was 54 months (p = 0.02).

Conclusion: We demonstrated that geriatric evaluation forms CS, CIRS score systems were effective parameters on overall survival. Due to deficient toxicity data, we could not give any information about the effect of scoring systems in determining adjuvant chemotherapy. CS and CIRS scoring systems can be used in evaluating geriatric patients. Further detailed studies about these tests will increase their practical use and importance.

No conflict of interest.

1581 POSTER

The impact of geriatric assessment on the treatment decision of elderly cancer patients

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Purpose Despite the World population is globally aging, general conditions are also improving. Multidimensional geriatric assessment has been shown to be useful in defining different frailty levels and the treatment strategy by eventually modifying a decision based not only on the chronological age but rather on the type of ageing profile. Our goal is to estimate the impact of a geriatric assessment in the final decision of oncology therapy.

Method: A total of 393 patients aged ⩾75 years with colorectal or lung cancer candidates for specific oncological treatment were prospectively included. All patients underwent Comprehensive Geriatric Assessment (CGA) that incorporated validated instruments to evaluate co-morbidity (number of comorbidities, Charlson Short Index), polypharmacy, functional status (Performance Status, Barthel Scale, Lawton-Brody Scale), geriatric syndromes, cognition (Pfeiffer test) and the vulnerability (Vulnerable Elders Scale (VES-13)). According to CGA results, patients were classified in 3 risk groups (fit, unfit, and frail). We compared the standard treatment plan based on the cancer stage with the one proposed based on the 3 risk groups.

Results: Median age was 79 years (range 75−97) and 277 (70.5%) were men. Disease was non-metastatic (stage I to III) and metastatic (stage IV) in 188 pts. (47.8%) and 205 pts. (52.2%) respectively.

The CGA results are described in table 1.

Table 1. Patient characteristics

Performance Status (0−1 and >1)	252 (64.6%) and 138 (35.4%)
Barthel Index (100 and <100)	169 (43.6%) and 221 (66.4%)
Lawton Index (8 and <8)	98 (31.7%) and 210 (68.3%)
Geriatric syndromes (0 and >0)	181 (48.9%) and 189 (51.1%)
Charlson Index (0 and >0)	140 (36.6%) and 248 (73.4%)
Number co-morbidities (⩽3 and >3)	206 (52.8%) and 184 (47.2%)
Polypharmacy (⩽3 and >3)	127 (32.8%) and 264 (67.2%)
VES-13 (⩽3 and >3)	197 (51.1%) and 195 (49.9%)
Abbreviated Yesavage (>2 vs ⩽2)	135 (35.7%) and 243 (64.3%)

Missing values have not been included in the table.

In up to 30% of the patients, CGA led to a change in based 'standard practice' therapy decision (table 2).

Table 2. Standard practice vs after-CGA plan

Standard practice	Oncogeriatric plan			
(n and % per file)	Radical	Palliative	Symptomatic	Total
Radical	120 (63.8)	59 (31.3)	9 (4.8)	188 (100%)
Palliative	0	115 (73.2)	42 (26.8)	157 (100%)
Symptomatic	0	0	19 (100)	19 (100%)
Total	112	83	73	268 (100%)

*Missing values not included in the table.

Conclusions: CGA had a significant impact on the medical decision. A consensus for developing tools and guidelines in order to better classify elderly cancer patients is warranted. The increasing use of a complete geriatric assessment might lead to a more tailored therapy plan.

No conflict of interest.

1582 POSTER

Neoadjuvant treatment with Taxol®-carboplatin in elderly patients with non-small cell lung cancer stage IIIA N2 disease

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Background: Lung cancer is one of the most important diseases in the elderly population because of its high incidence and mortality. Treatment in this population is an understudied topic, being excluded from most clinical trials. The aim of this case series is to analyze the toxicity, adherence, response rate, resectability, progression-free survival (PFS) and overall survival (OS).

Material and Methods: Retrospective analysis of 34 patients over 70 years with non-small cell lung cancer (NSCLC) stage IIIA N2 disease treated at the Hospital Virgen de las Nieves (Granada, Spain) between 2010–2011. The treatment consisted of the administration of neoadjuvant scheme with Taxol® 200 mgr/m^2 and carboplatin AUC 6 day 1, every 21 days for 3−4 cycles. After completion of treatment, surgery was evaluated. If surgical resection was possible, radiotherapy was assessed sequentially.

Results: We analyze 34 patients with ECOG 0−1. Median age was 73 years (71−78). 88% were males. 91% were smokers. Regarding histology, 61.8% of squamous cell, adenocarcinoma 17.6% and 20.6% were undifferentiated. 79% received 4 cycles of chemotherapy. Incidence of neutropenia GIII−IV was 35%, with 2 cases of severe febrile neutropenia. Non hematologic toxicity grade III−IV occurred in only 5%. Response rate evaluated by RECIST criteria: complete response ocurred in 1 case (2.9%), partial response in 16 (47%), stable disease in 9 (26.4%) and 8 progressed during treatment (23.5%). Underwent surgery 3 patients (8.8%), 21 patients (61.7%) received radiotherapy sequentially and 4 patients (11.7%) started second line chemotherapy. The median disease-free interval was 8 months and OS was 15 months.

Conclusions: Treatment with neoadjuvant scheme Taxol®-carboplatin in ederly patients with NSCLC was well tolerated. Response rates and OS were similar to younger patients, therefore cancer in the elderly age should not be a barrier to administer active treatment.

No conflict of interest.

1583 POSTER

Impact of the incorporation of comprehensive geriatric assessment tools (CGA) into clinical practice in a developing country

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Background: Population ageing is a global phenomenon not restricted to developed nations. In Brazil, more than 18 million people are now over sixty years. Geriatric oncology programs are present worldwide, but still emerging in developing nations. We hypothesized that incorporating CGA into daily practice can improve individualized care in elderly cancer patients.

Methods: The aim of the study was to assess the impact of CGA in the selection of treatment and its ability to predict treatment complications (dose reduction, hospitalization, treatment discontinuation) in a recently implemented Oncogeriatric Unit. From Mar/12 to Jan/13, 622 patients (pts), >70 y, candidates to receive systemic treatment underwent CGA assessment including Katz, Lawton, Nutritional Status and Depression scales, comorbidities and polypharmacy. Patients were classified as fit, frail or borderline. Fit pts received full treatment. For frail/borderline pts, modified treatment and/or specific supportive care (clinical/nutritional/

psychological) was indicated. Statistical analysis used chi-square or Fisher exact tests, when indicated, to evaluate the association of geriatric scales with the outcomes described.
Results: There was association between the choice of oncologic treatment with Katz (p: 0.018), Lawton (p and lt;0.001) and nutrition scales (p: 0.004). Lawton scale was more associated with changes in treatment (78.3% with altered scale received modified treatment). The ability to complete the proposed treatment was correlated with the Lawton scale (p = 0.006) and dose reduction with nutrition scale (p: 0.029). Hospitalization during chemotherapy was associated with presence of comorbidities (p: 0.038) and changes in Katz (p: 0.006) and Lawton scales (p: 0.017).
Conclusions: In this cohort, the incorporation of CGA in daily practice was feasible and useful to predict complications of systemic cancer treatment.
No conflict of interest.

1584 POSTER

The feasibility of using comprehensive geriatric assessment in frail or elderly patients with advanced gastric or oesophageal cancer

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Introduction: The population of elderly patients with cancer is heterogenous. Chronological age alone is a poor predictor of tolerance and outcome from cancer therapies. Comprehensive Geriatric Assessment (CGA) is a process that encompasses somatic, functional and psychosocial domains. It has the potential to be used for prognostication and prediction of benefit from treatment in elderly cancer patients, but may be burdensome to administer. There is a need to define the optimal composition of CGA for each tumour type, and to determine feasibility of administration. This study aimed to test the feasibility of using a questionnaire-based CGA in frail and elderly patients with advanced gastric or oesophageal (GO) cancer in the setting of a randomized controlled trial.
Methods: Eligible patients had a diagnosis of advanced GO cancer and were considered unfit for full-dose triple-drug chemotherapy but fit for reduced intensity chemotherapy. Patients completed a baseline CGA administered by nurses in clinic. This comprised the validated tools of Mini Nutritional Assessment, Charleston co-morbidity index, Nottingham activities of daily living (NADL) and the patient self-reported questionnaires EORTC QLQ C30, QLQ OG25 and EuroQoL EQ5D. A similar reduced assessment was completed at 12 weeks. At completion of the trial a focus group was conducted with clinicians, nurses and patient representatives to obtain feedback on the CGA process.
Results: 55 patients with advanced GO cancer met eligibility and were randomised. The median age was 75 (range 50−87). Performance status was 0, 1 or 2 in 6, 31 and 18 patients respectively. All but one patient completed the CGA at baseline. Average per-question compliance within each questionnaire was 99.5% for NADL, 99% for EQ5D, 98% for QLQ C30 and 95% for QLQ OG25. The Week 12 CGA was completed by 29 of the 42 patients alive at 12 weeks (69%). Average per-question compliance was 95% for NADL, 94% for EQ5D. 95% for QLQ C30 and 96% for QLQ OG25 questionnaires. Feedback suggested that duplication between tools hindered compliance.
Conclusion: In general, compliance with completion of questionnaires was good, but was greater in the initial CGA compared with completion at follow-up. Compliance may be enhanced by avoiding duplication of questions when multiple overlapping validated questionnaires are used. The modification of existing questionnaires requires further testing in clinical practice.
No conflict of interest.

1585 POSTER

Treatment decisions in gastrointestinal cancer patients older than 65 years of age

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Background: Aging is one of the important risk factor for increased incidence of cancer. Molecular changes and defective immunity associated with aging results in increased susceptibility for many carcinogens to tissues especially to gastrointestinal system (GIS). Co-morbidities and changes in the drug metabolism in the elderly makes the treatment of GIS cancers difficult. In the presenting retrospective study basic characteristics and differences of treatment of the GIS cancers in older age group were evaluated.
Materials and Methods: Between January 2009 and December 2012, seven-hundred and ninety patients who were diagnosed with GIS cancer evaluated retrospectively. Three hundred and eighty six patients older than 65 years of age were of our main interest.
Results: Median age of our elderly patient group was 72 years (Range: 65−90). One hundred and fifty one (39.1%) patients were women and 235 (60.9%) were men. Localisations of the GIS cancers were colo-rectal, gastric, pancreatico-biliary system and primary liver as an incidences of 184 (47.7%), 125 (32.4%), 57 (14.8%) and 15 (3.9%) respectively. In this older age group colo-rectal cancers were the common cancer types in both men and in women [101(43.0%),and 83(55.0%)respectively]. In contrast gastric cancer was more common cancer type in men than in women [92 (39.1%) vs. 33(21.9%)] respectively. The stages of GIS cancers in this age group were mostly advanced stage [stage IV, III,II and I were 190(49.2%), 119(30.8%), 66(17.1%), and 11(2.8%) respectively]. In older patient groups 104 (26.9%) of patients were not received any chemotherapy. Reasons were refusing to chemotherapy, low performance status, no indication to chemotherapy in 65 (16.8%), 17 (4.4%), 22 (5.6%) of patients respectively. Although 279 (72.2%) of patients received chemotherapy, 89 (35.3%) of patients were received inferior chemotherapy regimens rather than standard protocols.
Conclusion: Cancers of GIS are mostly diagnosed in advanced stage in older age patients since fatigue, debility and anorexia are common symptoms in both GIS cancers and senility. Thus screening programs and close monitoring of the symptomatic patients are important. There is a higher tendency to less treat and to deny chemotherapy in elderly. Physiological conditions and co-morbidities are more reliable factors to decide treatment strategies rather than chronological age. Assessment of good performance status by some tests like treadmill may be helpful before planning chemotherapy in this age group. Elderly patients who are in a good performance status should be encouraged for receiving chemotherapy.
No conflict of interest.

1586 POSTER

Predictive value of geriatric assessment for elderly patients, treated with first-line chemotherapy

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Background: Although comprehensive geriatric assessment (CGA) helps a clinician decision of chemotherapy in the elderly cancer patient, it is uncertain which factor has predictive value. We performed a single-institution retrospective study to determine the predictive factors for elderly cancer patients treated with chemotherapy.
Material and Methods: Between September 2011 and February 2013, 23 patients older than 70 years who were scheduled for first-line palliative chemotherapy for various types of cancer were eligible for the study. Baseline CGA including clinicopathologic factors, Mini Mental State Examination (MMSE) and Geriatric depression scale (GDS) was assessed. Progression free survival (PFS), time to treatment failure (TTF), and overall survival (OS) were measured. Survival analysis was evaluated using the Kaplan–Meier method and the Cox proportional hazard method.
Results: Of the 23 patients, the median age was 74 (rage, 70−84), 52% of patients had mild cognitive impairment (MMSE score $\leqslant$23) by MMSE, and 60% had mild depressive mood by GDS. Median follow-up duration was 3.3 month (range 1.2–13.6 months). Median PFS was 5.2 month (95% confidence interval [CI]: 3.54–6.86), median TTF was 4.6 month (95% CI, 2.35–6.85) and median OS was 12.7 month.
On univariate analysis, PFS was 1.6 months for patients with diabetes and 6.6 months for non-diabetes (p = 0.007), 2.8 months for patients with inferior MMSE score (MMSE $\leqslant$23) and 6.6 months for superior MMSE ($\geqslant$24) (p = 0.021). TTF was 1.4 months for diabetes and 5.2 months for non-diabetes (p = 0.044), 2.6 months for inferior MMSE score and 6.6 months for superior MMSE (p = 0.002), and 5.2 months for patients under age 80 and 1.2 months for over age 80 (p = 0.004). On multivariate analysis, diabetes (hazard ratio, 0.210; 95% CI, 0.046–0.964; p = 0.045) was significant independent prognostic factors for the prolongation of PFS and MMSE was significant for the TTF (hazard ratio, 0.126; 95% CI, 0.027–0.594; p = 0.009).
Conclusion: This study showed that cognitive impairment significantly increased the probability of early treatment failure, and DM was poor prognostic factor in patients greater than 70 years of age with chemotherapy.
No conflict of interest.

1587 POSTER

Analysis of cancer treatment toxicity in patients over 65 years of age

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Background: European statistics data show that patients above 65 years of age costitute 63% of adult patients population with cancer (www.eurocare). In Poland, people over 65 years of age account for about 50% of cancer patients (http://epid.coi.waw.pl/krn/).
Material and Methods: The medical records of patients treated in 2011 in Clinical and Experimental Oncology Department were reviewed. The frequency of enrolment for systemic therapy for patients above 65 years of age, treatment course and the incidence of toxicity were analyzed. Toxicity was assessed according to CTCAE (Common Terminology Criteria for Adverse Events). In the present study toxicity $\geqslant$3 were analyzed.
Results: A total of 1102 patients were treated in analyzed period. Patients older than 65 years of age accounted 23% (257). Median age was 72 years (range 65−88). The most common cancers treated were: colon, ovarian and breast cancer, 65 (25%), 45 (18%), 34 (13%), respectively. Median follow up was 29 months. All patients who were enrolled in chemotherapy, chemoimmunotherapy or chemoradiotherapy were in good performance status (ZUBROD 0−1) with no contraindication to the treatment. 98 patients (38%) required a dose reduction during the therapy due to excessive toxicity. The most frequent toxicity reported were: the hematologic, neurological, hepatic, and gastrointestinal ones, 56%, 29%, 28% and 20%, respectively. Premature treatment discontinuation was necessary in 124 patients (48%). During the follow-up 118 patients died, 70% of them due to cancer progression.
Conclusions: The results of the study suggest that in Poland older patients are less frequent diagnosed for neoplasm disease. The frequency of premature treatment discontinuation due to toxicity is high. Older patients cancer diagnosis and treatment needs to be improved in our region.
No conflict of interest.

1588 POSTER

Colorectal cancer in elderly patients: A single center experience

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Background: In Austria more than 40% of cancers occur in adults over the age of 75 years. As the current population ages and life expectancy is increasing, more people with colorectal (CRC) are presenting at an advanced age (>75). Several studies have shown that cancer treatment is beneficial for elderly pts in adjuvant and palliative setting. However, optimal management approach for this group of pts is not well defined as they are underrepresented in clinical trials. We now want to present our own experience in the treatment of elderly pts with colorectal cancer.
Methods: The Klinikum Wels-Grieskirchen collects data on all CRC pts since July 2006 in a clinical tumor registry. Patients were followed for treatment decision, progression free survival and overall survival. In this updated retrospective analysis elderly pts $\geqslant$75 years diagnosed with CRC have been evaluated.
Results: Overall, 277 pts $\geqslant$75 years (range 75−92) with a diagnosis of CRC stage I−IV were recorded from July 2006 − March 2013 in our registry. 132 (47.7%) and 145 (52.3%) out of these pts were men and women, respectively. Stage I has been diagnosed in 35 pts (12.7%), stage II in 89 pts (32.4%), stage III in 85 pts (30.9%) and stage IV in 66 pts (24%). 29.2% (81 pts) had a tumor located in the rectum and 70.8% had colon cancer. 226 out of 277 pts underwent surgery (tumorectomy or colectomy). Hemihepatectomy or lobectomy has been performed in 7 pts. Adjuvant chemotherapy was given in 10 pts with stage II and in 37.5% (32/85 pts) with stage III CRC. Of these, 90.5% received single agent chemotherapy (mostly capecitabine). Two-thirds of pts with metastatic CRC were treated with palliative chemotherapy. Chemotherapy regimens, updated progression free survival and overall survival data will be presented.
Conclusions: Although elderly pts often have co-morbidities and poor performance status, age alone should not determine treatment options and person's eligibility in clinical trials. A careful discussion of treatment risks and benefits, especially in elderly pts, needs to be considered in the therapy decision.
No conflict of interest.

Society Session (Sun, 29 Sep)
European Society for Paediatric Oncology (SIOPE)

1600 ORAL

Hepatoblastoma in patients aged less than 6 months at diagnosis: report from the International Childhood Liver Tumour Strategy Group (SIOPEL)

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Background: Little is known about specific characteristics of hepatoblastoma in infants. The objectives of this study were to describe clinical characteristics, outcome and toxicity of treatment in patients diagnosed with an hepatoblastoma (HB) before the age of 6 months (m).
Material and Methods: Data collected in SIOPEL database for patients diagnosed with an HB <6 m of age and entered into SIOPEL 1, 2 and 3 trials between 1990 and 2006 were studied.
Results: Among 695 patients included in SIOPEL 1, 2 and 3, 92 met the study criteria: 63 (68%) were male. The age at diagnosis was <1 m in 18 patients, between 1 and 3 m in 22 and between 3 and 6 m in 52. Among them, 13 were premature babies and 6 had Beckwith Wiedemann syndrome.
According to SIOPEL risk stratification, 64 patients were considered standard risk (PRETEXT I, II or III without extrahepatic extension, AFP above normal level for age) and 18 high risk (AFP level within normal range for age (n = 10) and/or metastases (n = 5) and/or PRETEXT IV group (n = 13)). Overall 13 patients had an AFP level under 1000 ng/ml. All patients received a cis-platinum based chemotherapy pre-operative chemotherapy with PLADO (n = 36), Cisplatinum alone (n = 31) or superPLADO (n = 24). All 18 patients <1 m at diagnosis received at least one course of cisplatinum before the end of the first month of life combined with doxorubicin in 2. The mean cumulative dose received during the treatment was 98% of the dose planned in the protocol (dose adjusted for weight in patients under 10 kg). Toxicity pattern was similar to the one observed in older patients except for ototoxicity which seems to be more frequent in this age group: 22/57 (39%) patients with an audiogram after the end of treatment had grade >2 ototoxicity (Brock grading system). Median follow-up is 5.6 years. Overall 8 patients died, 2 of surgical complications and 6 of progressive disease, one of them before the beginning of treatment. Among these latter 8 patients, 6 had an AFP level at diagnosis less than 1000 ng/ml. The 3 year EFS and OS are respectively 87 and 91%. No tumor failure occurred in patients with AFP >1000 ng/ml at diagnosis.
Conclusions: The prognosis of hepatoblastoma in patients less than 6 month at diagnosis is excellent with an overall survival >90% at 3 years. Chemotherapy combining cisplatinum and doxorubicin is feasible in infants but the risk of ototoxicity is high. A reduction of treatment should be considered in patients with no risk factors.
No conflict of interest.

1601 ORAL

The (EPOC) FP7-funded study of pharmacokinetics and pharmacodynamics of doxorubicin in children with cancer

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Background: Doxorubicin is a key component of a number of treatment regimens used in paediatric oncology, despite the very limited pharmacology data in children on which current dosing regimens are based.

Material and Methods:
- Multicentre, multinational phase II pharmacokinetic study investigating age-dependency in the clearance of doxorubicin in children with solid tumours and leukaemia
- 100 patients treated according to a tumour-specific national or European therapeutic trial, with a particular focus on children less than 3 years
- Blood samples were collected at optimal sampling times during and after doxorubicin administration.
- Concentrations of doxorubicin and its major metabolite doxorubicinol were measured using a validated HPLC method.
- Markers such as troponins and natriuretic peptides were measured to evaluate as clinical markers for cardiotoxicity
- Data were analysed using a population pharmacokinetic approach including pharmacogenetic covariates

Results:
- 100 patients recruited, all data collected and analysed. The target number of patients less than 1 year (5) and 3 years (20) were achieved
- Interim analysis on the first 30 patients indicated that we have sufficient data to address the key question of age-dependent pharmacokinetics
- A population pharmacokinetic model has been developed and validated for application to the full data set.
- Data on cardiotoxicity indicate a detectable acute effect of doxorubicin administration.
- Data on pharmacogenetic influences on pharmacokinetics and toxicity will be presented

Conclusions:
- A multinational study of doxorubicin PK can address issues relevant to the EMA priority list of off-patent medicines
- Results from this study could be used to guide dosing of doxorubicin, especially in very young children

No conflict of interest.

1602 ORAL

Characterization and activity of a new anti-idiotype antibody in neuroblastoma

H.N. Lode[1], C. Eger[1], D. Seidel[1], D. Brackrock[1], N. Siebert[1]. [1]*University Medicine Greifswald, Pediatric Hematology and Oncology, Greifswald, Germany*

Background: Immunotherapy targeting disialoganglioside GD_2 emerges as an important treatment option for neuroblastoma, a pediatric malignancy characterized by poor outcome. Here, we report the generation and characterization of ganglidiomab, a new anti-idiotype antibody to anti-GD_2 antibodies of the 14.18 family for monitoring of clinical trials and the development of neuroblastoma vaccines.
Material and Methods: Balb/c mice were immunized with 14G2a and splenocytes harvested to generate hybridoma cells. Clones were screened by ELISA for mouse antibody binding to hu14.18. One positive clone was selected to purify and characterize the secreted IgG protein (kappa, IgG1).
Results: This antibody bound to anti-GD_2 antibodies 14G2a, ch14.18/CHO, hu14.18 and to immunocytokines ch14.18-IL2 and hu14.18-IL2 as well as to NK-92 cells expressing scFv(ch14.18)-zeta receptor. Binding of these anti-GD_2 antibodies to the nominal antigen GD_2 as well as GD_2 specific lysis of neuroblastoma cells by NK-92-scFv(ch14.18)-zeta cells was competitively inhibited by ganglidiomab, proving GD_2 surrogate function and anti-idiotype characteristics. The dissociation constants of ganglidiomab from anti-GD_2 antibodies ranged from 10.8 ± 5.01 to 53.5 ± 1.92 nM as determined by Biacore analyses using 'steady state' analysis. The sequences of framework- (FRs) and complementarity determining -regions (CDRs) of ganglidiomab were identified. Finally, we demonstrate induction of a GD_2 specific humoral immune response after vaccination of mice and patients with ganglidiomab effective in mediating GD_2 specific killing of neuroblastoma cells.
Conclusions: We generated and characterized a novel anti-idiotype antibody ganglidiomab for immune monitoring of clinical trials with anti-GD_2 antibodies and provide an important baseline for the development of anti-idiotype vaccines against malignancies expressing GD_2.
No conflict of interest.

1603 ORAL

Disease- and treatment-related factors implicated in late neuroendocrine morbidity after paediatric optic pathway gliomas: a preliminary multivariate analysis of 128 patients over 30 years

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Background: Low-grade gliomas (LGGs) are the commonest benign childhood brain tumour and have high survival rates. However, their typical suprasellar position affecting the optic and diencephalic pathways renders them less surgically accessible or curable, with tumour and/ or treatment factors contributing to severe, life-threatening neuroendocrine morbidities. In the absence of major longitudinal studies, we sought to evaluate specific disease- and treatment-related risk factors for endocrine morbidity in a large single-centre 30-year paediatric cohort.
Materials and Methods: Multivariate regression analysis of retrospective, longitudinal data from case note review of the first 146/223 randomly audited patients diagnosed with optic pathway and diencephalic LGGs between 1980–2010 at Great Ormond Street Hospital.
Results: Patients were of median age 5.43 (0.18–15.07) years at diagnosis and followed up for a median of 7.75 (0.04–26.60) years. 5-year overall (OS), progression-free (PFS) and endocrine event-free survival (EEFS) were 95.3%, 60.5% and 41.9% respectively. Primary surgical intervention was positively predictive of OS (HR 0.02 (95% CI 0.00–0.72) and PFS (HR 0.16 (95% CI 0.07–0.41), whilst presenting hydrocephalus independently decreased OS (HR 78.03 (95% CI 2.36–2581.45). EEFS continued to decline up to 15 years from diagnosis with 79.4% of survivors experiencing at least one endocrinopathy, being independently predicted by hypothalamic tumour position (HR 7.85 (95% CI 2.48–24.80)) more than radiotherapy (HR 2.38 (95% CI 1.28–4.44). Both radiotherapy (β=0.68 (95% CI 0.44–0.92) and presenting diencephalic syndrome (β=0.51 (95% CI 0.02–0.99) were associated with increased numbers of endocrine deficits, most commonly GH deficiency (38.4%), followed by precocious puberty (24.8%), ACTH deficiency (16.4%), TSH/TRH deficiency (11.6%), LH/FSH deficiency (11.0%) and hyperprolactinaemia (9.6%). 12/18 patients with posterior pituitary dysfunction (9 SIADH, 6 diabetes insipidus, 6 cerebral salt-wasting) developed this peri-operatively (9 after biopsy/ ventricular shunt procedures only), of whom 3 died from resultant cardiovascular instability. 7/15 of the surviving patients had lifelong posterior pituitary dysfunction requiring treatment. 26.0% of patients developed obesity (BMI >98th centile for age), with the risk of insulin-resistance increasing with repeated surgical procedures (OR 1.47 (95% CI 1.02–2.11).
Conclusions: We provide new evidence to suggest a high prevalence of disabling endocrine morbidity in long-term suprasellar LGG survivors. This is more likely to result from hypothalamic involvement by tumour than irradiation. The role of surgery in aiding tumour control needs to be balanced against its significant attendant risks for life-threatening morbidity consequent on hypothalamic and posterior pituitary dysfunction incurred not just after repeated resections but also after minor surgical interventions.
No conflict of interest.

1604 ORAL

Ethical aspects of clinical trials in paediatric oncology. Two examples of literature reviews in the EU-FP7 ENCCA project

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Background: European public health agencies acknowledge the importance of multi-faceted evaluations of the effectiveness, economic, social and ethical issues of health interventions (as for example within the EUnetHTA consortium). Such evaluations have to meet stringent methodological constraints concerning literature retrieval, analysis of literature samples and drawing of conclusions. The ethics work-package (WP18) of the ENCCA project aims at applying these methods to document the ethical aspects of clinical trials in paediatric oncology.
Material and Methods: Literature retrieval workflows for documenting ethical aspects imply the use of search algorithms in various bibliographical databases. Each step (definition of search algorithms and selection of databases) has to be transparent and well-grounded, as in effectiveness assessments. Main specificity of ethics literature reviews lies in the possibility not to exclude articles based on methodological criteria. Where such criteria are applied, the literature review is systematic; otherwise, it is narrative. One narrative and one systematic review of literature have been performed by ENCCA WP18. The former aimed at identifying the variety of ethical issues in paediatric oncology research and the latter at analysing the debates surrounding the moral justification for making research with children.
Results: Results of each literature review are outlined. Advantages and limitations of both approaches to ethical evaluation are compared with regard to the scientometric analysis and qualitative analysis of literature samples they allowed as well as with regard to the kind of conclusions which could be drawn.
Conclusions: Systematic and narrative literature reviews are relevant for making a state of ethical knowledge, depending on whether conclusiveness or comprehensiveness is privileged. Regardless of their differences, both can fit basic requirements of transparency, pluralism and impartiality. They are therefore useful for professionals, stakeholders and policy makers for they avoid undue value judgements and leave space for decision making.

In counterpart, they clearly do not replace (but complete) normative and empirical ethics.
No conflict of interest.

1605 ORAL

Visual improvement following Nerve Growth Factor eye-drop administration in patients with optic pathway glioma-associated visual impairment; prelimary results of a double blind trial

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Background: To date, no specific therapy is available for optic pathway glioma (OPG)-associated visual impairment. The aim of this study was to evaluate the effects on visual function of murine nerve growth factor (NGF) eye drop administration in patients with visual impairment due to OPGs.
Methods: A prospective randomized double-blind controlled study was conducted in patients younger than 24 years with OPG-induced visual impairment, without or with NF1. All patients were off-therapy and with stable disease at 2 brain magnetic resonance imaging (MRI) controls, performed at least 6 months apart. NGF eye-drop was prepared by Policlinico Gemelli University Pharmacy according to standard required for human use. The patients were assessed by clinical evaluation and ophthalmological examinations including visual acuity, visual field, photopic negative response (PhNR), visual evoked potentials (PEV), Ganzfeld electroretinograms and optic coherence tomography. All patients were recorded at baseline and 15, 30, and 90 days post treatment. A further evaluation at 180 days is planned but no data are available at this time. Brain MRI was performed at baseline and is planned at 180 days after NGF treatment. All the evaluations were performed by considering the change of parameters values from baseline.
Results: Ten and 8 patients received a single 10-day course of 1 mg murine NGF topical administration and placebo, respectively. Preliminary results (up to 90 days) showed a 40% ($p = 0.02$) and a 50% ($p = 0.09$) improvement of visual field in at least one eye from the baseline evaluations with a better quality of life in the NGF group at 30 and at 90 days post treatment, respectively, compared to a 14% increase in the placebo group. An increase of the mean PhNR amplitude till 90 days was observed in the treated eyes but this was not statistically significant compared to the placebo group; mean PhNR latency increased significantly compared to the placebo group (1.3 vs −1.8 $p = 0.03$) at 15 days but then the difference disappeared. Mean PEV amplitude increase was borderline significant compared to placebo group ($p = 0.06$) at 30 days. No changes in the visual acuity were observed in both groups and no other significant differences were observed for the other ophthalmological examinations.
Conclusions: Preliminary results suggest a visual rescuing mechanism exerted by murine NGF on the residual viable optic pathways. NGF administration appears an effective and safe adjunct therapy in patients with OPG-associated visual impairment.
No conflict of interest.

Poster Session (Sat, 28 Sep)
Paediatric Oncology

1606 POSTER

Genomic background of neuroblastomas with intratumour heterogeneity of MYCN amplification

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Background: *MYCN* amplification (MNA) is the most powerful therapy-stratifying marker in neuroblastoma (NB). Although the existence of intratumour heterogeneity of MNA (hetMNA) is well known today, its clinical meaning is still unclear, compromising the patients' assignment to specific treatment strategies. To learn whether the genomic background of hetMNA tumours differ to the genomic background of homogenously MNA (homMNA) tumours and non-amplified NBs, we looked for common segmental and numerical chromosome aberrations, allelic imbalances and the expression of favourable NB marker CD44.
Material and Methods: Ultra high resolution SNParray analyses and interphase FISH on various tumour samples and bone marrows (BM) obtained from 18 NB patients were performed. Median patient age was 13.5 months (range 6–168), 11 patients were below and 7 above 18 months of age. CD44 staining was done by fluorescence labelled antibodies on cryo-sections.
Results: Besides hetMNA, five tumours showed no segmental chromosomal aberrations (noSCA), another five were heterogeneous concerning both, MNA and SCA (hetSCA), and eight exhibited a high number of SCAs (highSCA), one with chromothripsis. Whole chromosome uniparental disomy (wcUPD) occurred in 11/18 tumours (61.1%) hetMNA tumours, in 1/9 homMNA tumours and in 11/36 (30.6%) of the nonMNA NBs. wcUPD of chromosome 11 was exclusively found in the hetMNA group (6/11). The increase of SCA correlated with age (no/hetSCA: 10/11 infants and high SCA: 7/7 patients >18m). By contrast, UPD11 decreased with age (UPD11: 6/11 infants and 0/7 patients >18m), segmental chromosome 11 aberrations, however, increased and were found exclusively in patients >18m (4/7). Furthermore, hetMNA tumours were frequently $CD44^+$, which is not the case in homMNA tumours.
Conclusions: The high frequency of wcUPDs, especially UPD11, in hetMNA tumours has not been described so far and could represent a hallmark of hetMNA NBs. This data provide a more complete picture of the tumour genomics landscape portrayed from single tumour-biopsy.
No conflict of interest.

1607 POSTER

Pharmacogenomic analysis of high-dose methotrexate treatments in children with acute lymphoblastic leukemia treated with ALL-BFM 95 and ALL IC-BFM 2002 protocols

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Background: High-dose methotrexate (HD-MTX) is the key component of the consolidation therapy of childhood acute lymphoblastic leukemia (ALL). The pharmacokinetics of the drug show large interpatient variability even with the same treatment protocol. The aim of the present study was to investigate the influence of single nucleotide polymorphisms (SNP) in genes of the folate metabolic pathway, transporter molecules and transcription proteins on the pharmacokinetics and toxicity of methotrexate (MTX) and 7-hydroxy-methotrexate (7-OH-MTX) after HD-MTX treatments in children with ALL.
Methods: Totally 463 HD-MTX infusions were analyzed. Data of 48 children treated with 5 g/m^2/24 h and 70 children treated with 2 g/m^2/24 h HD-MTX according to ALL-BFM 95 and ALL IC-BFM 2002 protocols were collected [mean age: 6.4 years (1.1−18 years)]. 63 SNP of 14 genes were genotyped. Hepato-, nephro- and bone marrow toxicities, estimated by routine laboratory parameters were evaluated. Random forest analysis and regression trees were used for variable selection. Linear mixed models were established to prove the significance of the selected variables and to estimate effect sizes. MTX and 7-OH-MTX values were log transformed to ensure correct model diagnostics.
Results: The rs4149056 of SLCO1B1 showed significant association with the serum levels of MTX ($p < 0.001$). SNPs (rs4948502, rs4948496) of ARID5B gene were associated with serum levels of MTX ($P<0.001$), serum levels and AUC of 7-OH-MTX ($P<0.001$) and with hypoproteinaemia ($P<0.001$). Hepato-, nephrotoxicity, granulocytopenia and hypoproteinaemia were associated with novel genetic variations of SLC19A1, SLC22A8, MTR and MTHFD1 genes ($P<0.05$, respectively).
Conclusions: We confirmed the associations of novel genetic variations in folate related and ARID5B genes with MTX plasma levels and the development of acute toxicity. Further analysis and validation in a larger cohort is necessary to determine the predictive value of these associations.
No conflict of interest.

1608 POSTER

LINES as a paradigm of risk-adapted therapies using prognostic biomarkers: A SIOPEN trial

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Background: In the framework WP10 (ENCCA PROJECT), the LINES trial uses risk-adapted therapies in low and intermediate-risk Neuroblastoma (NB) according to international standards and regulations. Image defined risk factors, the presence or not of symptoms and for the first time the presence or absence of segmental chromosome aberrations are being used in the decision making process to stratify treatment.
Material and Methods: LINES (EudraCT: 2010–021396−81, ClinicalTrials.gov Identifier: NCT01728155) includes ten separate therapeutic groups, one of them randomised. All the cases are registered at SIOPEN-R-NET with check-points to control the quality of prospectively entered staging data and there is real time central review for biology and histology.
Results: In July 2011, the LINES trial sponsored by IIsLaFE (Spain) obtained approval from the Spanish National Competent Authority and the Ethic Committees of 28 participating Spanish sites. In addition to the Spanish sites the trial is also open in Austria (5 sites), Denmark (3 sites), France (1 site), Norway (4 sites) and Italy (21 sites). Thirty five patients have been enrolled since December 2011. The other 14 SIOPEN countries are still in the process of opening the trial. Under the current European Union (EU) Paediatric Regulation, academic paediatric trials are difficult to implement because of cost, bureaucracy and especially different national interpretations of the current legislation.
Conclusions: It is imperative to review and reassess the current European directive. We hope revision of the EU Clinical Trials Directive will result in minimising the current disparity in the interpretation of the directive that currently exists between different participating countries and therefore expedite the launch of future European academic paediatric trials.
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No conflict of interest.

1609 POSTER

Neoadjuvant chemotherapy in metastatic medulloblastoma: Changing paradigms

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Background: Treatment-related morbidity is a major concern in medulloblastomas, particularly because of surgical complications. Preoperative chemotherapy may be useful to decrease morbidity and enhance the efficacy of surgery.
Material and Methods: Seventy one children were treated for a metastatic medulloblastoma in a single reference center. We retrospectively compared children treated with 2 strategies according to the refering neurosurgical wards.
Results: Tumor surgery was performed either at the time of the diagnosis (42 patients) or after neoadjuvant conventional chemotherapy with carboplatin and etoposide (29 patients). Hydrocephalus was usually treated with a ventriculocisternostomy before initiatiation of the chemotherapy. In all the 29 cases treated with neoadjuvant chemotherapy, diagnosis was confirmed by a biopsy either of a metastasis during ventriculocisternostomy or directly of the primitive tumor. Children were treated with different post-operative protocols combining chemotherapy, eventually at high-dose with stem-cell rescue and radiotherapy adapted to age. The current retrospective study was designed to define the correlations between the timing of surgery and the post-operatives complications, neuropsychological outcome, and survival.
Chemotherapy decreased disease extension for 25 patients (86%) and delayed surgery allowed a complete tumor excision more often than with first-line surgery (100% vs 64%, $p = 0.002$). Differing the surgery did not have deleterious consequences on the local control of the tumor, on the rate of post-operatives complications and on patients' survival. Moreover, median IQ score was higher in the group 'delayed surgery' (88.5 vs 71.5), especially for children aged under 5 years at the time of the diagnosis ($p = 0.02018$). The IQ score was not associated with the dose of brain irradiation.
Conclusions: When treatment schedules are adapted to risk of disease and age, surgery-related risk factors then become critical for predicting intellectual impairment. Neoadjuvant chemotherapy significantly leads to more frequent complete tumor excision result and decreases the neuropsychological impairment.
No conflict of interest.

1610 POSTER

131I-mIBG therapy in the management of refractory and relapsed neuroblastoma: An individualised approach

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Introduction: An individualised form of ^{131}I-mIBG therapy using whole body dosimetry has been developed at our institution for the management of children with relapsed/refractory neuroblastoma. We report clinical parameters, toxicity and outcome data.
Methods: Case note review of children treated at the Royal Marsden Hospital from 1994–2012. In earlier years an initial tracer study was used to calculate the therapeutic activity needed to deliver a whole body dose (WBD) of 2 Gy, subsequently 4 Gy was delivered in 2 fractions by an initial therapeutic activity of 444mBq/kg followed by dose adjustment according to the measured WBD for the second therapy.
Results: 45 treatments were given to 26 patients. Mean age at diagnosis: 5 years 7 months, mean age at first mIBG: 7 years 5 months. Indication for mIBG therapy: Primary refractory disease (12), relapse (8), other (6). Mean administered mIBG activity: 10951mBq (range 3539–32871mBq), mean mIBG whole body dose 1.8 Gy (1−3.5 Gy).
10 patients received haemopoietic stem cell rescue (HSCR) after mIBG therapy, 5 further patients went straight from mIBG therapy to high dose chemotherapy followed by HSCR.
Grade 3−4 neutropenia was seen following 20/24 treatments, grade 3−4 thrombocytopenia in 20/26 treatments. There were no toxic deaths related to mIBG therapy. In 22/45 treatments there was acute toxicity, which was mainly febrile illnesses/documented infection. The only long term toxicity was prolonged thrombocytopenia in one patient who did not receive HSCR. Response rates on first post treatment mIBG scan were complete response (4.5%), partial response (52%), stable disease (30%), progression (9%) and mixed response (4.5%). 6 patients were alive with disease at last follow up (mean 11 months) and 3 are alive and disease free at last follow up (4 months, 20 months and 10 years).
Conclusions: Children with relapsed/refractory neuroblastoma are a heterogenous group who require an individualised approach to therapy. Personalised ^{131}I-mIBG therapy based on WBD is a viable treatment option which allows administration of relatively high activities. It is well tolerated and haematological toxicity is the dose limiting side effect. Our overall response rate of 57% compares very favourably with the response rates of 27−39% in other series. Prospective European multi-centre clinical trials are in preparation to further define the role of ^{131}I-mIBG therapy.
No conflict of interest.

1611 POSTER

High-resolution genomic profiling of disseminated neuroblastoma cells

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Background: Disseminated disease in neuroblastoma (NB) patients is not necessarily associated with an aggressive clinical course. Genomic features, such as amplification of the *MYCN* gene and/or segmental chromosomal aberrations (SCAs), help to separate aggressively behaving

tumours from less aggressive/benign NBs representing excellent markers for therapy stratification. This also applies to the two disseminated stages M and MS. Since tumour tissue is not always accessible, we searched for a bone marrow (BM) enrichment technique enabling detailed genomic analyses of disseminated tumour cells (DTCs).
Material and Methods: Altogether 49 BM and tumour samples from 34 patients were analysed with an ultra-high resolution SNP array technology (2.7 million probes). BM samples with <50% tumour cell content were enriched by magnetic activated cell sorting resulting in an up to four log step increase of tumour cells.
Results: Paired BM and tumour samples from diagnosis at the same time point showed nearly identical SNP array results. We found 30 breakpoints in 22 chromosomes in DTCs of 4 patients at diagnosis and identical SCAs in primary tumours except two more breakpoints in one tumour. DTCs of four other patients at diagnosis compared to tumours after induction chemotherapy three months later, showed 44 breakpoints in 23 chromosomes in tumours and DTCs with the exception of two more breakpoints in DTCs of one patient. In three further patients, primary diagnostic tumour samples were compared to DTCs at relapse, three to six years later. In the primary tumours 28 breakpoints were found, while the relapse DTCs showed 45. 17 breakpoints were identical at both time points. Thus, the frequency of SCAs and breakpoints in the relapse samples clearly differed from that of the diagnostic materials showing an acquisition of SCAs.
Conclusions: Magnetic bead enriched tumour cells from BMs of 'favourable' and unfavourable disseminated diseases (stages M/MS) give excellent and reliable results with SNP array technique providing detailed insights into the tumour genomics. Thus, this technique is suitable for clinical evaluation and genomic-based risk classification.
No conflict of interest.

1612 POSTER

Factors predicting induction outcome in paediatric ALL: Experience from Western India

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Background: Failure of induction therapy in paediatric ALL is an uncommon event − most western series report <1% failure rates, but it is still high and variable in Indian series ranging from 2 to 7%. MRD analysis is not available routinely. This study has analysed factors predicting induction outcome in Western Indian paediatric population.
Material and Methods: All newly diagnosed paediatric ALL patients at Gujarat Cancer and Research Institute from 1st October 2009 to 30th September 2011 were included in this study. Baseline data included demographic, clinical, bone marrow, cytogenetics, immunophenotyping characteristics. Induction outcome was defined by standard criteria. Univariate and multivariate analysis was done for factors predicting induction outcome.
Results: A total of 330 children were enrolled in this study. Median age was 6 years. Our patients had higher WBC count compared to western population. Cytogenetic abnormalities were found in 32%. Philadelphia chromosome positivity was seen in 7.3% of cases. Immunophenotypic analysis was done in 198 (60%) patients, and most common subtype was Early Pre B type (49%); T-cell phenotype constituted 20% of patients. Most patients (n = 296) were treated with MCP 841 protocol, few (n = 30) patients with BFM 90 protocol, based on financial, demographic, and subtype of ALL. Infants (n = 4) were treated with Interfant 99 protocol. In our study therapy abandonment rate was very high (17%). CR rate in our study was 87%, which is slightly lower to other Indian studies but far less than that of international trials. Present study had induction failure rate of 6% and induction mortality rate of 7%. Most common cause of induction mortality was infection (80%). On univariate analysis, factors predicting CR were − day 8 peripheral blast count of <1000/mm3, absence of CNS disease, haemoglobin levels of $\geqslant$8 gm/dl ($p \leqslant 0.01$), use of BFM 90 vs. MCP841 protocol ($p = 0.03$). On multivariate analysis, factors predicting induction failure were − day 8 peripheral blood blasts of $\geqslant$1000/mm3 ($p < 0.001$), LDH>500 IU/L ($p = 0.03$) and presence of CNS disease ($p = 0.07$).
Conclusion: The higher failure rates are likely to have arisen from a higher incidence of high-risk disease at diagnosis, intercurrent infections, poor socioeconomic status, level of hygiene achievable at home, and poor access to acute care. This highlights that heterogeneity in the patient population and resources can cause significant differences in outcome.
No conflict of interest.

1613 POSTER

Pediatrics surface osteosarcomas − a French multicenter study (SURFOS)

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Background and objectives: The great majority of osteosarcomas (OS) are intra-medullary lesions, but a small proportion arise from the surface of bone. Surface OS can be divided into three distinct histologic subtypes: parosteal OS, periosteal OS and high-grade surface OS. The objective of this study was to review and analyse the treatments of these tumors in order to upgrade and homogenize practises for the managment of surface OS in children.
Methods: We reviewed the therapeutic managment of 28 cases of pediatric (under 18 years) surface OS treated in 11 french Cancer Center between 1990 et 2010.
Results: Eleven patients had parosteal, sixteen patients had periosteal and one patient had high-grade surface OS. The median age at the diagnosis was 14.3 years (range, 5.8−17.9 years). Seven patients were male. None had metastatic disease at diagnosis. All 28 patients were treated with surgery, and 21 (7 with parosteal, 13 with periosteal and 1 with high-grade tumors) received chemotherapy. Three patients relapsed (local relapse for 1 patient with parosteal OS and distant relapses for 2 patients with periosteal OS) and four patients with periosteal OS developped a second cancer (at the origin of the deaths for three of them). The 11-year overall survival rate was 100% for parosteal OS and 63$\pm$18% for periosteal OS.
Conclusions: The histologic grade predicts the clinical behavior of pediatric surface OS. Complete resection is the treatment of choice regardless of tumor subtype. Whereas chemotherapy is not indicated for parosteal OS, its role in periosteal OS remains controversial.
No conflict of interest.

1614 POSTER

Pharmacogenetic analysis of high-dose methotrexate treatment in paediatric osteosarcoma

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Background: High-dose methotrexate (HD-MTX) infusion is a cornerstone of therapy for osteosarcoma. Our aim was to examine the influence of single nucleotide polymorphisms (SNPs) of folate related genes on the pharmacokinetics and toxicity of HD-MTX treatments in children with osteosarcoma.
Materials and Methods: Pharmacokinetic, toxicity and epidemiology data of 929 HD-MTX courses of 98 patients treated with osteosarcoma at the 2nd Department of Paediatrics, Semmelweis University, Budapest were evaluated. Pharmacokinetic parameters (MTX clearance, half-life and area under curve(AUC_{0-48}) of concentration-time function) were calculated based on MTX serum levels measured at 6, 24, 36, 48 hours after the initiation of the infusion. Hepato-, nephro- and myelotoxicity parameters were categorized according to Common Toxicity Criteria v.3.0. Twenty-nine SNPs of 11 genes were genotyped in 62 patients. Frequentist and bayesian statistical analyses were used to evaluate the relationships between the genotypes and the clinical data.
Results: Higher peak MTX concentrations ($p = 0.002$), 48 h MTX serum levels ($p = 0.0034$) and AUC_{0-48} ($p = 0.00001$), and significantly lower MTX clearance ($p = 0.0001$) was correlated significantly with the development of toxicity. Higher 48 h MTX serum levels were associated with a better 5-year overall and event-free survival. The incidence of serious acute hepatotoxicity was less frequent ($p = 0.0033$) and 48 h MTX serum levels were significantly lower ($p = 0.0003$) in patients homozygous for rs3758149 (*GGH*) variant allele than in the others. The frequency of serious acute hepatotoxicity was significantly higher ($p = 0.001$) in patients homozygous for rs1051266 (*RFC1*) variant allele than the others. The rs928256 (*ABCB1*), rs4793665 (*ABCC3*), rs3758149 (*GGH*) and the rs3814058 (*SXR*) SNPs showed significant associations with the pharmacokinetics of MTX according to both single- and multi-variate bayesian analyses.
Conclusions: However longer MTX exposure might lead to serious toxicity, it also improves treatment outcome. Our present results suggest the possibility of a future population pharmacokinetic model with pharmacogenetic data based dose individualization.
No conflict of interest.

1615 POSTER

Early PET-CT importance in determining survival of pediatric Hodgkin's disease

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Objective: To determine the effectiveness of Positron emission tomography (PET) as a prognostic predictor for Hodgkin's lymphoma children treated with risk-adapted therapy.
Methods: A prospective single arm study including 156 Hodgkin's disease children and adolescents were treated at Children's Cancer Hospital, Egypt during the period February 2008 to June 2010. The treatment was risk-adopted, receiving 4−6 courses of chemotherapy and involved filed low dose radiotherapy or 8 courses of chemotherapy without radiotherapy. All patients underwent PET-CT prior and after 2 courses of chemotherapy. A third PET-CT was performed at completion of chemotherapy for PET-positive patients.
Result: The 3-year overall survival rate (OS) was 96.8±1.8%. The OS rate were 100%, 94.4%, 81.8% and 69.6% for stages I, II, III and IV respectively. The event-free survival (EFS) was 86.4±5.0% for the whole group and 93.3%, 94.4%, 81.8% and 69.6% for stages I, II, III and IV respectively. All early PET-CT negative patients (after 2 courses) were alive (100%) and their 3-year EFS was 98.5±1.5%, while these who retained positivity had OS of 78.8±13.4% and EFS of 53.3±23.3%. This difference was statistically significant ($p = 0.001$). The OS and EFS for those who retained positivity after PET-CT completion of chemotherapy were both 50.0±25.0%. On the other hand those who showed PET-CT negativity after completion of chemotherapy enjoyed OS and EFS of 100%.
Conclusion: PET-CT is an excellent response-predictor for pediatric Hodgkin's disease who were treated with risk-adapted protocols.
No conflict of interest.

1616 POSTER

Possible influence of the N363S glucocortocoid receptor gene polymorphism on chemotherapy-induced toxicities and on the effect of chemotherapy in children with acute lymphoblastic leukemia (ALL)

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Background: Altough the fact the cure rate of childhood acute lymphoid leukemia (ALL) is above 80%, chemotherapy-induced toxicities are still concerned as a major challenge during the therapy. This study investigated a possible association between increased glucocorticoid sensitivity due to the N363S polymorphism of the glucocorticoid receptor gene and steroid-related toxicities during pediatric ALL therapy. The possible changing in the effectivity of the chemotherapy were analyzed as well.
Material and Methods: 346 pediatric ALL patients were involved in the present study. N363S polymorphism was identified by allele-specific PCR. We analyzed and compared clinical and laboratory signs of glucocorticoid related toxicities, day 8 prednisone response, and 5-year event-free survival rates retrospectively among carriers and non carriers.
Results: Thirty-two of the 346 patients were heterozygous carriers (9.2%). Glucose metabolism abnormalities (18.8% vs 3.8%, $P = 0.001$, carriers and non-carriers, respectively) and hepatotoxicity (31.3% vs 11.2%, $P = 0.004$, carriers and non-carriers, respectively) occurred more often among 363S-carries. No difference was appeared in the frequency of encephalopathy/psychosis nor of hypertension among carriers and non-carriers. 363S-carrier status is seemed to contributed to have a combination of toxicities. All carriers had good prednisone response (100%) and had more favorable 5-year event-free survival rates (93.1% vs. 71.86%, $P = 0.012$). Among non-carriers there were more poor prednisone responders (8.28%) and worse 5-year event-free survival rates.
Conclusion: In our study N363S polymorphism of the glucocorticoid receptor gene is proved to predispose to more severe steroid-related toxicity during ALL therapy. The identification of a possible 363S-carrier status could be a part of individualized therapy in the future.
No conflict of interest.

1617 POSTER

EPOC-experiences − conducting a multinational clinical trial on the pharmacology of doxorubicin in children with cancer

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Background: EPOC (European Paediatric Oncology off-patent medicines Consortium) is an EU FP7-fundet project with the goal to obtain missing pharmacology data for off-patent drugs for children with cancer to use for paediatric use marketing authorizations (PUMA).
Material and Methods: The first trial performed by EPOC, the 'Doxo-trial' (EudraCT No. 2009–011454−17), is a pharmacokinetic (PK) study of doxorubicin, which was performed in 4 European countries (Germany, UK, France and Italy) and recruited 100 children.
Results: Like most investigator-initiated multinational trials, the Doxo-trial faced a range of difficulties in order to be set up in the various countries. These came from:
– regulatory and ethical issues
– organisation of responsibility
– harmonising trial specific procedures and clinical work flows
– compliance with ICH-GCP, trial protocol and working procedures (WP)
– assurance of adequate patient recruitment.

In addition, it had to be ensured that the trial would fulfil all prerequisites for a PUMA application. To cope with this point, the EMA has been involved in regulatory discussions and a Scientific Advice. Work load and responsibility was split between project management, Sponsor and National Study Managers (NSM). The Sponsor organized all international challenges incl. contracts, insurance and pharmacovigilance. NSM set up the clinical network and dealt with regulatory and ethical issues on the national level. Despite other intention the time span for the first centre initiation to the last reached 18 months. Reasons included contractual issues and dealing with patient insurance.
For a PK trial it was important to harmonize differences in doxorubicin administration and sample handling. A precise WP was therefore written and trained. In enforcing compliance country or centre-specific practical and/or cultural differences were observed. Capillary sampling for example was an acceptable method in some centres but faced great barriers in others.
Conclusions: Organisation of the trial, extent of compliance and reasons for non-compliance to protocol and WPs will be presented and the consequences of this experience discussed for trials in paediatric oncology.
No conflict of interest.

1618 POSTER

Benchmarking teenage and young adult cancer professional developments across Europe: A Delphi Survey

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Background: The European Network for cancer research in children and adolescents (ENCCA) is a pan European research initiative aimed to improve outcomes for children and young people with cancer. A multidisciplinary European taskforce has been formed to deliver the remit of work package 17 which is divided into six work streams:
1. Create a European Multidisciplinary Framework for teenage and young adult (TYA) cancer
2. Develop TYA multi-professional education
3. Improve access to clinical trials for TYA
4. Develop a European TYA research initiative
5. Promote healthy lifestyles in TYA population and cancer survivors
6. Establish links to patient and support organizations.

Aims: We aimed to scope out TYA cancer professional, service and research developments to ascertain to what extent the above work streams are being addressed in each of the European Countries with a view to create a consensus of TYA service and research priorities. The exercise

also allows benchmarking and therefore tracking of changes over time within the ENCCA project.
Methods: A 3−4 round Delphi survey is being carried out. Participants were invited through known TYA professional bodies: Teenage and Young Adult Cancer (TYAC) in the UK and SIOP. Participants were encouraged to forward the questionnaire onto colleagues.
Results: A total of 116 questionnaires were returned of which 60 were fully completed and available for analysis in round 1. Respondents were mainly medical (n = 39, 65%) or nursing professionals (n = 12, 20%), and unknown (n = 3, 5.0%) and represented 21 countries. Analysis shows lack of consensus across Europe in a number of areas, including the age criterion, which defines teenagers and young adults with cancer. There is disparity in development of TYA services, research and patient advocacy across Europe. Communication and integration of paediatric, haematology, adult, palliative and primary care services also varied. Differences in research priorities are most likely related to differences in healthcare systems and infancy or development of TYA services.
Conclusion: The second round Delphi survey will be distributed May 2013 and will seek consensus of TYA definition, service configuration and prioritisation of research. This presentation will focus on rounds 1 and 2, present briefly the methodology used, and focus on the emerging trends, differences and similarities that defines the speciality of TYA care across Europe.
No conflict of interest.

1619 POSTER

Child cancer registration in Romania: Unveiling the gap

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Background: Despite mandatory reporting of all cancers being introduced since 1981, Romania still doesn't rely on a fully operational general cancer registration system, especially in terms of data aggregation, access and utilization. Pediatric oncology centers only have the picture of their own cases and there is no national perspective on child cancer.
Material and Methods: The Romanian Society of Pediatric Hematology and Oncology (RSPHO) has initiated a National Child Cancer Registry since 2009 with voluntary registration for 0−19 year incident cases. 10 out of the 12 pediatric oncology centers in Romania participate, covering approximately 80% of the country pediatric population. Incident cases are notified using the ENCR- recommended form with coding of tumors according to the ICD-O-3 and ICCC-3, and are processed by trained cancer-epidemiology.
Results: Currently the registry contains a number of 1534 notifications for 1186 incident cases (2009–2012), with more than half of the new cases nationwide being reported only by the 2 Oncology Institutes in Bucharest and Cluj. Average incidence rates for 2010 reported new cases were of $7.35_{\%000}$ (for 0−19 years) and $7.48_{\%000}$ for (0−14 years) compared to the $11.6_{\%000}$ expected from GLOBOCAN 2008 estimates. Distribution of new cases by diagnostic group was dominated by leukemia (27.2%), lymphomas (17%), and CNS tumors (17%). 92.7% of the incident cases had histology diagnosis and 29.3% received multimodality treatment. The percentage of stageable new cases that were actually staged raised from 42% in the first year to 67% in 2013. The registry faces major challenges in motivating and supporting voluntary data collection by busy burned out professionals. Difficulties also persist with heterogeneous definitions for staging and relapse as well as inconsistencies in using the fields of the form among participating centers.
Conclusions: Voluntary development of a National Childhood Cancer Registry is a major undertaking for a small organization such as RSPHO. Gaps between the projected and the reported incidence show significant underreporting that needs to be overcome. Existing data provide matters of concern regarding child cancer situation in Romania, in particular regarding delay to diagnosis which fatally alters the survival chances of the new cases.
No conflict of interest.

1620 POSTER

An evaluation of a specialist service for teenagers/young adults with cancer in the United Kingdom

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Background: This paper discusses findings from a formal service evaluation commissioned by the charityTeenage Cancer Trust, of a Teenage Young Adult (TYA) Cancer Service in the Northwest of England. United Kingdom (UK) incidence for cancer in those under age 14 is 134 per million and in age 15 to 24 years is 214 per million with more than 2000 TYA diagnoses per year (Birch 2005). Improvements for TYAs lag behind other cohorts. Suggested reasons include delays in diagnosis, poorer access to clinical trials, rarity of cancer, lack of education and the attention given to TYAs from health services, health professionals and research organisations (Bleyer, Budd & Montello 2006) and lastly their complex psychosocial needs. This evaluation aimed to evaluate the specialist support offered to Teenagers and Young adults with Cancer and their families and carers to strengthen and develop the service whilst informing future developments in service and policy. This project was part of a Knowledge Transfer Partnership in conjunction Coventry University.
Materials and Methods: A theoretical sample included young people aged 14−25 (n = 14), parents and young partners (n = 6) and staff (n = 20). All young people were between 4mths and 4.5 years from the end of treatment. Participant observations, along with semi-structured interviews were the selected methods of data collection. Thematic analysis using NVivo9 as a data management tool was used.
Results: The overarching themes identified included patient experience which was dependant on facilities, environment and social relationships; information sharing which in turn were dependant on multidisciplinary psychosocial support and service cohesion. Overall, patients were satisfied with the specialist service to include the facilities and environment provided, access to the multidisciplinary team with expertise in supporting TYAs with cancer specifically. This wider multi disciplinary team included Youth Support Co-ordinators and Learning Mentors, newer roles in this field of care. Aspects of care that could be enhanced included; the information provision on fertility, particularly for younger females; the support of friendships(existing and new); the cohesion of cross service relationships; the development of improved psychosocial screening processes and tools for both patients and carers; and the transition service for young people finishing treatment.
Conclusions: Findings add to the growing body of literature in this emergent cancer specialism which highlights the need for and value of age appropriate specialist care. Key recommendations will inform research, practice, policy and services for TYA's with cancer in the UK. This is robust evaluative study also assistsTeenage Cancer Trust, whose aim is to improve the quality of life and chances of survival for teenagers and young adults by providing these essential services, substantiate the work that they do and plan for the future.
No conflict of interest.

1621 POSTER

A decade of caring through multidisciplinary collaboration and evidence based practices at the Children's Cancer Center of Lebanon (CCCL)

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Background: The mission of the CCCL, established in 2002, is to improve the survival rates of children with cancer and provides the best possible treatment and care. The impact of care is focused on a multidisciplinary approach and evidence-based practice and grants treatment without any financial burden on patients. This paper will provide a brief overview of the multidisciplinary team efforts in fostering excellence in patient care and improving quality of life for children with cancer in Lebanon.
Materials and Methods: The CCCL is affiliated with St. Jude Children's Research Hospital in Memphis. The need for CCCL arose due to a lack in such centers in Lebanon for the treatment of children with malignancies. The cure rate was 40% much lower than what was reported in developed countries. Initially, there were 27 staff members and the number of registered patients was limited to 50 per year. In collaboration with the International Outreach Program at St. Jude's, 13 registered nurses, and other members of the multidisciplinary team, were sponsored to go attend pediatric oncology workshops in Memphis. The workshops covered a wide

range of education and hands-on experiences that are currently being implemented as ongoing processes in everyday utilization in clinical work. It was imperative for the team to strive in making the center develop. A Child Life department with psychosocial and educational services was created, encompassing volunteers for the entertainment of the children, as part of a holistic approach to care. A clinical educator, as well as a clinical nurse specialist was hired, respectively to: keep standards of care updated (through continuous staff competency insurance), and address patient needs.
Educational programs for patients and families in Arabic have been provided; evidence-based policies & protocols for treatment of cancer have been implemented, and updated routinely based on current needs as well as published studies. In order to prosper, there was a high need for a centralized research unit. A clinical data management unit, with two Masters-level prepared nurses, was thus established for generating new research, based on patient information.
Results: Since its inception, CCCL employed 76 staff members (33 staff nurses) and treated 880 patients. The cure rate is currently 88% for the highest childhood malignancy occurrence, a two-fold increase since prior to 2002. Ninety-six articles in peer review journals have been published, and over 50 abstracts were presented at national and international conferences. Psychosocial activities have significantly improved the well being of patients. Nurses are more involved in their education; international sessions are being broadcasted through the cure4kids website. Two nurses have become certified in Pediatric Hematology/Oncology. One nurse won the yearly APHON international scholarship award.
Conclusions: The multidisciplinary team efforts are a success story which we are proud of and eager to share.
No conflict of interest.

1622 POSTER

BET bromodomain inhibition as a therapeutic strategy to target N-Myc in neuroblastoma

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Background: Neuroblastoma is the most common malignancy in infancy and the most common extracranial solid tumor in children. Approximately 50% of human malignancies are characterized by over-expression of oncogenic Myc oncoproteins including N-Myc and c-Myc. Myc oncoproteins induce the initiation and promote the progression of malignancies by modulating gene transcription, leading to cell proliferation.
The bromodomain and extra terminal (BET) family of proteins BRD3 and BRD4 have recently been shown to play critical roles in c-Myc gene transcription, and the BRD3/BRD4 inhibitors JQ1 and I-BET151 considerably reduce c-Myc gene transcription. Importantly, JQ1 and I-BET151 exert significant anticancer effects in mice xenografted with leukaemia, Burkitt's lymphoma and multiple myeloma characterized by pathologic activation of c-Myc. Consequently, pharmaceutical companies are racing to test JQ1 in cancer patients in clinical trials.
Method and Material: We treated two neuroblastoma cell lines with the BET bromodomain inhibitor JQ1 or IBET151.
Results: RT-PCR and immunoblot studies showed that JQ1 and I-BET151 both reduced N-Myc mRNA and protein expression. The two BET bromodomain inhibitors also reactivated the expression of tumor suppressing genes including TP53INP1 which was suppressed by N-Myc in N-Myc amplified nerublastoma cell lines. Genome-wide differential gene expression studies with Affymetric gene array showed that two key oncogenic genes, BCL2 and MYB, were significantly repressed by JQ1 in neuroblastoma cells. Real-time RT-PCR experiments confirmed that BCL2 and MYB mRNA expression was reduced 24 hour after JQ1 treatment in neuroblastoma cells. Additionally, Alamar blue assays showed that treatment with the BET bromodomain inhibitors significantly reduced the number of viable neuroblasotma cells.
Conclusions: BET bromodomain inhibitors could be used as an efficacious therapeutic approach to reduce N-Myc expression, to reactivate the expression of tumour suppresser genes repressed by N-Myc, as well as to reduce the expression of other oncogenes such as BCL2 and MYB.
No conflict of interest.

1623 POSTER

Linc367, a novel long intergenic noncoding RNA, up-regulates N-Myc gene expression and neuroblastoma cell proliferation

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Background: Neuroblastoma is the most common solid tumour in early childhood. The worst subtype of neuroblastoma is caused by the N-Myc oncogene. At least 90% of the human genome is transcribed into non-protein-coding (noncoding) RNAs including microRNAs, PIWI-interacting RNAs and long intergenic noncoding RNAs (lincRNA). While numerous studies have associated microRNAs and PIWI-interacting RNAs with cancer, little is known about the expression and functional roles of lincRNAs in cancer, particularly in neuroblastoma. We have found a novel lincRNA, which we have named linc367, is associated with neuroblastoma.
Methods and Results: Using Rapid Amplification of cDNA Ends (RACE) PCR, we verified that linc367 contained three exons and two introns. RT-PCR studies showed that linc367 was highly expressed in N-Myc over-expressing, compared with N-Myc non-detectable, neuroblastoma cells. RT-PCR and immunoblot studies revealed that knocking-down linc367 expression with small interfering RNAs or antisense oligonucleotides significantly reduced N-Myc mRNA and protein expression. Cell proliferation/viability assays showed that linc367 enhanced neuroblastoma cell proliferation and/or survival. Moreover, RT-PCR studies demonstrated that linc367 expression in human neuroblastoma tissues predicted poor patient prognosis.
Conclusions: We have identified the novel long intergenic noncoding RNA linc367, and have demonstrated that linc367 enhances N-Myc gene expression, induces neuroblastoma cell proliferation and/or survival, and is a marker for poor prognosis in neuroblastoma patients.
No conflict of interest.

1624 POSTER

Impact of TH and DCX mRNAs detection in high-risk neuroblastoma patients' outcome

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Background: Survival rates for children with high-risk Neuroblastoma (NB) remain decisively low despite advances in multimodal treatment schedules. Accurate detection of minimal residual disease (MRD) could be crucial for outcome prediction in those patients. The aim of this study was to determine whether the presence of minimal disease (MD) and MRD is associated with bad prognosis and help us to improve selection of ultra-high-risk patients for new experimental therapies.
Material and Methods: Quantitative reverse transcriptase polymerase chain reaction QRT-PCR was performed for tyrosine hydroxylase (*TH*) and doublecortin (*DCX*) mRNAs detection on peripheral blood (PB) and bone marrow (BM) samples from high risk NB patients at diagnosis, post induction therapy and at the end of treatment. Time to death (overall survival-OS) and time to relapse/progression (Events Free Survival-EFS) were analyzed using the Kaplan–Meier method.
Results: At diagnosis the frequency of detecting *TH* and *DCX* was 67% (n = 86) in BM and 63.2 and 64.7% respectively in PB (n = 68). *DCX* in BM above median indicated worse outcome ($p = 0.03$) as well as *TH* in PB above median ($p = 0.003$). After induction therapy, *TH* and *DCX* were detected in 33.8% and 30.9% of BM (n = 71) and 13.3% and 6.7% of PB (n = 45). Patients with *DCX* and not *TH* positive BM have lower EFS ($p = 0.04$) and OS ($p = 0.02$) compared to patients with *DCX* negative BM. At the end of treatment the 38.1% and 28.6% of BM were positive for *TH* and *DCX* respectively (n = 21) and the 16.7% of PB analysed were positive for both markers. Despite the small number of samples, patients with *DCX* positive BM and *TH* positive PB showed significant lower EFS ($p = 0.02$).
Conclusions: According to our results, high-risk NB patients with high expression levels of *DCX* in BM and high expression of TH in PB at diagnosis would require new therapeutic strategies to avoid relapses and

death. *DCX* detection in BM after induction therapy could be a valuable predictive tool. At the end of treatment, *DCX* detected in BM and *TH* detected in PB might predict outcome. However these results were obtained in a small cohort of patients and require confirmation in multicenter studies.
No conflict of interest.

1625 POSTER

The paradigm in nephroblastoma: neoadjuvant chemotherapy or primary nephrectomy? Single center experience, 20 years of follow up

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Background: Nephroblastoma (Wilms tumor − WT) is the most common tumor of kidney in childhood. In the Czech Republic WT is treated according to SIOP protocols. The hallmark of these protocols is preoperative neoadjuvant chemotherapy (CHT), whereas nephrectomy is performed subsequently. In the present study we compare the survival of patients that underwent primary nephrectomy in comparison of patients treated with neoadjuvant CHT in a single center in more than 20 years period.
Patients and Methods: From 7/1988 to 5/2009 239 patients with WT were treated at Department of Pediatric Hematology and Oncology University Hospital Motol, Prague, Czech Republic. Event free survival (EFS) and overall survival (OS) was analyzed using Stat View statistical program.
Results: Patients we treated according to protocols: SIOP 9 (94 patients), SIOP 93 (80 patients) and SIOP 2001 (65 patients). Median follow-up is 12.5 years (3−21 years). 141 patients were classified as 1st clinical stage, 16 2nd stage, 29 3rd stage, 34 4th stage and 19 patients were 5th stage. 120 patients from 239 (50%) were treated with neoadjuvant CHT, 119 patients (50%) underwent primary nephrectomy. The most common causes of primary nephrectomy were: rupture of tumor or supposed rupture of tumor (23x), massive hematuria and/or anemization (26x), uncertainty of diagnosis (21x) and others. EFS and OS patients treated with neoadjuvant CHT or primary nephrectomy do not differ (EFS 76.6% versus (vs.) 79.8%, $p > 0.05$; OS 85.8% vs. 86.5%, $p > 0.05$). 29 patients from 239 (12%) suffered from tumor spillage, EFS and OS do not differ again (EFS 76.6% vs. 78.8%, $p > 0.05$; OS 83.3% vs. 86.5%, $p > 0.05$). Preoperative tumor spillage was diagnosed in 21 cases (7x abdominal injury in anamnesis); all were treated with primary nephrectomy. Perioperative tumor spillage occurred in 8 cases, only 1 patient was treated with neoadjuvant CHT (1 from 120, 0.8%), 7 of them underwent primary nephrectomy (7 from 98, 7%, $p = 0.02$). EFS of patients with spontaneous tumor spillage is 90% in comparison to 37% with perioperative tumor spillage, $p = 0.001$. OS is 100% vs. 37% $p < 0.001$, respectively.
Conclusions: We did not find any significant difference in EFS and OS in patients treated with neoadjuvant CHT or primary nephrectomy treated according to SIOP protocols at single institution. Patients suffering from perioperative tumor spillage have poor prognosis.
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No conflict of interest.

1626 POSTER

Basal neurocognitive function in the children with brain tumors before proton beam therapy

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Background: Neurocognitive function was evaluated in children with brain tumors who were planned to receive proton beam therapy (PBT). Clinical parameters associated with basal neurocognitive function was identified.
Materials and Methods: Forty-nine children aged 6−21 who were diagnosed with brain tumors were evaluated for neurocognitive function prior to PBT from March 2007 to December 2012 at National Cancer Center. Neurocognitive function tests included 1) Korean version of Wechsler Intelligence Scale for Children-3rd Edition (or Korean version of Wechsler Adult Intelligence Test): index for intelligence was composed of Full Intellectual Quotient (FIQ), Verbal IQ (VIQ), Performance IQ (PIQ), Verbal Comprehension (VC), Perceptual Organization (PO), Freedom from Distractibility (FD), Processing Speed (PS), 2) Rey-Kim Memory Test: Memory Quotient (MQ), and 3) Kim's Frontal Executive Function Test: Executive IQ (EIQ). All test scores were compared to age-matched standardization norms by *t*-test. The analysis of variance (ANOVA) was used to examine the effects of clinical factors on neurocognitive function.
Results: When compared to the age-matched normal population, patients group showed significantly lower PIQ (p=.007), PS (p=.000) and MQ (p=.031) in the patients<16, and lower MQ (p=.031) in the patients⩾16. Lower PS (p=.018) was noted in male gender. Lower FD (p=.051) was observed in the patients with hydrocephalus. Lower MQ (p=.000) was associated with supratentorial tumor location. Lower FIQ (p=.035) and VC (p=.019) were observed in the patients with lower performance status. Repeated surgeries before PBT was associated with lower FIQ (p=.031). Patients who had previous radiotherapy showed lower VC (p=.029) and FD (p=.039). History of high dose chemotherapy or stem cell transplant, age at diagnosis, surgical extent, and any pre-radiotherapy chemotherapy were not significantly associated with lower neurocognitive function (p>0.050 for all).
Conclusions: Children with brain tumors showed significantly different neurocognitive functions in several indices compared with the age-matched normal population. Our study suggests that clinical characteristics of tumors and surgical intervention before PBT were important determinants of children's neurocognitive function. These factors may need to be integrated in future longitudinal assessment for neurocognitive function after radiotherapy.
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No conflict of interest.

1627 POSTER

The spectrum of symptoms and its management in children with an incurable brain tumor; insight in the palliative phase

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Introduction: CNS tumors are diagnosed in 25% of pediatric oncology patients leading to a mortality rate of 30%. The aim of this study is to gain insight in how the palliative phase was managed.
Methods: A retrospective review of patients' medical charts from the Emma Children's Hospital who died of a brain tumor between May 2007 and September 2012.
Results: 34 children aged 0.4−17.2 years at time of death were included. After 0–2480 days from diagnosis (median 168) the infaust prognosis was evident with death following after 1–603 (median 80) days. Palliative cancer-directed therapy was given in 68% patients, comprising of chemotherapy solely in 11 (32%), and radiotherapy solely in 5 (15%) patients, while 6 (18%) received a combination of both. Thirty of 34 patients received dexamethasone at any point in the palliative phase. Frequent symptoms in the course were pain (91%), poor mobility (74%), somnolence (71%), disturbed cognition (65%), change of appearance (62%), seizures (56%), and vomiting (53%). Pain was treated satisfactory in 96%, necessitating systemic morphine and sedation eventually in 38% and 15% respectively, for a short amount of time; 0−44 days (median 0) and 0−6 days (median 0) respectively. Hospital visits were kept to a minimum during the palliative phase: the median amount of visits was 0 (range 0−37) and admission days were 5 (range 0−31). The visits and stays were mainly for anti-cancer therapy, supportive therapy such as transfusions and examinations.
A do-not-resuscitate code was discussed with all parents at a median of 2 (range 0–532) days after discussing the infaust prognosis and switch to palliative care which was 0–576 days before death (median 50). Even though the preferred place of death was at home for 33 out of 34 patients, 28 (82%) patients died at home in somnolent state. Six patients were admitted to the hospital for systemic anticonvulsants, pain medication and sedation until death.
Conclusion: A diversity of symptoms occurred during the palliative phase, necessitating intensive symptom management, mostly conducted at home. This knowledge facilitates advanced palliative care planning and helps to prepare parents and professionals to optimize the palliative care.
No conflict of interest.

1628 POSTER

Quality of life among adult long-term survivors of adolescent Hodgkin lymphoma: A follow-up study

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Background: The late effects associated with childhood Hodgkin lymphoma (HL) continue to increase. The treatment-related factors have been shown to impact subsequent quality of life (QoL). However, there is little data addressing the longer term outcomes of the adolescent survivors. Generally, data on adolescents lost in those for children. The purposes of the present study were to compare QoL of HL survivors with that of health young adults and to evaluate the relationships between disease/treatment features and QoL in the HL survivors.
Methods: A total of 22 male and 34 female survivors of HL with a median ages 27.5 years (range, 22−41) were evaluated. For comparison 94 (male − 44, female − 50) health subjects with a median ages 28.0 years (range, 22−46) was drawn to the study of QoL. All HL survivors were treated with modified pediatric protocol DAL-HD-90 in 1997–2007 in our clinic. Patients are allocated to three treatment groups (TGs). The original protocol is modified in the following positions: (1) procarbazin was replaced by dacarbazin; (2) young adults received vinblastin instead vincristin; (3) all patients with advanced stages received 2 cycles of ODPA independently from gender; (4) doses of involved field radiotherapy were increased from 20−25 Gy to 30 Gy. QOL was assessed by the Short Form 36 (SF-36), which generate 8 separate scales and 2 general scores (0 = worst health state, 100 = best health state). All survivors have a time of complete remission (CR) of Hodgkin's lymphoma $\geqslant$5 years.
Results: The HL survivors had lower scores than the normal controls on all scales and scores. Statistically significant differences were found in general health − GH (53$\pm$3 vs. 72$\pm$2, P <0.001), vitality − VT (55$\pm$2 vs. 72$\pm$2, P <0.001) and mental health − MH (57$\pm$2 vs. 72$\pm$2, P <0.001). Patients with the international prognostic scores for advanced stages (IPS; Hasenclever, 1998) $\geqslant$4 (n = 7) had the lowest scores in role physical − RF (29$\pm$15 vs. 81$\pm$5, P <0.001) and role emotional limitations − RE (33$\pm$15 vs. 77$\pm$5, P = 0.006). The adverse events including relapsed disease (n = 7) and second malignancies (n = 2) correlated with IPS $\geqslant$4 and reduced QoL. The patients with ages on moment of HL diagnosis $\geqslant$18.5 years (methods of ROC-curves, P = 0.047) have reduced QoL when compared to younger patients in GH (48$\pm$3 vs. 61$\pm$4, P = 0.027), VT (50$\pm$3 vs. 61$\pm$4, P = 0.013) and physical component scale − PCS (48$\pm$1 vs. 53$\pm$2, P = 0.046). Time since diagnosis, ages on QoL evaluation, gender, treatment groups (2, 4 or 6 cycles of chemotherapy plus radiotherapy), Ann-Arbor stages, bulky disease, current married status and education levels were not associated with statistically significant differences in QoL.
Conclusion: Long-term HL survivors have poorer physical and mental QoL than the general population of young adults. The age on moment of LH diagnosis $\geqslant$18.5 years was associated with significant reduced predominantly physical QoL. IPS $\geqslant$4, relapsed HL and secondary malignancies were associated mostly with the deterioration of role physical and emotional functioning, which may indicate a lack of confidence in the future health.
No conflict of interest.

1629 POSTER

Association between MTHFR, SLC19A1 and DHFR genetic polymorphisms and clinical and biochemical parameters of methotrexate induced toxicity in children with acute lymphoblastic leukaemia

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Acute lymphoblastic leukaemia (ALL) is the most common paediatric malignant disease, curable in 80% of children. Current protocols are designed to ensure the minimal acute and late adverse effects and to increase the overall survival. Despite improved contemporary guidelines, children are still exposed to chemotherapy induced toxicity. Methotrexate (MTX) is very potent cytotoxic agent, established in paediatric ALL protocols, but also well known for its potential toxicity.
We correlated pharmacogenomic, pharmacokinetic and clinical parameters of toxicity during intravenous MTX therapy in children with ALL. Single nucleotide polymorphisms (SNPs) in *methylene tetrahydrofolate reductase* gene (*MTHFR* 677C>T), *solute carrier family 19, member 1* gene *(SLC19A1* 80G>A) and *dihyfrofolate reductase* gene (*DHFR* −317A>G) were analyzed, due to their role in MTX pathway. Detection of SNPs was performed using PCR-based methodology. Pharmacokinetics of MTX was measured by standard serum concentrations at usual time points, determined by current BFM protocol. We graded clinical signs of MTX toxicity (gastrointestinal (GI), liver, renal, skin and neurological) according to WHO/NCI toxicity scale.
Study enrolled 153 children (62% boys) with *de novo* ALL, diagnosed from January 2003 until January 2012, age ranged from 3 months to 17.5 years, median 5.5 years. Genotype frequencies of *MTHFR* 677TT, *SLC19A1* 80AA and *DHFR* −317AA, for which has been shown that can influence MTX toxicity, were 11.2%, 27% and 30%, respectively. Decreased MTX pharmacokinetics was seen in 15% of children, of which 56.5% carried *DHFR* −317AA, 17.3% *SLC19A1* 80AA and 8.7% *MTHFR* 677TT genotypes. GI toxicity was found in 35.9%, of which 40% had either *SLC19A1* 80AA or *DHFR* −317AA genotypes, liver toxicity in 23.5%, where 50% of children had *MTHFR* 677TT, *SLC19A1* 80AA or *DHFR* −317AA genotypes, neurotoxicity in 5.2%, of whom 75% had *MTHFR* 677TT, *SLC19A1 80AA* or *DHFR* −317AA genotypes, while renal and skin toxicity was observed in less than 2% of all patients. The highest grade of toxicity was seen in 9.6% of children, in whom more than one of the above mentioned genotypes was detected.
We report the relation between pharmacokinetic and clinical markers, as already established parameters of toxicity, with pharmacogenomic ones. Preliminary results of our study revealed the possible role of *MTHFR*, *SLC19A1* and *DHFR* genetic polymorphisms as independent pharmacogenomic markers for prediction of acute MTX toxicity.
No conflict of interest.

1630 POSTER

The impact of ABCG2 C421A gene polymorphism on high dose methotrexate level in Egyptian Pediatric Acute Lymphoblastic Leukemia patients: Children's Cancer Hospital-Egypt [CCHE] Experience

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Background: Acute Lymphoblastic leukemia [ALL] represents 80% of the childhood leukemia. High Dose Methotrexate [HD-MTX] is the cornerstone antineoplastic drug in most of contemporary treatment protocols of pediatric ALL. Among the membrane efflux transporters of MTX, The Human breast cancer resistant protein (BCRP) which is the second member of the G subfamily of ATP-Binding cassette (ABC) efflux; also called (ABCG2). Among polymorphisms in ABCG2 gene, C421A Polymorphism represents 13% in the Middle Eastern population. We studied the effect of this polymorphism o the level of HD-MTX in Egyptian Pediatric ALL.
Materials and Methods: We recruited 200 ALL patients from Children's Cancer Hospital 57357-Egypt homogeneously treated according to modified St Jude TOTAL XV study in the period between 2010 to 2012. The study was approved by the ethics committee and informed consent was obtained. Methotrexate level was done at 23 hr, 42 hr and 68 hr. Also genotyping ABCG2 C421A gene polymorphism of was done.
Results: The age of the patients ranged from 1.0 to 18 years (Median age; 4.5) and 78.5% of the patients were younger than 10 years old. Within B-lineage (84%), the percentage of patients took HD-MTX at 2.5 g/m^2 was 50.6% while those took HD-MTX at 5.0gm/m^2 were 49.4%. For T-lineage, all patients took HD-MTX at 5.0 g/m^2. The Steady State Plasma Concentration (CPss) of HD-MTX in the Low risk group (82 patients) equals 33μM which was achieved in 68 patients (82.9%), while CPss in High/ Standard risk groups (112 patients) equals 66 μM which was achieved in 97 patients (86.6%). We tested the association between ABCG2 C421A genetic variation and the MTX plasma concentration at 23 hour, 42 hour and 68 hour after the intravenous infusion. We found no statistical significance between BCRP C421A polymorphism and MTX toxicity levels for either 2.5 g/m^2 [Low Risk] or 5.0 g/m^2 [Standard /High risk] groups at the various time points tested. Furthermore, No statistical significance was detected between BCRP C421A SNP and the Steady State Plasma Concentration (CPss) of HD-MTX at 23 hr in the two groups.
Conclusion: It is the largest study performed on Acute Lymphoblastic Leukemia Egyptian pediatric patients which showed that there is no significant correlation between the genetic variation of BCRP (C421A) and HD-MTX level. Correlation with other Trans-membrane protein mediated efflux of HD-MTX is needed to determine the mechanism of resistance and the toxicity.
No conflict of interest.

1631 POSTER

Observer-independent quantitative measurement for the interpretation of 123I-mIBG Scintigraphy in pediatric neuroblastoma (NB)

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Background: 123I-mIBG uptake has been shown to be a highly sensitive and specific method to detect NB and to evaluate response to therapy. The image interpretation is limited due to the resolution and size of the image. An automatic quantitative method has been created in order to measure and compare different scintigraphies in a multicenter setting. A methodology and a mathematical operator and procedure for the quantitative measurements of the areas with 123I-mIBG uptake has been developed and tested over 38 Images. On this paper a new observer-independent quantitative measure unit for uptake level in a single 123I -mIBG Scintigraphy is proposed.
Material and Methods: Medical records and good quality 123I-mIBG Scintigraphies from 19 patients from 2009 to 2013 were restrospectively reviewed. Scans were performed and informed by the Nuclear Medicine Unit of 'La Fe' Hospital. We transformed the values of all pixels of planar images into a normalized scale based on its standard deviation value. At each diagnosed tumour, we used the new values average of tumour's pixels as measurement of uptake in tumour.
Results: By using this new uptake unit, value of uptake of patients body background is constant in every 123I-mIBG Scintigraphy of the whole test set. Quantitative uptake values measured in tumours were correlated with qualitative uptake diagnosis in terms of increase or decrease of intensity observed in lesion area. Quantitative measurement of tumour's uptake could be compared with uptake level of patient's body background for monitoring the evolution of lesion.
Conclusions: A threshold of reference at uptake level of body's body background could be determined by this new quantitative metric and used for quantitative analysis of uptake. This new observer-independent 123-I-mIBG measurement method seems to have good correlation with the qualitative standard one, and could be used in a multicentric setting avoiding inter-observer differences.
No conflict of interest.

1632 POSTER

The impact of cancer on psychological morbidity of adolescent cancer patient: An experience from eastern India

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Background: The morbidity rate is very high among the Cancer patients and it is difficult to analyze the traumatic experience and the changes that happen in the body and mind of the cancer patients.
Materials and Methods: To study the impact of Cancer on Psychological Morbidity of Adolescent Cancer patients(11−20 years) and help them overcome it.
Sample: The sample comprises of 100 Adolescent (boys and girls) Cancer patients within the age group of 11−20 years undergoing treatment and surveillance in the Psycho-oncology department of Netaji Subhash Chandra Bose Cancer Research Institute, Kolkata during the period from January 2012 to December 2012.
Tool: The tools used for this research is General Health Questionnaire (GHQ-28) by Goldberg, D.P and Hillier, V.F and various play materials were used to divert their attention from the disease.
Result: The result explores the overall Mental Health and the four areas of Mental Health i.e somatic symptoms, Anxiety and Insomnia, Social and Cognitive Dysfunction and severe Depression of Cancer Patients. It was found that 60% were suffering from Somatic symptoms, 64.29% boys and 62% girls were suffering from Anxiety and Insomnia. 50%of the patients were experiencing Social and Cognitive dysfunction and majority were depressed. After that they were given psychotherapy in the form of playing carom games, playing on computer, musical instruments and singing songs. 80% of the patients (48) responded well to the therapy and came back to their normal rhythm of life.
Conclusion: The study undertaken showed that they had deterioration in Mental Health and they responded well in the form of psychotherapy. Hence this methodology should be used widely among the Adolescent Cancer patients.
No conflict of interest.

1633 POSTER

Determination of social support needs and expectations of parents of children with cancer from nurses

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Introduction: Identifying the social needs of families of children with cancer and providing social support is one of the most important responsibilities of the nurses.
Objective: This descriptive study aimed to determine the social support needs and expectations of parents of children with cancer from nurses.
Methods: The study was conducted in pediatric hemato-oncology wards of two hospitals in Ankara, Turkey in 2013. The sample consisted of 80 parents of children aged 0−18. Data were collected with a descriptive form and the Multidimensional Scale of Perceived Social Support (MSPSS) with the three dimensions of support related to family, friends and a special human. High score indicates the higher perceived social support. The highest possible scores for subscales and the total scale are, respectively, 28 and 84. Data were analyzed by percentages and frequency distributions.
Results: The average age of the children was 8.4±5.3 and 58.8% were male. Most of the children followed with the diagnosis of leukemia (46.3%), receiving the first treatment (48.8%). Average disease duration was 1.2±1.8 months. Mothers' and fathers' average ages were, respectively, 34.1±7.11 and38.6±7.2. Almost all of the mothers stayed in hospital with their child. 76.3% of parents stated that their child's disease affected the family budget. Only 20% of working mothers could have continued their works. Most of the parents (70%) stated that they received social support. This support was taken mostly from families (55.0%), physicians (31.3%) and nurses (28.8%). Social support expectations of parents were 72.5% from health care professionals and most of the expectations were about emotional (53.8%) and information (36.3%) support.
It was determined that 45% of parents were knowledgeable about the national social institutions/organizations. Mean total MSPSS score was 50.1±26.1. When dimensions of scale were analyzed, means scores found as 18.7±9.5, for family, 12.2±9.6 for friends, and 19.4±10.6 for special person.
Conclusion: The majority of parents stated their needs about social support. On the other hand, low subscale and total scale mean scores indicated the social support needs of parents. However, parents had little social support expectation from nurses. Nurses have to give importance to parents' social support needs in their interventions.
No conflict of interest.

1634 POSTER

Choroid plexus tumors in children − single center experience

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Choroid plexus tumors (CPT) are rare brain tumors defined as papillary neoplasms derived from choroid plexus epithelium. Three types of CPT can be distinguished, choroid plexus papilloma (CPP), atypical papilloma (APP) and choroid plexus carcinoma (CPC). We have evaluated characteristics, treatment and outcome of patients with CPTs diagnosed within 1982–2013 in our pediatric oncology center. Our cohort consisted of 30 patients (16 boys vs. 14 girls) with CPTs; 14 were CPC, 2 APP and 14 CPP. Median age at the time of diagnosis was 4.1 years (0.25 to 18.3) with 48% of patients younger than 3. The primary tumor site was located predominantly in lateral ventricles (62.5%), less frequently in 4th ventricle (25%), in 3rd ventricle (2 pts) and spinal cord (1 pt). Only one patient with CPC initially presented with metastatic disease, all others had localized disease. Patients with CPP and APP were treated with neurosurgical resection only, except one patient with CPP located in spinal cord, who received focal irradiation (XRT). Two out of 16 patients with CPP and APP died of neurosurgical complications and one patient with APP experienced metastatic recurrence. Patients with CPC were treated with surgery and chemotherapy alone (<3 years) or in combination with focal XRT (⩾3 years). In 45% of patients gross total resection (GTR) was achieved. Six patients with CPC experienced recurrence; four of them were initially resected subtotally (STR). Two patients with CPC developed metachronous tumors (glioblastoma and hemangioendothelioma) and one patient was diagnosed with synchronous adrenal neuroblastoma at the time of diagnosis of CPC. Four patients with

CPC have died, three of them with progressive disease and one of surgical complications. Probability of 5-years EFS of patients with CPC was 35.9% and 5-years OS 77.6%. Six CPC patients were tested for TP53 germ-line mutations and Li-Fraumeni syndrome was confirmed in four of them. Examination of four more patients is currently in process. Experience with our cohort of CPC indicates that patients after STR are in higher risk of recurrence. Some patients with recurrent disease can be cured. Higher 5 y OS observed in our cohort compared to published data is probably caused by lower incidence of metastatic disease among our patients. Furthermore all CPC patients should be tested for TP53 germ-line mutation to reveal Li-Fraumeni syndrome.
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No conflict of interest.

1635 POSTER

Clear cell sarcoma of the kidney

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Background: Clear Cell sarcoma of the kidney (CCSK) is a rare and aggressive tumor which accounts for 3% of pediatric renal tumors with incidence of 20 cases per year in US. CCSK is known as a Bone metastasizing renal tumor of the childhood with poor prognosis.The purpose of this paper is to show the demographic data of the patients, clinical presentation, staging in correlation with the survival analysis.
Material and Methods: All cases pathological CCSK in the period between I July 2007 till March 2012 at Children's Cancer Hospital − Egypt were reviewed. Patients age, gender, clinical presentation, medical history, CT chest and abdomen,pathological results and management for patients including chemotherapy, radiotherapy and surgery were reviewed.Follow up for those patient was continued till April 2013.
Results: Twenty-five cases of clear cell sarcoma of the kidney were found in the defined time interval, this accounts for 7% from all renal tumors. Mean age 36 month ranging from 1 to 104 months, 13 males and 12 females, Abdominal Swelling, Hematuria, Pain and Fever were the most common presentation found. According to COG staging system, stages I, II, III, IV and V were 9 (36%), 3 (12%), 9 (36%), 3 (12%) and 1 (4%) respectively. Aggressive chemotherapy was given containing Vincristine, Cyclophosphamide, Doxorubicin, Etoposide, and Carboplatin. Abdominal radiotherapy was given for local stage II and III (stage I did not receive radiotherapy). Radiotherapy was given for all sites of metastasis. At time of evaluation twenty two cases were in complete remission (CR), one case in partial remission with regressive course and two patients died due to progression and relapse.Overall survival was 88% and event-free survival (EFS) of 87.8% at 45 months. Stage I disease had overall survival of 100%.
Conclusion: CCSK patients showed an improved overall survival and event free survival when using an aggressive chemotherapeutic regimens and radiotherapy adapted to the stage of the disease, stage I clear cell sarcoma cases showed an excellent survival outcome inspite of not receiving any local radiotherapy.
No conflict of interest.

1636 POSTER

Burden and pattern of childhood malignancies in Western Kenya

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Background: Cancer registries worldwide have evolved to provide useful information on the burden and patterns of cancer. Kenya has no national data to provide an accurate view of the cancer situation. However, it is estimated that cancer is the third leading cause of death in the country after infectious diseases and cardiovascular diseases. The health systems in the country have traditionally concentrated on the prevention and control of communicable diseases at the expense of non-communicable diseases such as cancer. This has resulted in major weaknesses in cancer prevention and control initiatives in Kenya. About 80% of reported cases of cancer in Kenya are diagnosed at advanced stages, when very little can be achieved in terms of curative treatment.
Materials and Methods: The objective of this study was to determine the burden and pattern of childhood malignancies in Western Kenya from 2007 to 2010. A hospital based retrospective analysis of health records from Eldoret cancer registry located in Moi University, School of Medicine was done.
Results: Total number of childhood malignancies from 2007 to 2010 was 382 representing 9.3% of all cancers. The top five cancers were Non-Hodgkin lymphoma (22.8%), acute lymphoblastic leukaemia (13.1%), Kaposi sarcoma (7.6%), nephroblastoma (7.3%), rhabdomyosarcoma (5.8%). Male:Female ratio was 1.6:1, with a bimodal peak age distribution at 4 years and 10 years. Eight nine percent of these cancers were diagnosed by histology.
Conclusion: The burden of childhood malignancies is a significant health problem in Western Kenya with hematologic cancers being the most common.
No conflict of interest.

1637 POSTER

Retinoblastoma-clinical spectrum and treatment outcome in developing country

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Background: In developing countries usually children present with advanced disease and there is a high prevalence of disseminated extraocular disease. Though therapeutic approaches have been improved for eye preservation, but mortality is higher due to toxicity. In this study we have analysed the clinical spectrum & treatment outcome and evaluated the impact of combined chemotherapy & radiation on visual preservation in patients of retinoblastoma.
Material and Methods: In this retrospective analysis, a total of 61 patients of retinoblastoma were studied from Jan 2004 to Nov 2008. Evaluable 40 patients were analysed for presenting features; sites of involvement, treatment received and stage wise visual preservation. Most common age of presentation was 2−3 years (40%) and leucocoria was the most common finding (75%). More than 50% of the involved eyes had stage III−IV disease. Treatment was multimodal except in stage I and II in which patients received only external beam radiation with a dose of 45 Gy/25#/5 weeks. Rest patients received radiation after chemotherapy with OPEC regimen D_{1-4}, 3 weekly regimen or postoperatively. Following external beam radiation and chemotherapy response assessed by USG, ophthalmoscopy and EUA in ophthalmology department.
Results: With the median follow up of 30 months, this study showed that overall visual preservation rate of 100% in stage I and II, 64% in stage III, 45% in stage IV and 30% in stage V disease. None of the patients reported had significant radiation or chemo induced toxicities.
Conclusion: Visual preservation is excellent in retinoblastoma with current treatment modalities. With the advent of neoadjuvant chemoradiation, treatment goal has now shifted from surgery to visual preservation in most of patients. External beam radiotherapy has a definite role as primary or adjuvant treatment in management of retinoblastoma.
No conflict of interest.

1638 POSTER

Experience of blood, marrow and cellular transplantation at the children's hospital of Pittsburgh, 2000–2010: Family, psycho social issues surrounding adverse events

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Background: Blood or marrow transplantation, as well as the newer cellular therapies are usually a last resort treatment for children with pediatric malignancies. This study compares the family experience of the United States through selected transplantation programs with those of the National Health Service centers in the United Kingdom in the period 2005–2010. The reporting centers around the issues of medical complications, intensive care experience and psycho social impact overall on patient and caregivers.
Material and Methods: The archival materials and published materials of the UK Medical Research Council and the Children's Oncology Group in the United States are compared as part of this longitudinal study. Parental interviews in the United States and the United Kingdom as permitted through questionnaire are part of the study analysis.
Results: Moderate to severe stress related issues were reported by more than 90 percent of families surveyed. Post traumatic stress syndrome either diagnosed or sub clinical was also nearly 100 percent in these groups. Further analysis by regions over earlier (1980–2005) periods will be particularly useful to compare stress levels as the sophistication of transplantation has developed.
Conclusions: For family members as well as patients the transplantation experience in pediatric oncology is medically and psychologically traumatic.

As transplantation as a treatment continues to expand for both malignant and non malignant pediatric diseases, documenting and evaluating the multi faceted impact on patient and family should become increasingly relevant.
No conflict of interest.

1639 POSTER

Physicians' attitudes towards patient participation in decision making in the pediatric oncology setting and their assessment of patient competency − preliminary findings from a qualitative study

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Background: Children's and adolescents' participation in healthcare decisions depends on their competency. Only if minor patients demonstrate a sufficient level of maturity are they entitled to exercise decision making powers. The gatekeepers to participation are parents and physicians. Especially physician's role is important as parents can feel insecure as to how much to involve their child in decisions surrounding cancer care. Physicians' attitudes and motives towards including children and adolescents in these processes may influence the assessment of minors' competency to make or participate in therapeutic decisions. It thus seems crucial to carefully look at factors that physicians consider when deciding if a minor patient should be involved. This exploratory and descriptive study aims at identifying some of these factors while also capturing various positions pediatric oncologists take on patient participation in decision making.
Method: Semi-structured interviews will be carried out with pediatric oncologists in various children's hospitals in Switzerland. Interviews will be analysed using content analysis to code for general attitudes towards children's and adolescents' participation in decision making as well as for factors that physicians reported to associate with minors' competence.
Results: Findings from the on-going analysis present that physicians report various factors that they relate to competency in children and adolescents. These factors are driven by careful medical considerations, experience, personal attitudes, acknowledgment of other health care colleague's views and not least the parents' opinions. Additionally, positions on patient participation in pediatric oncology decision making differ among practitioners, even when legal provisions on the matter do not vary.
Conclusions: Preliminary results indicate that physicians' perception of skills children and adolescents must possess to be included in therapeutic decision making and of the degree of competency necessary in the oncology setting is crucial. These perceptions might guide physicians' assessment of patient's capacity to participate in decision making and thus ultimately influence recommendations given to parents as to the inclusion of a particular minor. They consequently significantly shape minors' autonomy in healthcare. Furthermore, general attitudes will influence physicians' own behaviour towards the child or adolescent. Thus, these convictions strongly affect aspects of patient care in the oncology setting.
No conflict of interest.

1640 POSTER

Non-Wilms' tumors (NWT) of the kidney in childhood: 15-year experience

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Aims: Wilms' tumor accounts for 7% of pediatric malignancies. Other primary renal pediatric malignancies however represent a much smaller proportion. They constitute a heterogeneous group that includes renal cell carcinoma, clear-cell sarcoma, mesoblastic nephroma, rhabdoid tumor of the kidney and renal medullary carcinoma. The aim of the present study was to investigate the cases of primary malignant NWT treated from 1996 to 2001, and to emphasize the importance of the early surgical excision of the tumor.
Methods: All children with renal malignancies were identified among the 750 patients treated in the Pediatric Oncology Department of our Hospital from January 1st, 1996 to December 31st, 2011. Patientsfiles were reviewed and the following data were collected: gender, age at the diagnosis, clinical presentation, operation and pathology reports, treatment scheme, follow-up and outcome.
Results: During this 15-year period a total of 73 children (29 male) were diagnosed with kidney tumors. Sixty-one had Wilms' tumor and 12 (16.4%) had a NWT. Diagnostic biopsies were performed on all patients and showed: renal-cell carcinoma (2), clear-cell sarcoma (2), rhabdoid tumor of the kidney (2), mesoblastic nephroma (3), cystic-cell nephroma (3). The median age at diagnosis was 2.2 years (range 2 months to 15 years). Four (4) patients, 2 with clear-cell sarcoma and 2 with rhabdoid tumor of the kidney received preoperative chemotherapy according to standard national protocols, followed by surgery. The rest submitted to an early surgical management. Post operative chemotherapy was given to 4 patients. 3 patients also received radiation therapy. 3 to 15 years after the ehd of treatment 10 patients are alive and disease free (median duration of follow-up: 92 months). Two patients died due to the progressive disease.
Conclusions: Non Wilm's renal tumors are rare in children. Nephrectomy as first-line therapy should be seriously considered in compination with pre- and post − operative chemotherapy wherever it needs.
No conflict of interest.

1641 POSTER

Humoral immunity findings in acute lymphoblastic leukemia in children

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Background: Cancer and chemotherapy are frequent causes of secondary immunodeficiency. Acute lymphoblastic leukaemia (ALL) is the most frequent paediatric cancer and the associated immune changes are relevant due to an increased risk of infection and comorbidity. The aim of this study was to analyse the evolution of serum immunoglobulin (Ig) levels from the onset of leukaemia to the end of treatment and to assess the impact of hypogammaglobulinemia on hospital admissions and ALL course.
Material and Methods: A retrospective longitudinal study of 90 children diagnosed with ALL during the last 10 years was conducted. Eleven patients were excluded: 2 Down' syndromes, 2 incomplete medicals records and 7 still on treatment. ALL types, Ig levels (at diagnosis and during chemotherapy) and data on admission for fever, relapse, transplantation, and mortality were analyzed.
Results: Main characteristics of 79 included children were as follows: mean age at diagnosis, 5 years (range 4 months-13 years); 46 boys: 33 girls; 66% had common B ALL; and 46% were classified as high risk. At onset, low levels of at least one Ig (isolated or multiple deficits) were found in 15% of patients. Of the 63 children with no relapses or transplant, 93.6% had low levels during chemotherapy (47.6% of IgG+IgA+IgM). Decreased IgM was often observed both at diagnosis and during treatment. Main reasons for admission were febrile neutropenia and respiratory infections. Ig levels were available in 44% of admissions and were low in 36.5%. No differences in Ig values among children who died (6), relapsed (10) or after transplantation (11) and the others were detected, but the small sample size limits the power for this analysis. Replacement therapy with Ig was given to 6 children with good clinical response. After therapy, gradual recovery was observed, reaching normal values in 12 months except for 4 children.
Conclusions: Reduced immunoglobulin levels are common in children with ALL. At diagnosis, 15% of patients showed one or several decreased Igs. During chemotherapy, low levels were detected in 93.6% of children. Although IgM is the most common affected value, the combination of low IgG-IgA-IgM is often seen during maintenance therapy. Most patients recover normal values after finishing treatment. More complete immunological studies should be included in the management of children with ALL.
No conflict of interest.

1642 POSTER

Low level laser therapy in oral mucositis

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Background: Oral mucositis remains a morbid side-effect of anticancer treatments and will complicate recovery due to discomfort and infection. Low Level Laser Therapy (LLLT) can contribute in healing and pain relief. As there are no guidelines available in the world literature it was the goal of this study to focus on the treatment frequency and the released energy related to the healing process.
Material and Methods: Children from the University hospital, department of paediatric oncology, suffering from chemotherapy-induced mucositis were treated. At the intake, prior to the start of the oncologic treatment, all patients were examined by a paediatric dentist and received oral hygiene instructions. The mean age of 9.4 years old. Most of them suffered from

ALL. At baseline, the mucositis grade was evaluated using the WHO-classification. The related discomfort expressed by oral pain was measured by a visual pain scale. An AsGaAl diode laser with 830nm wavelength and a potency of 500mW was used. The energy (J) released depended on the severity of the stomatitis. The children were visited on a regular basis until wound healing occurred. At each visit, the mucositis grade as well as the impact on oral functions was noticed. Pain assessment, before and immediately after treatment, was monitored using an age-adapted pain scale. Information about treatment sequence, treatment sessions and frequencies related to the comfort results were registered. At any visit, related blood cell counts were recorded.
Conclusion: From this survey, it became clear that 2 to 3 treatments per session seems a realistic approach resulting in a advanced healing. All patients recorded a gradual pain relief after each session.
No conflict of interest.

1643 POSTER

Medulloblastoma below the age of 3 years: Treatment and prognostic factors

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Background: Medulloblastoma patients below 3 years had inferior survival rates due to several reasons.
Aim: To investigate the treatment end-results of medulloblastoma under 3 years of age and determine the factors that affects its prognosis.
Patients and Methods: Eighteen children below the age of 3 years were treated at Children's Cancer Hospital, Egypt during the period from July 2007 and December 2010. Safe maximum resections were attempted in all patients. Gross total resection was performed in 10 children (56%), subtotal excision in 7 children (39%) and biopsy in one patient. Fourteen children (78%) proved to be non-metastatic, while 4 belonged to M3 category (spinal seedling). Eight out of the 18 (44%) children received infantile medulloblastoma chemotherapy protocol, while the other 10 received other chemotherapy protocols. All the 4 metastatic children received craniospinal irradiation (CSI) with boost to the seedling site. Six out of the M0 patients received posterior fossa (PF) irradiation (5580 cgy), while the other 8 received CSI, as they reached the age of 3 years, with booster dose up to 5580 cGy to PF.
Results: The 3-year overall survival (OS) for all children was 55±16%. The OS for non-metastatic was 61±15% and 50±29% for M children. The infantile chemotherapy protocol led to 3-year OS of 71±17% compared to 24±18% for other protocols. The OS for CSI was 71±17% compared to 49±25% for conformal PF irradiation. None of the CSI group developed CNS relapse, while only one (17%) who received PF irradiation had spinal relapse. It is worthnoting that non of the these detected differences were statistically significant. All children tolerated treatment with minimal immediate toxicity and acceptable, so far, late effects.
Conclusions: The 3-year OS of children below 3 years were modest with improved OS in non-metastatic patients who received infantile protocol and CSI.
No conflict of interest.

1644 POSTER

Treatment of paediatric brainstem glioma: A single-institution retrospective analysis

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Background: The role of chemotherapy in the treatment of children with newly diagnosed brainstem glioma is uncertain.
Materials and Methods: Between 1996 and 2012, 33 children with a defined clinico-radiological diagnosis of brainstem glioma were treated with radiotherapy or radiotherapy and chemotherapy in paediatric oncology department. Seventeen patients underwent biopsy. Histopathological investigation showed low grade gliomas in 2 cases, glioblastoma multiforme (2 pts), anaplastic astrocytoma (13 pts). The study involved 18 males and 15 females (median age, 7 years) with a median follow-up of 10 months (1−84 months). All diagnoses were established using MRI and in 12 patients Methyl-[11C]-L-methionine (MET) positron emission tomography (PET) was used. Twenty MET-PET scans from 12 patients were analyzed. PET was a tool in the monitoring during and after a treatment. Metabolic characteristics assessed with MET standardized uptake values (SUV). In our group SUV was 1.64−3.4 (median 2.1).
Thirty one patients were irradiated and received 53−60 Gy. Eleven children didn't receive any chemotherapy after irradiation (the first group). In two cases radiotherapy was interrupted because of the very fast progression. In the second group 7 patients received temozolomide (TMZ) as single-agent 150–200 mg/m^2 administered on 5 consecutive days every 28 days (number of courses 1−6, median 3), 6 pts also received concurrent chemotherapy during irradiation with TMZ (75 mg/m^2/day). The third group of patients (13 pts) received one of different chemotherapy regimens that contained: cyclophosphamide (or ifosfamide), etoposide, cisplatin and vincristine or ifosfamide, etoposide, carboplatin and vincristine (number of courses 1−17, median 8).
Results: The median OS for the first, second and third group was 6.0 and 8.0 months and 14.5 months respectively. The 1 year and 2 year overall survival in 20 patients that received RT and chemotherapy were 40.8±10.9% and 15.3±8.1%; in 13 patients that received only RT − 18.2±11.6% and 0% ($p = 0.19$). The overall survival rate dependent of the chemotherapy regimen was 11.1±10.5% (second group) and 60.0±15.5% (third group) at 1 year after diagnosis ($p < 0.05$). There are 3 long-term survivals in our group with follow up 64−84 months, who were treated with radiotherapy and intensive chemotherapy (third group).
Conclusion: In our series, TMZ did not result in a better outcome when compared with irradiation alone.
No conflict of interest.

1645 POSTER

Clinical outcomes and prognostic factors of pediatric Wilms tumor with initial metastases: CCHE experience

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Background: Renal tumors represent 6.3% of cancer diagnoses in children, where Wilms' tumors is the most common. Metastatic Wilms' tumors have the worst outcomes where the lung is the most common site of metastasis, followed by the liver then extra-abdominal lymph nodes.
Material and Methods: Forty-one pediatric patients with Wilms' Tumor having metastases at diagnosis were registered in the Children's Cancer Hospital Egypt (CCHE), between July 2007 and June 2011, and followed up until March 2013. Initial metastases were evaluated by CT chest and abdomen. Patients received pre-operative chemotherapy then response of pulmonary metastases was assessed. Patients were evaluated as either showing Rapid Complete Response (RCR), or Slow Incomplete Response (SIR), where slow responders should be shifted to more intensified chemotherapy and receive pulmonary irradiation. Overall (OS) and event-free survival (EFS) were calculated by Kaplan–Meier curve. Patients' outcomes were correlated with prognostic factors using log-rank test.
Results: 25 patients (60%) were females, while 16 (39 %) were males. Mean age at diagnosis was 4.6 years. 32 patients (78%) presented with pulmonary metastases only, 9 (22%) presented with lung and other metastases in liver. Post-operatively, 5 patients were locally stage I, 2 were locally stage II and 34) were locally stage III. 26 patients (63.4%) showed favorable histology, while 15 patients (36.6%) showed unfavorable histology as anaplasia in 5 cases and Blastemal predominance in 10 cases. 27 patients who presented initially with lung metastases only and showing favorable histology were assessed for their response; 8 patients (19.5%) showed RCR, while 18 patients (80.5%) showed SIR. One patient died before assessment of response due to progressive disease. Patients who showed pulmonary RCR were all in complete remission at final clinical status where 6 of them received pulmonary irradiation. 33 patients received local irradiation, 28 of which were locally stage III. At a median follow-up of 25 months, 5-year OS was 66.1% and EFS was 55.2%. 2 patients relapsed, one locally and lung metastases, and another relapsed as lung metastases only. Other 2 patients never reached complete remission showing progressive disease. The EFS was significantly correlated with histology, where patients with favorable histology showed EFS equals to 75%, compared to 18% in unfavorable histology (p-value= 0.001). OS was correlated with histology, showing 80.8% in favorable histology vs. 35.8% in unfavorable histology (p-value= 0.031). Other prognostic factors as pulmonary response to neo-adjuvant chemotherapy, site of metastases and local staging didn't show any impact on survival.
Conclusions: Initially metastatic wilms' tumor patients with favorable histology have significantly better outcomes compared to unfavorable histology. Response of pulmonary metastases to neo-adjuvant chemotherapy also plays a vital role in predicting disease prognosis.
No conflict of interest.

1646 POSTER

Evaluation of outcome of febrile neutropenic children with hematologic malignancies: The impact of different therapeutic modalities within the ICU environment

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Background: Many studies have succeeded in identifying a subset of children with febrile neutropenia (FN) who are at lower and higher risks of infectious complications and eventual death, but only few discuss the role of ICU and the uses of different modalities in diagnosis and treatment of those children with FN.
Methods: Between January 2009 and July 2011, 200 episodes of FN in 143 children were included in a prospective study in South Egypt Cancer Institute Assiut University, Assiut, Egypt, to evaluate the outcome of febrile neutropenia in children with hematological malignancies and to determine the impact of different therapeutic modalities within ICU environment.
Results: In the present study profound neutropenia (ANC less than 100 cell/m3) was significantly observed in high risk febrile neutropenic patients in comparison to low risk group. Profound neutropenia also was significantly observed to be associated with monocytopenia (96%) in comparison to mild and moderate neutropenia (3%). Patients with profound neutropenia were also significantly observed to be more liable to develop shock (86.6%) more than of that of higher ANC (5%). The outcome of patients with profound neutropenia were 59% improvement and that for mild and moderate neutropenia were 94%.
The outcome of treatment in our study group showed that from 100 episodes of high risk febrile neutropenia 72 (72%) patients improved, 39 (54%) inside ICU and 33 (46%) outside ICU. The low risk group showed that from 100 episodes 93 (93%) improved. Out of 15 patients put in mechanical ventilation 9 patients were improved.
Conclusions:
– From this study the patients of febrile neutropenia may be classified to high risk and low risk according to many clinical and laboratory parameters.
– It was concluded that sepsis level of serum PCT is a useful marker strongly suggestive of severe sepsis and severity of the illness.
– As estimation of serum PCT may predict the outcome its use may support the decision to start antibiotics therapy and ICU admission.
– High serum level of PCT may help in stratification of patients with febrile neutropenia in high risk and low risk group.
– Treatment of patients in a protocol manner according to risk criteria appears to be applicable for patients in the study group.
Recommendations: Profound neutropenia is notably predictive of the outcome in patients with febrile neutropenia. Use of serum PCT level, ANC and AMC in combination with clinical parameters might be useful in management of febrile neutropenia.
Conflict of interest: *Ownership: no. Advisory board: no. Board of directors: no. Corporate-sponsored research: no. Other substantive relationships: no*

1647 POSTER

Interactive multimedia pediatric surgical oncology

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Background: The educational need of pediatric surgeons, all the professionals related with child with cancer care and to contribute to supplement the programmes for the studies of medicine and nurse encouraged us to carry out this multimedia. Pediatric malignant diseases in Cuba represents 2% of all the annual cases according to the National Register of Cancer; however, this relative low incidence it is a health problem with a serious impact on the family, the health workers and society as a whole. For more than 20 years, I have worked as pediatric surgeon within a multidisciplinary team to care about children with cancer. That important experience (as national reference center) has allowed to our team to contribute to the results of the National Cancer Program in Cuba whose figures of survival have gradually increased for the last 40 years to more than 70%.
Material and Methods: Our Multimedia consists of five great chapters: Generalities, The Most Important Solid Tumors, Emergencies, The Family and Can Cancer be Cured? The chapter Generalities is about the history of general and pediatric oncology and surgical oncology synthesized up to now, both international and in Cuba; it also deals with general and particular statistics of each area, survival before and after the implementation of the National Program and the main concepts. We clearly and accurately approach the criteria and principles of pediatric surgical oncology, the main achievements, challenges and present difficulties and also our concept of rescue surgery in cancer.
The chapter on 'The most important tumors' deal it Renal Tumors, Embrionary Tumors, Neuroblastoma, Rabdomiosarcoma, Hepatoblastoma, Thyroid Tumors, Metastatic Tumors, among other topics with a comprehensive and up dated approach where we present our selection criteria for surgery treatment based on the cost-benefits-risk balance within the general treatment program, according to the approved protocols for each type of tumors. We present the surgical protocols and the statistic results in most of topics.
The chapter 'Can Cancer be cured?' deals with modern criteria about prognostic, early diagnosis and life quality.
The chapter 'The Family' is about all the issues related with the impact on each members of the family, since the moment of diagnosis to the cure or death and the behavior of the family health staffs.
Results: Through an attractive user interface, with hyperlinks texts, videos of interviews to experts and surgeries in real time, as well wide gallery of pictures charts and diagrams, our Multimedia fulfils the didactic objectives. It so adheres to international standards.
Conclusions: This multimedia mainly addressed to Pediatric Surgeons as ones in charged of one of the treatment modalities. This informatics product has been validated by the Cuban Pediatric Surgery Society, according to the informatics programs used and the contents.
No conflict of interest.

1648 POSTER

Molecular iodine adjuvancy in the antineoplastic effect of retinoic acid on neuroblastoma cells

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Background: Neuroblastoma (NB) is a childhood cancer that arises from precursor cells of the sympathetic nervous system and is responsible for 15% of all childhood cancer deaths. All-trans retinoic acid (ATRA) is an established component of the treatment given to children with high-risk NB to reduce minimal residual disease; however, its use has been limited because, at the therapeutic dose, it rapidly induces toxicity. On the other hand, several studies have demonstrated that molecular iodine (I_2) decreases cell proliferation and induces differentiation and/or apoptosis of several cancer cell lines. Our group has proposed that such actions are exerted by the formation of a lipid known as 6-iodolactone (6-IL), which binds to peroxisome proliferator-activated receptors type gamma (PPARγ); heterodimers of PPARγ, in turn, co-active ATRA receptors.
Materials and Methods: In the present study, we analyzed the antiproliferative (trypan blue assay) and apoptotic effects (AnexinaV/calcein) of I_2 and ATRA alone or in combination in ATRA-responsive (SH-SY5Y) and ATRA-resistant (SK-N-AS) NB cell lines.
Results: Our results confirm previous studies showing that in SH-SY5Y, ATRA induces differentiation (neuritic process), whereas in SK-N-AS ATRA has no effect at any analyzed dose. The molecular iodine supplement is accompanied by moderate, dose-dependent antiproliferative and apoptotic effects in both cell lines. When I_2 and ATRA are added together, a significant adjuvant effect is observed: at 200 μM I_2 is able to reduce the effective dose of ATRA by 1000 fold for induction of differentiation in SH-SY5Y and for the antiproliferative ATRA-response in SK-N-AS.
Conclusions: This finding indicates that I_2 sensitizes NB cells to ATRA and leads us to propose that it be assessed in therapeutic protocols as a possible way to reduce toxicity and avoid side effects. Analyses to determine the molecular pathways involved in this effect are currently underway in our laboratory.
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No conflict of interest.

1649 POSTER

Intracranial atypical teratoid rhabdoid tumour: A single institute experience of fifteen patients from North India

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Background: We intended to assess the clinicopathological features and treatment outcome in patients of intracranial atypical teratoid rhabdoid tumour (AT/RT), a rare malignant tumour of the brain.

Materials and Methods: Medical records were reviewed and clinical data collected on AT/RT in a 6 year period (2006−12). Histopathology slides were reviewed and relevant immunohistochemistry stains were done. Overall survival was analysed by Kaplan–Meier method. Univariate analysis of factors predictive of overall survival was done by Log Rank test.
Results: 15 patients met the study criterion (male: female=4:1). Median age at presentation was 5 years (range 0.8−8 years). Presenting complaints included vomiting (73.33%), headache (46.67%), orbital symptoms (33.33%), motor impairment (26.67%), gait abnormality (20%) and seizure (20%). Median duration of symptoms was noted to be 2 months (range 0.5−6 months). On contrast enhanced MRI of brain, tumour location was supratentorial in 60% patients and infratentorial in 40% patients. Cystic component and hydrocephalus were noted in 73.33% patients each whereas contrast enhancement and calcification were discerned in 53.33% and 40% of the patients respectively. All patients underwent tumour resection − gross total (26.67%), neartotal (13.33%) and subtotal (60%). Histopathology was confirmative of AT/RT with MIB-1 labelling index varying from 11−85% (median 45%). There was lack of immunostaining for INI-1 suggesting INI-1 mutation. Majority of tumours exhibited immunopositivity for EMA (93.33%), synaptophysin (80%), cytokeratin (66.67%), vimentin (66.7%), SMA (60%), GFAP (46.67%). Adjuvant radiation (36 Gy/20#/4 weeks to entire neuraxis followed by local boost 20 Gy/10#/2 weeks) was started in 6 patients (40%) and completed in 5 patients. Young age at presentation and poor performance status precluded the use of radiation in the remainder. Systemic chemotherapy was administered in 10 (66.67%) patients. Median number of cycles given was 3 (range 1−12) with ICE (ifosfamide, carboplatin, etoposide) and VAC (vincristine, dactinomycin, cyclophosphamide) being the common regimens (26.67% and 20% respectively). After a median follow-up of 8.33 months (mean-12.27 months), median overall survival was noted to be 10 months. At last follow-up, 2 patients are in complete response, 1 patient is on treatment, 3 patients are alive with evidence of disease and 9 patients expired due to disease progression. The 1 and 2 year actuarial rate of overall survival was noted to be 48.1% and 24.1% respectively. On univariate analysis, extent of surgery ($p = 0.0149$), use of craniospinal radiation ($p = 0.0087$) and MIB-1 labelling index ($p = 0.0034$) were significant predictors of overall survival while age ($\geqslant$5 years versus <5 years) was of borderline significance ($p = 0.08$).
Conclusion: Median survival of 10 months reflects the aggressive biology of this rare neoplasm. Maximal safe resection followed by craniospinal irradiation and systemic chemotherapy with ICE or VAC regimen is a reasonable treatment strategy in this uncommon malignancy.
No conflict of interest.

1650 POSTER

Clinical outcome of paediatric brainstem glioma treated with concomitant and adjuvant temozolomide: An institutional experience of 40 patients

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Introduction: Brainstem glioma (BSG) is an aggressive tumour of childhood. Treatment outcomes remain dismal and role of concurrent chemoradiotherapy (CTRT) is not established in these patients. We intended to study the clinical characteristics along with outcome of paediatric BSG patients treated with CTRT.
Methods: We retrospectively evaluated 40 patients, age less than 18 years, with BSG treated at our department in the period Jan 2007 to December 2011. Demographic and disease characteristics in this patient cohort were recorded. Progression free survival (PFS) was estimated by the use of Kaplan Meier method and univariate analysis (log rank test) was done to assess the impact of sex, grade, use of CTRT and adjuvant chemotherapy on PFS. SPSS version 12.0 was used and p value of <0.05 was considered significant for all statistical analysis.
Results: Median age at presentation was 9 years (range 3−18 years), with a male: female ratio of 1.5:1. 8 patients presented with gait ataxia and 16 presented with cranial nerve palsies. 24 patients were diagnosed radiologically as high grade. None of the patient underwent surgery. Radiotherapy dose was 56−60 Gray over 5.5 −6 weeks at 1.8−2 gray/fraction. All patients completed their radiotherapy except 4 patients. 15 patients received concurrent temozolomide (75 mg/m^2), 7 patients received adjuvant temozolomide (150–200 mg/m^2 D1−5 q4 weeks for 3−6 cycles) and 4 patient received both concurrent and adjuvant temozolomide. Median follow up duration was 7 months (range 1−39 months). At last follow up, 17 patients had progressive disease. Median PFS for the entire group was 16.6 months. PFS was significantly poorer in the patients who received concurrent temozolomide than those who did not (median PFS 7.9 vs. 16.7 months; p 0.03) on univariate analysis and also on multivariate analysis (p 0.01). Sex, grade, and adjuvant chemotherapy did not statistically alter treatment outcomes.
Conclusions: Outcome of paediatric BSG remains dismal. CTRT with temozolomide has detrimental effect on survival and its use should be discouraged. Radiotherapy alone with standard fractionation remains the treatment of choice in inoperable paediatric BSG.
No conflict of interest.

1651 POSTER

Paediatric nasopharyngeal carcinoma − management and experience of two Egyptian institutions

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Background: Nasopharyngeal carcinoma (NPC) is rare in children, accounting for 1% of paediatric malignancy. Neoadjuvant chemotherapy helps to decrease radiotherapy dose, limits its side effects and controls metastases. However, standard treatment as regard the optimal dose of radiotherapy and timing of chemotherapy is still not established yet.
Objectives: To investigate treatment outcome of paediatric NPC patients diagnosed and treated at the Children's Cancer Hospital Egypt 57357 (CCHE) and the National Cancer Institute (NCI), Cairo University during the period between July 2007 and July 2011.
Methods: Retrospective review of patient charts with histologically proven, paediatric NPC diagnosed and treated at CCHE and the NCI during a 4 years period. All patients were followed up till end of July 2012.
Results: Twenty-five patients were included in our study. Age of the patients ranged from 7.8−17 years with a median of 12 years. They were 19 males (76.0%) and 6 females (24.0%). Median follow up period ranged between 6 −54 (median 22 months).
All patients were diagnosed pathologically as WHO type III (undifferentiated NPC).
According to AJCC staging system, 3 patients (12%) were stage II, 6 patients (24%) as stage III and 16 patients (64%) were stage IV; 12 patients (48%) stage IV A:, 2 patients (8%) stage IV B, and 2 patients (8%) stage IV C.
Twenty patients (80%) received neoadjuvant chemotherapy with cisplatin/5-fluorouracil followed by concurrent chemo-radiotherapy in total dose of 61.2 Gy. Five patients (20%) received upfront radiotherapy with carboplatin as radio-sensitizer followed by adjuvant chemotherapy of cisplatin/5-flurouracil.
After completion of treatment, complete response was accomplished in 17 cases (68%), partial response in 3 cases (12%) and 3 patients lost follow up. After the end of follow up period, 4 patients relapsed and another 4 patients had progressive disease, out of those eight patients, six patients died. The 2-year OS and EFS rates were 79.7% and 60.8% respectively. Whereas the 4-year OS was 53.2% and EFS was 60.8%.
Conclusion: In our study, high systemic failure (32%) is still unacceptable and challenging. More efforts should be made to improve survival by investigating other prognostic factors and developing more efficient and less toxic therapeutic strategies.
No conflict of interest.

1652 POSTER

Langerhans cell histiocytosis (LCH) in Egyptian children − a single center experience

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Background: Langerhans Cell Histiocytosis (LCH) behavior ranges from spontaneous regression to rapid progression and death, or repeated reactivations. Localized disease (skin, bone or lymph node) have a good prognosis without treatment. In contrast, high risk organs (liver, spleen, hemopoietic system) have a poor outcome and may need aggressive chemotherapy.
Materials and Methods: Retrospective review of pediatric LCH patient charts diagnosed and treated at Children Cancer Hospital CCHE in the period between July 2007 and December 2011. Chemotherapy was given according to the LCH III protocol with follow up till 02/2013.
Results: 80 LCH patients, 43 males and 37 females were analyzed. Median age was 4.1 years (3 months − 13.4 y). Patients were stratified into 4 groups: Group I: monostotic lesion n = 14 (17.5%) received no systemic treatment, group II: multisystem with no risk organs (RO -): n = 29 (36%) received Vinblastine (VBL) and Prednisone (PRED) for up to 1 year, group III: multisystem with risk organs (RO+): n = 19 (24%) received (VBL), (PRED) methotrexate (MTX) and 6 mercaptopurine (6-MP) for 1 year and group IV: unisystem multifocal lesions +/− special sites: n = 18 (22.5%) received (VBL) and (PRED) for 6 months. After a minimum 1 year and up to 5.5 year follow up from end of induction, 70 patients (87.5%) were

better with No Active Disease (NAD) or Active Disease Regressive (ADR), 3 patients were intermediate (4%) in Active Disease Stable (ADS), 3 patients were worse (4%) in Active Disease Progressive (ADP). Three patients (4%) died (all in group III). The 5 years Overall Survival (OS) was (96.3%), while the 5 year Event Free Survival (EFS) was (54.7%) distributed per group as follows: Group I 93%, Group II 52%, Group III 47%, Group IV 83% $p < 0.013$. EFS was worse if age <2 years old (38%) compared to 2−10 years (71%) and >10 y (90%) $p < 0.001$. 2) Slow response (need for a 2nd induction) was responsible of a worse EFS (48.7%) in relation to rapid response (80.5%) $p < 0.009$. Reactivation occurred in 25 patients (38%), while post induction progression in 3 patients (4.5%). The probability of reactivation or progression was 47%. Shorter maintenance 8 months mean duration favored reactivation in relation to longer 10 months mean duration p0.043.
Conclusion: In our series, response to induction chemotherapy is satisfactory. Although a greater incidence of reactivation, survival remains the rule. Low age and slow responder carry a worse prognosis.
No conflict of interest.

1653 POSTER

Long term risk of cardiac morbidity after craniospinal irradiation a prospective from a developing nation

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Background: Craniospinal irradiation is an integral part of management of medulloblastoma. Late toxicity is major concern in long term survivors and significantly affects their quality of life. The purpose of study was to evaluate long term risk of cardiac morbidity for patients treated with 3-DCRT.
Patients and Methods: Study included twelve medulloblastoma patients, assessed as per age & risk stratification. All patients underwent planning CT scan in prone position under thermoplastic immobilization. Organs at risk contoured included heart, lungs, thyroid, esophagus, cochlea, kidney, intestines, stomach and liver. Heart was contoured as per RTOG guidelines. Target delineation generated CTVbrain, CTVspine, CTVposterior fossa. Seven mm margin was given to generate PTV. Dose of 30−36 Gy/20#/4wks was prescribed to spine, whole brain received 30 Gy/20#/4wks, posterior fossa boost was 24 Gy/12#/2.5wks. Planning was done by virtual simulation on eclipse version 6.2 for varian CL2300 linear accelerator with 6MV photons. Single direct spinal field prescribed at 90−95% isodose was used at an extended SSD whereas for cranial fields and posterior fossa boost fields dose was prescribed at 95% isodose. Adequate cranio-spinal junction matching was ensured by collmator angle and half beam block. For evaluation of late cardiac morbidity D_{max}, D_{mean} and volume of heart were recorded. Odds radio for development of late long term cardiac morbidity was calculated by formula OR= $1+ \alpha_1 D + \alpha_2 D^2$ where D was the mean dose of heart and value of α_1=0.19 and α_2=0.002 were used in equation.
Results: Median age of presentation was 7(2−18) years. Nine patients were in standard risk medullblastoma whereas three presented in high risk category. Spinal field were planned at median extended SSD of 115(105–120) cms. Median volume of heart was 291(256–356)cc. D_{max} for heart was 29(27−39) Gy where as D_{mean} was 19(16−24) Gy. Our study recorded substantial higher risk of long term cardiac toxicity median Odds ratio of 5.3 (2.75−5.8) as compared to non-radiated medulloblastoma patients (approx. OR 2.3).
Conclusions: With use of 3DCRT risk of late long term cardiac morbidity is substantially high (OR 5.3). Modern techniques of radiation such as IMRT should be evaluated to reduce the risk late cardio-toxicity.
No conflict of interest.

1654 POSTER

Current management and aspects of acute lymphoblastic and acute myeloblastic leukemia at a hospital based study in Iran

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Background: One of the main national referral centers for childhood malignancies in the capital city of Iran is MAHAK's Pediatric Cancer Treatment and Research Center (MPCTRC). Due to large number of referrals with leukemia, data compiled at this center can consider as reference for any issues related to managements and long-term effects in order to facilitate and optimize medical services for pediatric malignancies. This report provides data regarding long-term results and management of childhood acute leukemia at MPCTRC.
Materials and Methods: The enrolled patients consisted of 258 childhood acute leukemia cases that have been referred since 2007 to 2010 to MPCTRC. Basic epidemiological information recorded in standard checklist for each individual patient. All of the patients were followed for consideration long-term results.
Results: Out of patients, 198 (76.7%) had ALL and 60 (23.3%) had AML. In the ALL group, 111 were males (56.1%) but In the AML group, 32 were males (53.3%). The mean age in the ALL group was 5.6 ± 0.92 years in the AML group 6.2 ± 0.96 years. Eight (4%) of ALL and seven (11.7%) of AML cases had delayed complications. In ALL group 52 (26.3%) cases died and 4 (2%) were lost to follow-up. In AML group 28 (46.7%) cases died and 1 (1.7%) were lost to follow-up. The three years survival rate of ALL group was 92% and AML group was 85%. The median survival time of all cases was 12 ± 0.05 month.
Conclusions: The medical problem of childhood acute leukemia therapy is long-term effects that persist months or years after treatment and consist of learning problems, fatigue, bone or joint pain, also the risk of secondary cancers. Childhood cancer survivors should have physical examinations yearly. Regular medical follow-up for assessing the effects of therapy can lead to identify recurrence of the disease and long-term effects.
No conflict of interest.

1655 POSTER

Metronomic chemotherapy in pediatric relapsed or metastatic CNS tumors

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Background: Metronomic chemotherapy uses the very well known cytostatic agents in a new way. Instead of large doses, according to patient's tolerance, there are used small amounts of medication in a daily administration. The goal is to inhibit the angiogenesis, targeting the tumoral endothelial cells more than the tumoral cells. The inhibition of blood-vessel growth and the diminished blood supply could cause the tumor regression with favorable outcome and less toxicity. Recent studies show the efficacy of the metronomic therapy in pediatric solid tumors (neuroblastoma, sarcomas, CNS tumors) which are proved to be resistant to aggressive treatments. The cytostatic drugs have been used in small oral daily doses, in three weeks cycles (cyclophosphamide, etoposide, temozolomide) associated with anti-angiogenetic medication (fenofibrate, celecoxib).
Material and Methods: We have been prescribing the metronomic therapy since 2011 in 14 cases of CNS (medullar or cerebral) tumors which underwent prior surgery and chemo-radiotherapy and are in metastasis after the treatment. The patients have been taking fenofibrate 90 mg/m^2 q.d, celecoxib 100 mg b.i.d and have to rotate the 21-days cycles of etoposide 50 mg/m^2 q.d and cyclophosphamide 2.5 mg/kg q.d. They have been hematological monitored and doses are modified according to patient's tolerance. We have treated 3 cases of ependimoma (one case- medullar metastatic ependimoma, 2 cases of cerebral ependimoma), 4 cases of metastatic medulloblastoma (3 cases with leptomeningeal metastasis) and 7 cases of astrocitar relapsed or metastatic tumors.
Results: The outcome has been favorable in 9/14 cases. The treatment has been administered 2−24 month. Imagistic assessment revealed stable disease (reduction <50 % of the tumoral mass). EFS, psychomotor development and quality of life have been very good.
Conclusions: 1. Metronomic chemotherapy represents a good therapeutic alternative in relapsed or metastatic CNS tumors after the aggressive oncological treatment. 2. Survival with a good quality of life is offered by less toxicity and better tolerance.
No conflict of interest.

1656 POSTER

Prevention of infectious complications in children with bone tumours after the arthroplasty

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Background: The treatment of bone tumours in children requires numerous courses of chemotherapy − both before and after surgery. An

initial problem to be solved is providing venous access: comfortable for the patient and entailing minimal risk of infections. This is particularly important to prevent infection of bone implants in the joints. The best option is fully implantable venous port systems.
Materials and Methods: From 2008 to 2012 we observed 175 children with bone tumours of extremities (aged 3 years to 17 years). Sparing surgery (limb arthroplasty) was performed in 167 patients (95.4%): in 2008−24 patients, in 2009−34, in 2010−28, in 2011−44, in 2012−37. The lowest age of the patient, who underwent surgery for knee replacement − 3.5 years, the shoulder joint − 4 years. We have used venous ports since 2010 and implanted them in 80 (45.2%) patients with limb bone sarcomas: in 2010 5 (17.8%) patients, in 2011 39 (88.6%), in 2012 36 (97.2%). Subclavian catheters were implanted in 96 (54.8%) patients.
Results: Infectious complications developed in 18 patients with limb endoprosthesis (10.8%). There were 3 infected implants (12.5%) in 2008, 5 (14.7%) − in 2009, 3 (10.7%) − in 2010, 4 (9.0%) − in 2011, 3 (8.1%) − in 2012. Two-step re-arthoplasty was performed in 11 (61.1%) patients, conservative treatment (antibiotic therapy with Maxipime, Amikacin, Zyvox or Cubicin) helped to keep the implants in 7 patients (38.8%). In this early − developed within 3 months after the operation − infectious complications occurred in 64.3% of patients, delayed − from 3 months up to 2 years − 24.1%, and late − over two years − in 11.6%. Catheter-related bloodstream infection developed in 28 (29.1%) patients with subclavian catheters, while in patients with implantable venous ports such infections were not noted. The most common cause of catheter-related infections − S. epidermidis (71.8%) and S. aureus (18.2%), also inoculated when infected implants.
Conclusion: The introduction of implantable venous port-systems for the treatment of child patients with bone tumours has significantly reduced (1.8 times) the number of infectious complications and infections of limb prostheses, improving quality of life.
No conflict of interest.

1657 POSTER

Study of the role of palliative radiotherapy in the management of incurable pediatric malignancies

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Background: Palliative radiotherapy has a important role in the management of the pediatric malignancies, that are not curable and need only palliation for symptom control.
Methods: Patients coming to the department of radiotherapy S.M.S Hospital were included in the study. 36 pediatric patients were selected between nov 2010 to nov 2012. All of theses 36 children received palliative external beam radiotherapy for symptom control. Palliative radiotherapy was given either as single modality or in addition to surgery, chemotherapy and symptom relief drugs. Information recorded for each patient included age, sex, and extent of disease, histological types, symptomatology, treatment methods and symptom relief. The various dose schedules were used (1) 625cGy/week for 3 week, (2)20 Gy in 5 fractions and (3) 30 Gy in 10 fractions.
Results: There were 26 boys and 10 girls in the age group of 1 to 19 years, with a median age of 14 years (range of 1−19 years). Predominant symptoms were swelling with or without pain, bleeding, and weakness of limbs. The median duration of symptoms was 80 days (range of 4−40 days). The diagnosis of these children varied with different histologies, most in the group of malignant round cell tumors (17), retinoblastoma (6), neuroblastoma (5), Ewing's sarcoma (8). All patients presented with advanced stages of disease. Out of 36 patients 18 (50%) had disseminated disease at presentation. Six patients underwent surgery while 30 patients received chemotherapy and all patients received palliative radiotherapy. Three patients showed complete resolution, 18 patients showed good, while 14 patients had little, 1 did not have any relief in their symptoms. At the completion of multimodality treatment, 16 patients had partial response, 6 patients had progressive disease, 8 had stable disease and 2 patients had complete response. The disease status of 4 patients could not be known.
Conclusions: The role of radiotherapy is very important as palliative modality in children with locally advanced lesions. It provides better symptom relief.
No conflict of interest.

1658 POSTER

Obesity in childhood leukemia survivor

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Background: Obesity is the one of the most important health problems that increasingly seen in survivors of children with leukemia. Although the etiology of obesity in survivors of leukemia is not yet fully understood, the hypothalamic-pituitary axis affects the treatment methods, lifestyle and genetic factors are thought to be effective in.
Material and Methods: This systematic review was aimed to analyze the obesity situation and effecting factors in survivors of children with leukemia. Review of the literature was made on PUBMED and WILEY INTERSCIENCE databases by using 'child, leukemia, survivor and obesity' keywords. Thirteen descriptive researches which are suitable for criterias of 57 articles were included in research which was published from 2003 to 2013. The sample of it consisted of the patients whose treatment was finished after at least two years to define the frequency of obesity case among the childeren who are still alive from leukemia.
Results: Most of the researchs were done in the USA. Sample size of the all researchs was consisted of 9419 alive children. Most of the children who were alive were observed with the diagnosis of acute lenfoblastik leukemia. The average age of children in the researches was 16.4 and average diagnosis age of children was 4.9 The average age after the treatment was 10.8 years.
The frequency of obesity was between %4.6 and %47.2, the average was %34. The prevalence of obesity showed increases in the kranial radyoterapy and steroid therapy. At the same time, it was found that obesity mostly went on the children who had high body mass indexes during the treatment.
Conclusion: Alive children after a very long time after the treatment are under the risk of obesity according to nomal population. Children should be followed during and after the treatment to decrase the side effects of obesity and promote the healthy weight.
No conflict of interest.

1659 POSTER

Choice of treatment method in angiofibroma nasopharynx in children and adolescent

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Background: To perform analysis of treatment efficiency in angiofibroma nasopharynx in children and adolescent.
Materials and Methods: In 36 patients performed analysis results of angiofibroma nasopharynx in children and adolescent.
All patients examined with clinic-x-ray, endoscopy with tumor biopsy and CT and MRT.
Main symptoms: disorder of nasal breathing (100%), admixture of blood (81.1%), snuffing tinge (86.5%) and impediment of nasal breathing (67.6%). Most of patient's long time treated with rhinitis, pharyngitis, antritis.
In 36 patient performed surgical operations with Muru and bandaging of external carotid artery, part resection of maxilla, moving off tumor. Out of 36 patients in 14 (39%) tumor is spreading base of cranium and performed preoperative radiotherapy with 2 Grey dose, total 40−60 Grey dose. After radiotherapy tumor size decreased, in 14 patient carried out radical surgery operations. In 19(53%) patients performed surgical intervention without radiotherapy. In 3(8%) patients were taken postoperative radiotherapy, 2 grey dose, total dose was 40−60 Grey. Because tumor process was spread to pterygopalatine and subtemporal area.
Results: In 36 patients with nasopharynx benign tumor survival rate was 100%. Out of all patients in control group 3 (8%) revealed recidivating of tumor. In group of preparation's and post operations do not detected any recidivating.
Conclusion: Analysis of treatment results showed that, surgery and radiotherapy is choice of method in angiofibroma nasopharynx in children and adolescent.
No conflict of interest.

1660 POSTER

The use of implantable venous port systems in oncopaediatrics: Implantation technique and tactics of exploitation

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Background: Central venous catheterisation − a frequent but dangerous manipulation, requiring general anaesthesia, without which no chemotherapy is possible. Subclavian catheters have a finite period of service and a high risk of complications. Implantable venous port system − stitched in soft tissue chamber connected to the catheter, the distal end of which is located in the superior vena cava (SVC).
Materials and Methods: From 2010 to 2013 we implanted venous ports at 278 cancer patients (aged 4 months to 17 years). All implants were

performed with the use of intraoperative fluoroscopy for inserting port of the catheter into the SVC and precise positioning of the distal end of the catheter above the entrance to the right atrium. To ensure security we punctured internal jugular Vienna (IJV) for insertion of the catheter into SVC only after ultrasound navigation and marking of vessels, and in some complicated cases (thin, mobile vein) the puncture was performed with the use of intraoperative ultrasound imaging of blood vessels. Then in the subclavian area we created a subcutaneous 'pocket' where the portal camera was implanted. The catheter was inserted in a specially created subcutaneous tunnel from the puncture site to the place of the implanted chamber and connected with it. The tissue was then sutured in layers. As a solution to close the systems in time of no use, we applied a medicine containing taurolidine, which prevents the formation of biofilm on the inner surface of the catheter. In case of catheter thrombosis we inserted 3 ml of a fluid containing a 25,000 IU dosage of urokinase into the system, with exposure time of 15 minutes.
Results: No pneumothoraxes were noted. From the first attempt we managed to puncture IJV in 271 cases (97.4%). In this case, inserting a guidewire into ERW from the first attempt succeeded only in 189 cases (67.9%). In 69 cases (24.8%) there was the migration of the guidewire into internal jugular vein against the blood flow in 17 (6.11%) − into the subclavian vein on the side of puncture and in 3 cases (1.07%) − into the IJV on the opposite side. Periportal tissue infection was observed in 2 cases (0.71%). Port catheter thrombosis was observed in 6 cases (2.15%). Catheter-associated bloodstream infections were not reported.
Conclusions: Implementation of implantable venous port systems in oncopaediatrics reduces a number of vein punctures, general anaesthesia, and complications associated with these manipulations.
No conflict of interest.

1661 POSTER

Late effects and survival in children with cancer: A single-center experience

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Background: High cure rates of childhood cancer entail an increase of sequelae due to the disease or its treatment. Despite the existence of numerous reports on survivors and their clinical, neuropsicological, legal and social status, the real incidence of late effects is unknown and it is probably underestimated due to loss of follow-up data. The objective of this report is to know the evolution of children diagnosed with cancer in our center and to analyze survivors' late effects.
Material and Methods: Cohort study which includes patients aged 0−15 diagnosed with childhood cancer from 1990 to 2008. Age at diagnosis, gender, type of malignancy, treatment received, events appearance (recurrence or exitus) and number, type, severity and likely cause of sequelae were recorded. Kaplan Meier survival analysis was performed.
Results: 248 patients were analyzed (59% were male), with an average age of 5.7±4.2 years. The most frequent diagnoses were leukemia (30.6%), central nervous system malignancy (18.1%), lymphoma (11.3%) and neuroblastoma (12%). 50.6% required surgical treatment, 74% received chemotherapy, 14.9% radiotherapy and 14.6% hematopoietic stem cell transplantation. 21% recurred. The 5-year global survival rate was 71%. Leading cause of death was mostly progressive disease (44%) and infectious causes (30%). Of the 180 survivors, 40% presented some type of sequelae (42% considered as severe), due to surgery (49%), chemotherapy (20%), radiotherapy (13%) and the disease (11.6%). The sequelae were endocrinological (41.8%), neurological (21%), renal (15.5%) and musculoskeletal and aesthetic (both 9.7%). 4.2% developed a second tumor.
Conclusions: Survival rate is similar to that reported in other series. Percentage of severe sequelae is disturbing, due to the incapacity, continued health care needs and repercussion on the professional and personal projection of patients. Multidisciplinary teams promotion and continuous surveillance of childhood cancer survivors is needed to achieve the early detection of illness derived chronic problems and their treatment; as well as to implement programs to facilitate social insertion of these patients.
No conflict of interest.

1662 POSTER

Treatment strategy in children with medulloblastoma

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Background: The aim of our non-randomised study was to evaluate results of treatment and analysis of prognostic factors in patients over 3 years of age with medulloblastoma.
Material and Methods: From 1991 to 2005 we treated 102 patients(pts) with medulloblastoma, median age 8 (range 3 to 15 years). Gross total resection was performed in 43 pts, subtotal resection in 20, and partial in 39 pts. After surgery, all patients were treated with craniospinal irradiation. The majority received full dose neuroaxis radiation therapy, and 55 Gy to the primary site.
Adjuvant chemotherapy regimen Vincristine (Vcr), CCNU was administered in 47 pts, while 55 pts received platinum based adjuvant chemotherapy (Vcr, CCNU, CDDP regimen 44 pts, 8/1 8 pts, Baby brain protocol 3 pts).
Results: During the the 10 to 216 months follow-up period 5-year disease free survival (DFS) rate was 55.8% and 5-year overall survival (OS) rate was 58.8%.
5-year OS rate in adjuvant chemotherapy Vcr, CCNU group was 46.8% and 72.6% in Vcr, CCNU, CDDP group (statistically significant $p = 0.02$), while OS in 8/1 group was 61.7%.
The most significant prognostic factors were extent of surgery, absence of brain stem invasion and M2/M3 stage.
Conclusion: Adjuvant chemotherapy regimen Vcr, CCNU, CDDP is therapy of choice in multidisciplinary treatment of medulloblastoma. Complete resection, absence of brain stem invasion and absence of M2/M3 stage are predictors of better prognosis.
No conflict of interest.

1663 POSTER

Use of brentuximab vedotin in a 10 year old boy with relapsed Hodgkin's lymphoma − clinical case

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Background: Hodgkin's lymphoma has a very good survival rate in pediatric patients. In some cases of relapse is however very difficult to achieve a second remission. New drugs in Pediatric Oncology are introduced sometimes only some years after their introduction in adult context. We present a clinical case of relapse in Hodgkin's lymphoma in a ten year old boy, after 4 lines of therapy, autologous bone marrow transplant and radiotherapy. Brentuximab vedotin (BV) was used as a compassive drug, with good results and very few side effects.
Material and Methods: MFA was diagnosed Hodgkin's lymphoma (nodular sclerosis, Ann Arbor Stage IIA − mediastinum and cervical adenopathies) in July 2008. He started chemotherapy according to institutional protocol (adaptation of Cancer Children's Group protocol 5942), COPP (cyclophosphamide, vincristine, prednisolone, procarbazine)/ABV (doxorubicin, bleomycin, vinblastine) x 6 cycles due to bulky disease; and entered remission. In August 2009 relapsed was diagnosed and he started chemotherapy according to Euro-Net protocol IEP (ifosfamide, etoposide, prednisolone)/ABVD (doxorubicin, bleomycin, vimblastine, dacarbazine) with no response. He then started salvage chemotherapy with DECA (dexamethasone, etoposide, cisplatin, cytarabine). A new adenopathy was found after 2 cycles and he then started vinorelbine/gemcitabine with a slow but gradual response that permitted to proceed with autologous bone marrow transplant in September 2010. In December 2010, before programmed radiotherapy, CT showed multiple pulmonary lesions. Vinorelbine/gemcitabine was again started with partial response and in May 2011 he proceeded with radiotherapy. Disease progressed through radiotherapy. MFA clinical case was submitted to use with BV − compassionate drug use - and approved. He started therapy with BV in September 2011, with response (PET and CT). He had no need for packed red blood cells or platelet transfusions, he had one episode of fever (with pneumonia) and it was possible for him to have a normal life with school attendance during the 16 doses (1.8 mg/kg per dose each 3 weeks) of BV.
Results: Until today he remains in remission, being without treatment since July 2012. No late side effects related to BV have been noted.
Conclusion: Therapy with brentuximab vedotin was feasible in our patient, with anti-tumor activity, even after several lines of therapy and with very few side effects.
No conflict of interest.

1664 POSTER

Metastatic malignant melanoma in children and management of the complications

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Background: Malignant melanoma is a relatively rare diagnosis for childhood and in the adolescent population as well. Annual percentage change inrising incidence is observed during the past few years also for children older than 10 years of age and for whole group of adolescents. The incidence of malignant melanoma during adolescence has doubled in 10 years. This is not the case for the incidence of melanomas in children younger than 14 years, which seems to be unchanged. Current incidence in Slovakia is unknown. It is necessary to be aware of the risk of malignant melanomas in children after puberty.
Method: We present two casereports of a 16- and 17-years-old boys with metastatic malignant melanoma. The incidence of melanoma grew rapidly in adults over thepast several decades.
Results: Currently we treat 2 patients with metastatic malignant melanoma. Both of them were diagnosed previous in the last 2 years and they were initiated on specific treatment with vemurafenib and they are still in very good response to the therapy with clinically controlled disease without metastases. In the presentation we will discuss difficulties with the diagnostic process (in one from the patients it was initially diagnosed Ewing's sarcoma and after 4th cycle of the chemotherapy there was strong suspicion for double malignancy at once) and management of rare complications among these boys, which have not been published yet in the literature.
Conclusion: Melanoma in children and teenagers differs from melanoma in adults in presentation, complications, and survival. Further investigation is needed to elucidate possible biologic correlates of the unique aspects of melanoma in children and teenagers and to use these findings in therapy.
No conflict of interest.

1665 POSTER

Experience of using implantable peritoneal port systems for regional chemotherapy in patients with malignant peritoneal mesothelioma

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Background: Mesothelioma − is a rare form of cancer that develops from transformed cells originating in the mesothelium. Intraperitoneal chemotherapy − one of the essential components of a multi-modal approach in the treatment of this disease. The safest and most comfortable way of its implementation − using implantable peritoneal port inserted as a stage of cytoreductive surgery.
Methods: Since 2011 6 children with peritoneal mesothelioma aged 10 to 14 years receiving treatment underwent peritonectomy with one-stage implantation of peritoneal port systems and intraoperative intraperitoneal administration of the Cisplatin drug at a dose of 120 mg/m^2 at 90 minutes. Patients received adjuvant chemotherapy according to the Alimpta scheme 120 mg/m 2 first day, Cisplatin 75 mg/m^2 in intra-abdominal first day. The interval between courses was 21 days.
The portal body is implanted in the soft tissue of the front abdominal wall in the VIII − X rib area. An approximate 5-cm incision in the skin is made at the selected site. A 'kangaroo' pocket is created approximately two cm away from the incision line and 0.5-cm to 2.0 cm deep into which the portal body is placed. The portal body is fixed in the bottom of the 'pocket'. A catheter is placed into the abdominal cavity and through an opening in the abdominal wall is connected to the portal body. Soft tissue sutured in layers. In the port system Huber needle with a rounded tip is installed, so that it does not cut, but push the silicone chamber membrane.
Results: Patients and medical staff admit ease of the port systems operation. Recurrence of the disease and port systems infection were not noted.
Conclusion: Use of peritoneal ports is easy and safe way of intraperitoneal chemotherapy.
No conflict of interest.

1666 POSTER

Off-label use of bevacizumab in association with irinotecan in pediatric low grade gliomas: Not more than a short-term salvage treatment?

C. Pasqualini[1], A. Cuinet[1], S. Canale[1], A. Christin[1], I. Aerts[2], S. Puget[3], C. Dufour[1], D. Valteau-Couanet[1], J. Grill[1]. [1]*Institut Gustave Roussy, Pediatric and Adolescent Oncology, Villejuif cedex, France;* [2]*Institut Curie, Pediatric and Adolescent Oncology, Paris, France;* [3]*Necker Children Hospital, Pediatric and Adolescent Oncology, Paris, France*

Background: The combination of irinotecan and bevacizumab has shown efficacy in the treatment of some adult and children high and low-grade gliomas. It is now proposed as a new strategy for refractory or recurrent low-grade pediatric brain tumors.
Materials and Methods: Data concerning 26 children with recurrent or refractory primary low-grade glioma (LGG) treated in a single center were reviewed. Patients received treatment at a median age of 6.6 years, range 1.0–19.1 years. The majority had diencephalic tumors, five had disseminated disease, and nine had neurofibromatosis type 1. Six of 26 patients had progressed after at least three chemotherapy regimens (median of 1 line, range 0−5), sixteen had had surgery and no one had received radiotherapy. Intravenous bevacizumab (10 mg/kg) and irinotecan (125 mg/m$^{2)}$ were administered every 14 days, with a median of 15 cycles (range 5−26). Evaluation was carried out using Macdonald response criteria for contrast enhancing lesions and 2D size for the other. Treatment was continued until progression or grade 3 toxicity and usually for a maximum of one year. Primary end point was progression-free survival (PFS). Secondary end points included overall survival (OS) and radiological and clinical response.
Results: 24 patients had a radiological response after 4 cycles (92%) and two patients had a stable disease. Clinical improvements were noted in thirteen, including improved visual acuity (6), improved motor function (2), improved pain control (2), weight gain in two with a diencephalic syndrome, and reversal of psychomotor retardation (1). Five children remained on treatment for at least one year. 4 patients relapsed while on treatment. Response was not durable in the majority of patients (median 0.9 years, range 0.3−1.8).
Two-years PFS and OS rates were 21.5% (95% CI, 6.7 to 51.1%) and 86.7% (95% CI, 62.1–96.1%), respectively. No significant difference for PFS and OS has been showed based on NF1 status, number of previous chemotherapy lines and duration of bevacizumab-irinotecan association treatment. The only dose-limiting toxicity was one grade 3 proteinuria.
Conclusion: Recurrent pediatric LGG appear to be responsive to the combination of bevacizumab and irinotecan. A majority of patients achieve an objective response, whose stability seems, however, to be at short-term. The drug association has been relatively well tolerated, and warrants further study.
No conflict of interest.

Proffered Papers Session (Sat, 28 Sep)
Nursing − Advanced Nursing Roles

1700 ORAL

The constitution of a "Peripherally Inserted Central Catheters Team" (PICC team) at the Oncology Institute of Southern Switzerland (IOSI): a multidisciplinary approach

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Background: At the beginning of 2010 the creation of a nursing PICC Team was suggested by the Nursing Officer to the Director of the Oncology Institute of Southern Switzerland (IOSI) in order to offer to patients a different and more suitable vascular device chance and to nurses an opportunity of professional development.
Material and Methods: Four nurses were trained to the specific placement technique, two doctors were identified in order to manage clinical problems due to PICCs (indications and complications) and several nurses and health professionals were trained inside and outside the hospital for the device management.
After a literature review, it was decided initially not to use PICCs with hematological patients because of a higher risk of complications. For each patient, until the catheter removal, data were collected for the management

and continuous evaluation of the process by a multidisciplinary coordination group (nurses and doctors).
Results: At the end of February 2013, 102 PICCs had been placed and removed, out of 124 inserted (93% in oncological patients). On average, every PICC had been on site 87.7 days (range 2–348), with a median of 61.5. In 8 cases (8%) we had mechanical problems (unintentional take off and/or obstructions) and in 6 cases we had symptomatic venous thrombosis (0.67/1000 cath.days), but with negative catheter's tip culture.
Patients satisfaction (38 questionnaires) is high (average of 8.7 out of 10).
The collected data and the comparison with the scientific literature have improved internal guidelines and allowed to extend the PICC use also to hematological patients.
Moreover, by now, 15 training meetings, with around 200 participants, have been provided to internal and external nurses.
Conclusions: The project of a PICC Team constitution, started on the initiative of nurses, has been developed and consolidated thanks to a multidisciplinary collaboration. The PICCs introduction has promoted a development of nurse professional competences and patients have now a higher chance to receive the correct vascular device. The database periodic analysis and the multidisciplinary collaboration have allowed to constantly update the process, contain complications and keep high quality and security standards.
No conflict of interest.

1701 ORAL

The telephone follow-up as a strategy to improve the adherence to treatments of cancer patients

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Background: Treatment adherence is a subject of great importance in oncology because it impacts on the effectiveness of treatments, patient safety and health costs. Early identification of poor adherence will help to prevent treatment failures. Information and education are the best strategies used by health professionals to ensure adherence to treatments. Telephone follow-up appears to be a good way to share information, provide health education and improve the adherence to treatments. The aim of this study was to evaluate the influence of telephone follow-up information support to promote adherence to treatments of cancer patients.
Material and Methods: An experimental design was used to evaluate our telephone follow-up intervention. Participants were randomized into a control or a treatment group. The independent variable was the telephone follow-up and the dependent variable was the adherence to treatments.
The subjects of experimental group were followed by telephone once a week during 4 week and the subjects of control group were contacted by phone at thirtieth day after discharge. The adherence to treatments was assessed with Morisky-Green test and a weighted scale of adherence to treatment in both groups. We compared the adherence in each patient of the experimental group before and after each intervention and the adherence of all patients of experimental group and control group at thirtieth day after discharge.
The inter group differences were assessed using Student t-test, ANOVA, Mc Nemar test, and Chi-square test. A difference between observed variables was considered statistically significant when $p < 0.05$. Statistical analysis was performed using statistical packages STATA 10.0.
Results: We carried out 319 telephone interventions with a range of 20 and 40 minutes duration. Patients from the experimental group experienced an important increase in their adherence after in each intervention. There are significant differences between the first statement and the following ($p = 0.000$). The patients of experimental group achieved better adherence at 30 days after discharge than subjects of control group at the same period ($p = 0.000$). The same differences were found with the Morisky-Green test ($p < 0.001$).
Conclusions: Our results show that systematic information by telephone follow-up improves the adherence to treatment of cancer patients.
Verification by the health professionals of the correct compliance with medication may motivate and reinforce behavior, and is essential to ensure the maintenance of the adherence.
No conflict of interest.

1702 ORAL

A telephone hotline for women newly diagnosed with breast cancer

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Background: Telephone contact is widely used as part of psychosocial counselling for breast cancer patients. Few studies have described the topics raised by newly diagnosed breast cancer patients using telephone calls. This study took place at the Department of Breast Surgery where 600 operations are conducted annually in a fast-track concept and examines a telephone hot-line service offered to patients from the day of diagnosis. Our objectives were to register the number of calls and describe the most common problems raised by the patients on the open telephone hot-line.
Material and Methods: This study used a descriptive design. All patients were informed about the telephone hot-line on the day of diagnosis and were free to use it 24 hours a day for the entire stay as an out-or inpatient. For a period of 8 weeks telephone calls were recorded. The recording was conducted by the nursing staff using a chart covering demographic and clinical data as well as detailed registration of the main themes of the conversation. Subsequently the themes were categorised.
Results: A total of 140 calls were included in the study. 56% of calls were questions regarding skin and tissue (e.g swelling, seromas, infection). Psychosocial concerns such as sadness and worry were raised in 18% of the cases and issues related to pain and the use of analgesics counted for 10% of the calls. Another 4% asked questions related to hormonal treatment and finally 18% consisted of various different topics. 6% of the patients reported more than one problem.
Conclusion: The present study evaluates an open telephone hot-line and demonstrates the need for a permanent possibility for newly diagnosed breast cancer patients to contact a breast care specialist. The hot-line provides an opportunity for patients to discuss problems and needs with a nurse. The most frequently reported problems concerned skin and tissue, psychological issues and pain.
The study also provides valuable knowledge about newly diagnosed breast cancer patients informational needs. These findings can be useful for future clinical nursing improvements.
No conflict of interest.

1703 ORAL

Oncology nursing research: How can we improve it? Results of a project based approach

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Background: The implementation of nursing research in oncology nursing is still in its infancy. In the Erasmus MC Cancer Institute professionals and managers were dissatisfied on the utilisation of research by nurses. Improvement in factors promoting research in the organizational context yield the decision to start a project on promoting nursing research and Evidence Based Care (EBC).
Materials and Methods: Between June 2009 and July 2012 we aimed to achieve three objectives:
1. Increased involvement of nurses in nursing or multidisciplinary research, by promoting the use of EBC and improving nurses' access to research findings.
2. A minimum of 4 nursing studies, resulting in publications or presentations, by coaching young scientists in the performance of their study.
3. Policy on oncology nursing research, by optimizing contextual factors, like leadership and culture.

A project was set up, led by a nurse scientist, and with participation of staff nurses, nurse practitioners, nurse scientists, managers, and physicians. We determined an incremental approach, to be able to satisfy the requirements of nurses, nursing teams or others.
Results: During this project many staff nurses were involved in at least eight literature searches on clinical problems. Thirteen nurses started and/or finished a scientific or evaluation study. Five reference meetings were held on study results, in attendance of 10−40 nurses per meeting. Nurses were first, second or last author in >100 presentations and publications, of which nine publications in international peer reviewed journals, and 19 oral and 24 poster presentations on international conferences. Additionally € 142.000 on external funding was raised. In accordance to the Promoting Action on Research Implementation in Health Services (PARIHS) framework, promoting factors and pitfalls of research utilization were examined, and yield to adaptation of the project strategy.
Finally the project resulted in the establishment of the Oncology Care Research Group for oncology nurses and allied healthcare researchers.
Conclusion: These results on the implementation of oncology nursing research show that promoting research utilization can be achieved within a few years. In our project, attention to various promoting factors and pitfalls, and a gradual approach contributed to the success, but the commitment of nurses and managers are essential.
No conflict of interest.

1704 ORAL

Smileon: supporting innovative learning approaches through mobile integration in the workplace − oncology nursing: Results from the first pilot

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Background: Use of mobile technology can allow the learning process to be facilitated outside and beyond the classroom contexts in which most oncology nursing training currently takes place.
Objectives: The aim of the project is to develop a new approach to training using mobile devices to extend learning activity into daily practice. This methodology was supported by a toolkit designed for tablets that use the Android operating system. Using these devices, nurses will be able to communicate in real time in the work place and access relevant content according to their needs.
Material and Methods: The project has involved needs analysis, development of appropriate learning methodology and mobile toolkit to support it. The approach were piloted in each of the partner countries (Spain, Czech, Italy, Slovenia, Lithuania and Turkey). The focus of the first pilot was the validation of the learning methodology and approach. The aim was to ensure that the toolkit and methodology proposed actually do facilitate and enrich the learning experience for the nurses. Sixty-six nurses from partnering countries were involved into first pilot and have been using the system. It was took a period of one month. Data were collected via both quantitative and qualitative; the quantitative instruments were series of questionnaires, based on Likert scale items (0−5) and semi-structure questionnaire were used for qualitative data.
Results: Nurses indicated that this approach was useful (mean = 5) and it was excellent choice for learning, it was relevant and effective (mean = 4). They mostly used tablets at home (mean = 4). They suggested some technical applications such as space for discussion under documents or photos, list of latest news, email notification daily activities etc.).
Conclusions: The methodology was certainly found as positive, relevant and effective in health workplace. Users are able to introduce the use of the methodology in clinical practice (for example for beginning nurses) with some technical modifications.
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No conflict of interest.

1705 ORAL

Understanding nurses' roles in nurse-led chemotherapy clinics: A two phase study using survey and ethnographic observational methods

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Background: The purpose of this study is to investigate the nursing role within nurse-led oncology clinics. There has been a rapid expansion and development of nursing roles and responsibilities in oncology, but little understanding of how roles are enacted nor their impact on patient experience and outcomes.
Materials and Methods: A two stage approach comprised a phase 1 survey of UK oncology specialist nurses (OSN) followed by a phase 2 ethnographic observational study of nurse roles in nurse led chemotherapy clinics. Ethics approval was obtained prior to each study; research and development approval was obtained from each hospital prior to Study 2. Study 1 used a questionnaire survey to explore the scope of nurses' roles. A purposive sample of OSN was recruited using snowballing methods. Descriptive and inferential statistics were used in data analysis. Study 2 used ethnographic methods to explore nurse-led chemotherapy clinics. A purposive sample of nurses from Study 1 was recruited to ensure geographical representation within the UK. Observations of nurse-led chemotherapy clinics and interviews with OSN were undertaken for data collection. Findings were coded and thematic analysis undertaken.
Results: Study 1 (n = 103 response rate 64%) showed development in nurse roles and services but little congruence between nurses' titles and roles. There were significant differences in practice: clinical examination ($p = 0.004$), history-taking ($p = 0.008$), nurse prescribing ($p < 0.0001$). Study 2 included observations (61 consultations by 13 nurses) and interviews (n = 11). There was variability in patient numbers within nurse-led clinics, identifying implications for service delivery and sustainability. Disparities in nurses' roles and responsibilities revealed 4 different levels of nurse-led chemotherapy clinics, from chemotherapy administration to totally nurse-led clinics. 5 main themes were identified: autonomy, knowledge, skills, power and beliefs. A key finding was reduced emphasis on compassionate care with greater medicalization of nurses' roles.
Conclusions: Despite a great diversity in oncology specialist nurses' roles, the lack of clarity in roles and responsibilities is creating confusion. Similarly the rapid increase in nurse-led chemotherapy clinics has been ad hoc with no formal evaluations. Nurse-led clinics have adopted a medical model of doctor-nurse substitution, which may have led to reduced emphasis on nursing skills and compassionate care.
No conflict of interest.

1706 ORAL

Improving the nursing care of patients with peritoneal surface malignancies who are treated with cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) by use of a phase model clinical pathway

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Background: The relatively low frequency of the HIPEC procedure can lead to indecision in the care process amongst inexperienced ward physicians. This in turn often leads to dissatisfaction amongst experienced nurses.
Also the ward physicians made decisions about nursing actions based on the nurses' observations. This led to delays in the nursing process and therefore in delays of the recovery of the patient.
To improve nursing work satisfaction and reduce patient hospitalization time, a clinical pathway was drafted. Due to the unpredictability of recovery after HIPEC a phase model clinical pathway was developed. In contrary to other pathways this model divides the care process in phases: pre-operative, postoperative and discharge phase.
Method: In April 2009 the phase model clinical pathway was implemented. Details on patient hospitalization were obtained by reviewing charts of a pre-implementation cohort of 10 patients and 2 post-implementation cohorts of 33 and 38 patients.
Open label interviews with nursing staff were conducted to evaluate nurses' sense of autonomy as well as sense of effectiveness of nursing actions. These interviews occurred in 2009 and 2013.
Patient satisfaction will be measured by a patient panel in early summer of 2013.
Results: Mean hospitalization time was 15.6 days in 2012 compared to 23.0 days in 2008: a reduction of **7.4** days.
In 2009, 47% of nurses had a sense of autonomy in decision making; in 2013 this proportion increased to 78%: an improvement of **31%**.
Also in 2009, 59% of the nurses were positive about the effectiveness of their actions, while in 2013 this was 93%: an improvement of **34%**.
The outcome of the patient panel will be presented during the congress.
Conclusion: The development and implementation of a phase model clinical pathway makes it possible to structure unpredictable care. The improvement in nursing care of HIPEC patients brought about by implementation of this pathway has led to a reduction of admission time and enhancement of the nursing work satisfaction.
No conflict of interest.

1707 ORAL

Feasibility and safety of replacing outpatient visit with telephone consultation before administrating chemotherapy in patients with metastatic prostate cancer

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Background: The work flow of patients receiving chemotherapy is a pre-chemo outpatient consultation with blood test day 1 and treatment day 2. The purpose of this study was to test the feasibility and safety of telephone consultation with nurse specialist instead of visit at the clinic in patients with metastatic prostate cancer receiving palliative chemotherapy.
Methods and Materials: The prospective study included patients with metastatic prostate cancer which was found eligible for palliative chemotherapy with docetaxel every 3 weeks. 33 patients were included in the period may 2011 to march 2012. The median age was 74 (range 51−85) years. The intervention consisted of telephone consultation with specialist nurse instead of outpatient attendance the day before chemotherapy in series 2, 3 and 4. Adverse events were scored according to CTC version 3.0.

More than grade 2 of dose-limiting toxicity resulted in dose reduction or treatment delay and additional consultation (physician) if relevant. The grade of toxicity was confirmed right before chemotherapy was administrated.
Patient satisfaction was recorded by semi-structured interview and by using a 5-step Likert scale from 'very poor' to 'very satisfactory'.
The study recorded the number of minutes the patient spent at attendance for consultation at the clinic before the first series and of phone consultation before the second series of chemotherapy.
Results: A total of 24 patients completed the intervention. 23 were interviewed.
Safety: Grading of patients toxicity in telephone consultation was identical to the grading performed by nurse specialist colleagues. No patients required additional medical consultation. 9 patients had dose reduction due to toxicity.
Patients expressed relief to avoid transportation and stay in the outpatient facility.
21 patients responded 'very satisfactory' and 2 'satisfactory' to phone consultation as a method.
The patient's time spent on telephone consultation was significantly lower than attendance: median (range): 21.5 (9−45) vs. 180 (75–485) minutes. ($P = 0.001$). Patients avoided transportation (median 30 km (range 7–100 km) to the clinic), which reduced private costs.
Conclusion: The method can be considered feasible and safe. Patents expressed great satisfaction with telephone consultation. Especially due to the time saved to transport and shorter stay at the hospital. Further studies must be performed to establish whether the method can be used in other patient populations.
No conflict of interest.

Proffered Papers Session (Sat, 28 Sep)
Nursing − Impact of Cancer on Patients and Families

1708 ORAL

Suffering in silence: A qualitative study on the repercussions of having an adult child with cancer on the life of older parents

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Background: Increased life expectancy enhances the likelihood that older people face a cancer diagnosis in an adult child. Only a minimal amount of research has been directed towards this topic. We aimed to gain insight into the lived experience of the parenting position and role of these older parents of an adult child with cancer.
Material and Methods: Qualitative study using loosely structured interviews to elicit accounts of 20 parents ($\geqslant$70 years). Data were analyzed with support of NVivo 10 using the constant comparison technique, based on the principles of grounded theory.
Results: 'Suffering in silence' emerged as the core category encapsulating parents' experiences of shielding and unwillingly being shielded by their child. Shielding and being shielded contains two broad areas of mutual protection, information and emotion work, both reinforcing their suffering in silence. First, some parents had a feeling of being in the margin of events, as their adult child preferred to divulge information incrementally on a 'here and now' basis. Second, older parents experience a multitude of feelings and considerable distress, often tactfully contained in the presence of their sick child, in order not to stimulate the others' suffering. Older parents consciously suppressed thoughts related to an uncertain future and tried to keep up the façade of normalcy by keeping an optimistic view and displaying upbeat attitudes.
A balancing act of involvement was described between being involved without disturbing and keeping an appropriate distance. Older parents have taken gradual steps back from direct parental care with decreasing levels of parental involvement. Due to illness renegotiation of their position takes place and most parents resume their parental responsibilities by means of 'being there', in many forms and intensities along a continuum. The envisaged parenting is influenced by several factors i.e. their relationship history, their degree of care dependency and the marital status of the adult child. Parents were willing to provide support to their children and grandchildren to the extent permitted by their resources and the nature of their existing relationship with their adult child and partner.
Conclusions: Older parents' situations can be envisioned as facing a delicate balancing act on two areas (1) between shielding their child while being shielded by their child, and (2) between being involved while keeping an adequate distance. Faced with the adult child's illness and possible death, older parents are confronted with overwhelming feelings often underestimated by their close environment. Health care professionals can play a pivotal role in protecting the autonomy and privacy of adult children while practicing family-centered principles.
No conflict of interest.

1709 ORAL

Oncology nurses use of family assessment in the acute care setting

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Background: Family assessment in the oncology setting is a crucial step in determining the appropriate family support and guidance required. Oncology nurses are the coordinators of patient and family support services and are relied upon to identify patient and family concerns. A cancer diagnosis has a physical and emotional impact on the patient, however during this time the family caregivers providing support are often at risk of physical, emotional and practical problems themselves. This study investigated the oncology nurses use of a framework for family assessment, exploring the nurse's experience and perception of family assessment.
Methods: An interpretive study was conducted to investigate oncology nurses' family assessment practices across cancer care inpatient and day-treatment areas of three metropolitan hospitals in South-east Queensland. In total 20 focus groups consisting of 50 oncology nurses were conducted to provide demographic and qualitative data. Using a constant comparative technique, analysis of the nurses' responses was used to identify themes which related to the process of family assessment.
Results: Themes around family assessment related to models of patient care, nurse's philosophy, ward culture and physical environment. Most oncology nurses considered family assessment as their role however family assessment was often conducted informally with no structured framework or documentation. The family assessment process varied according to experience of the oncology nurse with nurses who were less experienced relying on referral to a social worker if they considered the family required support. The participants highlighted that the use of a structured approach would improve their family assessment techniques, suggesting a set of questions to ask the patient and family might help the less experienced oncology nurse.
Conclusion: The informal process of family assessment provides some way of identifying the family's needs, however this was often conducted in an ad hoc manner. A simple framework such as the Calgary Model of Family Assessment may assist nurses in the promotion of appropriate family support.
No conflict of interest.

1710 ORAL

Quality of life (QoL) assessment in patients with head and neck cancer (HNC): A pilot study comparing touch screen technology and paper questionnaires

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Background: Health care interventions must be judged not only by their impact on survival, but also on QoL. QoL in HNC patients is frequently impaired by disease and/or treatment which can have impact on general health but also on specific important functions i.e. swallowing and speech. Multiple standardized questionnaires exist for evaluation of general QoL (EQ5D [5L], FACT-G, EORTC QLQ-C30). FACT-H&N and EORTC QLQ-H&N35 are specific questionnaires for HNC patients while SWAL-QOL and Voice Handicap Index (VHI) are questionnaires for the specific evaluation of swallowing function and speech, respectively. Paper questionnaires are less attractive for the patient, difficult to collect, burdensome and costly in terms of data input.
The aim of this pilot trial was to evaluate whether the use of a touch screen technology was feasible in HNC patients visiting the MOCA head and neck outpatient clinic.
Material and Methods: The questionnaires were filled out by the patients either on paper or using a touch screen during the waiting time between registration at the outpatient desk and the visit. Selection of method was at random. For each patient, starting and finishing time were registered. Patients received a short introduction by a qualified nurse. Assistance by a relative was allowed.

Results: 10 evaluable HNC patients (7 male) filled out the paper questionnaires. Median age: 67 years (range: 57−82). 25 evaluable patients (19 male) filled in the touch screen version of all questionnaires. Median age: 67 years (range: 47−76). Median time required for filling in the paper and electronic version was 35 minutes (range: 20−57) and 28 minutes (range:13−53), respectively. Mean times were 38 and 28 minutes, respectively (unadjusted p: 0.016; p adjusted for age: 0.02).
Conclusion: The touch screen technology for the assessment of QoL measures using multiple validated questionnaires is feasible, even in an elderly population of HNC patients. It takes significantly less time to complete the electronic version as compared to the paper version. The calculated output of the questionnaires is immediately available in the electronic patient file and can be used by the physician during the consultation, allowing special attention to particular patient needs. Moreover, the results can be easily extracted for scientific purposes. Further comparisons and intra-patient validation of the 2 methods are planned. Screen shots will be presented at the meeting.
No conflict of interest.

1711 ORAL

Fatigue in informal caregivers of cancer patients during active treatment in the palliative phase

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Background: Fatigue is the most frequently occuring symptom in patients (pts) with advanced, incurable cancer, with a profound effect on daily life. However, hardly anything is known about fatigue of informal caregivers (CG) of these pts and the impact fatigue might have on their experienced burden related to care provision. We investigated the presence of severe fatigue in CG, and studied the relation between fatigue severity of pts and CG, and whether fatigue changed over time. Additionally we wanted to know whether fatigue severity negatively affected the burden experienced by CG, indicated by more strain.
Material and Methods: Pts with advanced, incurable cancer, still on active treatment at the department of Medical Oncology of a University Hospital or a regional hospital in the Netherlands and their CG were asked to participate. Both groups filled in the Checklist Individual Strength (CIS) to measure fatigue severity twice, at T=0 and 6 months later (T1). A score of $\geqslant$35 at the subscale CIS-fatigue was indicative for severe fatigue. To measure the experienced burden CG also filled in the Caregivers Strain Index (CSI) at both time points. Descriptive analyses and regression analysis were performed.
Results: At T0 137 pts and 111 CG participated, at T1 89 pts and 78 CG did so. At T0 90% of CG (n = 100) were the partners of the pts. Of the CG at T0 24% (n = 27) was severely fatigued, at T1: 21% (n = 16). Within subjects we found significant correlations on fatigue severity at T0 and T1 (.645 for CG and. 543 in pts). We did not find a correlation on fatigue severity between pts and CG (at T0:. 057, at T1:. 172). Concerning the impact of fatigue we found that fatigue severity of CG and pts, at both time points significantly correlated with the CSI (in CG; at T0:0 .461 & at T1: 0.505 and in pts at T0; 0.334 & at T1: 0.297). At both time points, 30% of CSI could be explained by fatigue.
Conclusions: A fifth to a quarter of CG of pts with advanced cancer were severely fatigued somewhere during the active palliative treatment phase of the pts. We did not find a relation between fatigue severity of CG and pts. Fatigue severity of pts was related to CG's burden, as was the case with fatigue severity of CG. Fatigue and CG's burden remained relatively stable over time. Remarkably, fatigue severity only explained 30% of the CG's burden, which suggests other factors involved in CG's burden. This observation warrants further research which may finally help to address the needs of the CG.
No conflict of interest.

1712 ORAL

The AYA box: A patient centered instrument in communication with adolescents and young adults with cancer and their care giving parents

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Background: There is a growing recognition that the perception of AYAs diagnosed with cancer is distinctive from that of children or adults. The main objective of this project is understanding how AYAs and their care giving parents experience cancer, diagnosis, hospitalisation, treatment and survivorship to develop a patient centered tool wich can be used by the multidisciplinary team.
Methods: A qualitative study was performed based on the principles of grounded theory. 24 semi-structured interviews were held with AYAs between 15 and 25 years of age. Additionally 21 care giving parents (19 mothers and 2 fathers) were interviewed. Sampling was based on situational diversity (e.g. gender, age, social context, education, time since diagnosis). The interviews were transcribed and coded (NVivo7) and constant comparison was used to analyse the data. Data collection and -analyses took place in a cyclic process.
Results: From the AYAs' perspective, cancer is something temporarily passing their life-path. Their coping strategies are focused on preserving identity and guarding normal life, not only during treatment, but also in follow-up and survivorship. Findings suggest that AYAs prefer care, tailored to their needs. The AYA box has been devoloped to meet these specific needs and to enhance the communication with the AYA. The box belongs to the AYA only and contains a booklet with revealing stories of AYAs' experiences, postcards, a unique AYA tag, useful stickers mention feelings or concern, cards with information or instructions, a brief symptom scale and smart aids in communication with their relatives and professional caregivers. The whole multidisciplinary team work with this instrument and can use it to talk about more difficult or emotional topics.
When confronted with the cancer of AYAs, the care giving parents face various fears and insecurities. In relation to each other findings demonstrate poor communication about emotions between the AYAs and the care giving parents. The box can provide a means to promote this communication.
Conclusions: This study revealed that cancer seems to have a different meaning for AYAs than for their care giving parents. The results are translated in a practical box, based on the experiences of the AYAs and can inspire caregivers to provide patient centered care in accordance to the specific preferences and wishes of the AYA.
No conflict of interest.

1713 ORAL

Family life when a parent is diagnosed with cancer: Impact of a psychosocial intervention for young children

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Background: In the United Kingdom, 1 in 10 cancer patients are aged 25−50 years and the incidence rate of cancer for this younger patient group has steadily increased over the past three decades. When a parent is diagnosed with cancer it can have a profound impact on the family, especially the children. As a result the family unit can experience major changes in living patterns, roles and relationships and parental cancer has the potential to cause familial dysfunction and distress. The aim of the study was to explore the experience of families when a parent has cancer and evaluate the impact of a psychosocial intervention (CLIMB®) to support young children whose parent has cancer.
Material and Methods: Using a descriptive qualitative design, data was generated from separate focus groups with children (n = 7) and parents (n = 6). One-to-one interviews were conducted with professionals delivering the intervention (n = 2). Interviews were transcribed verbatim to facilitate analysis. Thematic analysis, by two researchers was carried out using methods formulated by Miles and Huberman (1994).
Results: Parental cancer is a challenging life event for the family. Parents clearly articulated the devastation and whirlwind of emotions after finding out they had cancer. They often felt ill-equipped and expressed a lack of confidence and skills as they considered communicating with their children about cancer. Parents were often the gatekeeper to how, when and the context in which children learn about parental cancer.

Children reported that prior to learning about their Mum or Dad having cancer they sensed that something was wrong at home. They had a number of fantasies and misconceptions, including concerns that cancer was contagious and believing they were responsible for their parent's cancer.
The psychological intervention (CLIMB®) normalised the children's experience of parental cancer through peer support. It also improved their understanding of cancer as they learned factual information and it equipped the children with coping strategies to help them deal with negative emotions surrounding parental cancer. Professionals perceived the intervention led to improved family communication. For parents, it provided them with reassurance that some of their child's emotional and informational needs were being met by professionals and provided a vehicle for greater open communication between the children and parents regarding the cancer diagnosis.
Conclusion: Open communication is pivotal for children whose parents have cancer but parents need supported and resourced to promote family coping when diagnosed with cancer.
No conflict of interest.

1714 ORAL

Comparison of the relationship between depressive symptom levels and self-concept in healthy children and children with cancer

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Background: Children with cancer have to cope with the disease, frequent hospitalizations, intensive treatments and the numerous side effects of these treatments. These children may encounter physical, social and psychological problems. These issues may adversely affect children's self-perceptions. Oncological diseases can especially cause low self-perception, depressed mood, anger, despair, and feelings of inadequacy and insecurity in children.
Purpose: The aim of this study was to determine and compare the depressive symptom levels and self-concept in children with cancer and healthy children between 9 and 16 years of age.
Material and Methods: 66 children with cancer and 66 healthy children of the same age and gender were included in the sample. *The* 'Child Introduction Form', 'Children's Depression Inventory' (CDI) and 'Piers-Harris Children's Self-Concept Scale' (PHCSS) were used for data collection. The cut-off point of CDI is 19. The maximum score is 54. A high total score shows a high level of depressive symptoms. The possible scores of PHCSS range from 0 to 80. The scale contains six different dimensions of self-concept (happiness and satisfaction, anxiety, popularity and social appreciation − being the favorite, behavior compliance, physical appearance, intellectual and school status). A high score indicates the presence of a positive and a low score of a negative self-concept.The data were analyzed with the Kolmogorov-Smirnov test, Mann-Whitney U test and Pearson's correlation coefficient.
Results: The mean age of the children with cancer and healthy children was 13.14±2.9 with 53% males. Acute lymphoblastic leukemia (ALL) was present in 31.8% of the children with cancer. A significant difference was found between the self-concept of children with cancer and healthy children ($U=1731.5, p < 0.05$). No significant difference was found between the depressive symptom levels of children with cancer and healthy children ($U=2124$, $p > 0.05$). A moderate, negative and significant relationship was found between the depressive symptom levels and self-concept of children with cancer and healthy children and the depressive symptom levels decreased when the self-concept increased($p < 0.05$).
Conclusions: Our study determined depressive symptoms to increase in children when their self-concept decreased, similar to other studies. We believe that providing psychological assistance according to results of studies on depressive symptom levels and self-concept will have a positive effect on the treatment of children and adolescents with cancer.
No conflict of interest.

1715 ORAL

Patients with a high-grade glioma and their family caregivers: A qualitative research of their lived experience and needs related to professional care

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Background: With poor prognosis and disabling symptomatology, diagnosis of a high-grade glioma affects the patient and his family caregivers. Quality care to both parties requires a better understanding of their experience and needs.
Purpose: The aim of this qualitative research is to improve our insight into the experiences and needs related to professional care of patients with a high-grade glioma and of their family caregivers.
Method: The data of this qualitative study, using a Grounded Theory approach, were collected through semi-structured, individual interviews. Data analysis was performed by 3 researchers looking for predominant themes in both the patients' and the caregivers' stories.
Results: Seventeen patients and sixteen caregivers were interviewed. The patients' experience is marked by many losses, and caregivers find it difficult to see their beloved one lose independence and functional capabilities. As a response to these losses, family caregivers perceive a fast growing set of caring tasks, in which they engage almost without limits but to which they feel unprepared and sometimes insecure. Perceived lack of professional support and difficulties in considering or accepting help, add to their feeling to become solely and completely responsible. Patients themselves on the other hand feel as if they are sidelined, not only because of physical or cognitive loss of function, but also because of caregivers taking charge at the expense of the patient's freedom, simply out of worry. At the same time they manage to keep hope, of getting good results, of keeping some abilities.
Patients and caregivers both express the need for information and for willingness to listen. Caregivers underscore the accessibility, availability and expertise of professional caregivers. They also need to feel that professionals are aware of the seriousness of the diagnosis and that they take this into account in their approach of both patient and family caregiver.
Conclusion: Loss and responsibility mark the experiences of patients and family caregivers respectively. The results of this qualitative research enable professionals to provide care from a better understanding of patients' and caregivers' difficulties, strengths and needs.
No conflict of interest.

Proffered Papers Session (Sun, 29 Sep)
Nursing − Improvements in Cancer Nursing Care

1716 ORAL

Implementing the use of survivorship care plans: Understanding the barriers

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Background: The number of individuals who are living after a diagnosis of cancer is growing steadily. Unfortunately, cancer survivorship does not come without cost. It is increasingly evident that there are late and long-term effects that cancer survivors experience. These physical and psychosocial effects can compromise quality of life and increase the burden of suffering. The Institute of Medicine has recommended that patients who are finishing their treatment receive a survivorship care plan to assist in their coping with the after effect of treatment and moving on with their lives. To date, few cancer programs utilize survivorship care plans in Canada.
Objectives: The purpose of this work was to create and implement a sustainable survivorship care plan approach. The objective was to learn about the barriers to implementing survivorship care plans in our Canadian health care environment.
Methods: Four jurisdictions were selected through a competitive process to mount survivorship care plan projects. The jurisdictions were selected in part to reflect a broad range of settings for the delivery of care plans and included a community-based agency, a cancer centre, a cancer-centre/community-based consortium (urban/rural), and a national volunteer based organization (on-line). Each designed a unique approach for using a survivorship care plan based on the template draft provided in the call for proposals. Evaluations included patient and staff satisfaction as well as program utilization.
Results: The project illustrated that use of survivorship care plans in Canada was feasible. Survivors reported that the plans helped them in understanding the next steps in their cancer journey. Each jurisdiction reported the following elements were important factors for successful implementation of survivorship care plans: leadership, teamwork and collaboration, tailoring the care plan, education and training, communication and dissemination, and conceptualization of survivorship. Barriers identified included infrastructure support (information technology in particular), process for developing the actual care plan, access to services, and engaging in robust evaluation.

Conclusions: In all cases, the projects served to streamline the transition from treatment to survivorship, and to significantly increase the capacities of patients and health care providers to address this gap in care provision. It is possible that the community, cancer centre, and on-line modalities could all work as complementary systems to bridge the gap for cancer survivors, offering care plan services at a variety of times and places to suit the range of patients' needs along the survivorship trajectory.
No conflict of interest.

1717 ORAL

Capturing in real time the support needs and the self-management behaviours for prostate cancer survivors: Application of an electronic behavioural diary

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Background: Prostate cancer and its treatments can cause profound physical (urinary, bowel and sexual dysfunction) and psychological sequelae. Men are keen to engage as active partners in the management of their condition, but unmet support needs are prevalent which can make self-management difficult. The aim of this Ph.D. study was to monitor mens' symptoms, support needs, coping efforts and self-management experiences over time as an important step towards the development of a supportive self-management intervention at address areas of unmet need.
Materials and Methods: This study had two phases: phase one was a prospective longitudinal survey (N = 74), and phase two captured real time patient reported outcome measures in the form of an electronic behavioural diary. A sub-sample from the prospective, longitudinal survey (n = 12) completed the electronic behavioural diary in the weeks following treatment. A Research Steering Group (men with prostate cancer and clinicians) informed the development of the electronic behavioural diary. Data collection was managed using the Dell X51 and Pocket Interview Software. Self-reports were collected for 31 days prompted by an audio alarm 3 times per day (a total of 93 data entries) for each of the 12 case studies. Electronic diary data were analysed in SPSS v.17.0 using time series analysis.
Results: The majority of diary completion rates were >90%. Results demonstrated that men used a variety of self-management behaviours to improve their urinary, bowel and sexual dysfunction, but often, with little relief. A common theme across the case studies was that men very frequently experienced symptoms for which they did not perform any self-management. Men reported dissatisfaction with their support over time with particular reference to: informational, practical, emotional and financial support. The most frequent source of self-management suggestions came from mens' partners, and prostate cancer specialist nurses were infrequently reported to provide self-management advice.
Conclusion: This innovative study has demonstrated the acceptability of e-health technology in prostate cancer survivors and may provide a platform to deliver a supported self-management intervention in the future. Real time data collection by means of an electronic behavioural diary, is patient-centred, and enabled men to share their experiences without having to verbalise their concerns aloud.
No conflict of interest.

1718 ORAL

Czech nurses' knowledge, attitudes and behaviors towards tobacco dependence and treatment

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Background: Tobacco use is the top preventable cause of cancer in the Czech Republic and in Europe. Tobacco dependence treatment is a cost-effective strategy to prevent morbidity and mortality. Nurses, the largest group of health professionals, can play a pivotal role in implementing this intervention in clinical practice. The purpose of this report is to describe information about the frequency and correlates of Czech nurses' delivery of intervention in tobacco dependence treatment prior to an educational intervention.
Material and Methods: A train-the trainer program to provide evidence-based tobacco dependence treatment and the nurses' role was developed by tobacco control experts in the US and the Czech Republic, in collaboration with the International Society of Nurses in Cancer Care (ISNCC). The program was delivered by Czech nurses in Czech at the 2012 ISNCC congress to 22 nurses. Subsequently, 10 workshops delivered by the trainees were held throughout the country. Prior to each workshop, participants were asked to complete a survey that included questions about demographics, clinical practice, attitudes about tobacco control, and frequency of delivery of tobacco dependence treatment.
Results: 157 nurses completed the survey. While 63% of nurses 'always/usually' asked patients' about their smoking status, 46% provided advice to quit, 26% assisted in developing a cessation plan, and only 11% always arranged for follow up and referred smokers to the telephone quitline. Few, 22%, reported that nurses could play an important role in helping patients quit; 63% rated their ability to help patients quit as 'fair/poor'. Approximately 30% of nurses were current smokers. Smokers were less likely to 'always/usually' assess ($p = 0.02$), arrange ($p = 0.02$), or recommend a smoke-free environment ($p = 0.002$). The average age of nurses who 'always/usually' arranged or referred was significantly higher as compared to those nurses who did not ($p < 0.01$).
Conclusions: These data indicate that few nurses in the Czech Republic consistently intervene with smokers. The majority underestimated their power to provide effective smoking cessation interventions and assessed that they needed additional training. Although they have potential to significantly contribute to decrease the burden of tobacco-related diseases, they underestimate the importance of their role. Capacity building programs in tobacco control for nurses are critical.
No conflict of interest.

1719 ORAL

Evaluation of the use of information sources among breast cancer patients during radiotherapy period

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Background: The importance of the knowledge of radiotherapy (RT) among breast cancer patients is observed. There is an assumption that patients' sense of empowerment is supported by knowledge. Though professionals cannot empower the patient, they can support the patients to get knowledge to be empowered. There is much evidence describing patients' use of information sources and their preferences for information. Yet little is known about whether breast cancer patients with different preferences for information vary in use of information sources during their radiotherapy (RT) period. Therefore, the aim of this study was to evaluate whether high preferences for information leads to higher amount of information sources.
Material and Methods: Breast cancer patients (n = 128) were followed during RT period. Preferences for information (KHOS-I) pre RT period and information sources during RT period were evaluated. For the associations between use of information sources and preferences for information the statistical analyses were used.
Results: In total, mostly used information source was written patient education material (83 % +/−0) and secondly, patients contacted the personnel of RT department (76 % +/−1). Thirdly, was ranked other professionals on hospital (72 % +/−0.5) and near next were relatives and significant others (70 % +/−2). Internet was a source of information for two of third (65 % +/−0) of the patients, for half (50 % +/−1) public sources like library, television and radio and for third (31 % +/− 2) the local patient associations. Patients with higher preferences for information had significantly higher information seeking on public sources like library, television and radio ($p = 0.0061$) and the personnel of RT department ($p = 0.0359$).
Conclusions: Understanding differences in use of information sources among breast cancer patients during RT period may reflect more effective patient education development for future cancer care.
No conflict of interest.

1720 ORAL

Exploring patient experiences of neo-adjuvant chemotherapy for breast cancer

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Background: Neo-adjuvant chemotherapy is recommended for locally advanced and inflammatory breast cancers to reduce tumour size (enabling surgery) and assess response to therapy. The advantages for women with *operable* breast cancer are not clearly defined although trials indicate no survival differences between women treated with chemotherapy pre

or post-surgery. Communicating evidence based information to patients is complex and studies examining the patient experience of neo-adjuvant chemotherapy are lacking. In this exploratory study we aimed to examine patient experiences to identify if this patient group had particular information needs and concerns and were receiving the support they needed.
Methods: A qualitative approach was taken using in-depth individual interviews with women (n = 21) who had completed neo-adjuvant chemotherapy for breast cancer, referred from four different hospitals across the North West of England. Interview data were analysed using thematic analysis.
Results: The sample included a relatively young group of women (mean age 49 years), many of whom had young children and/or were caring for elderly parents. The main themes that emerged from the data included: coping with the rapid transition from 'well' to 'ill', challenges of processing complex information, perceived lack of emotional support, needing empathy, impact on family, regaining control, and creating a new 'normal'. This group of women had specific information and support needs related to key time points in the treatment trajectory. In particular, support was needed towards the end of chemotherapy, when side effects were at their most toxic, and when decisions about forthcoming surgery were being made. Information provision and support from health care professionals was reported as variable. While some patients reported adequate support, most reported feeling left alone to cope with debilitating side effects (that often warranted hospital admission) and complex emotional problems. A number of women had been referred to psychological services but this was usually when a crisis point had been reached.
Conclusion: The women in this study were able to identify key timepoints when information and support would have been beneficial. This information is vital in developing services and interventions that will meet the complex needs of these patients and potentially prevent hospital admissions and late referral to psychological services.
No conflict of interest.

1721 ORAL

Unmet supportive care needs and resilience in cancer patients under early treatment: A descriptive study

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Background: Patient engagement in healthcare via self-management is recognized as crucial to improve outcomes for cancer patients. Current supportive care still results in high degree of unmet needs and urges for new approaches. The concept of resilience is gaining increasing importance as a key component for self-management support in cancer care but to date has rarely been addressed in studies in adult cancer patients. We explored the potential relationship between resilience and unmet needs in cancer patients under early ambulatory treatment.
Materials and Methods: We conducted a descriptive study. Adult patients with solid tumors, having been diagnosed 4−14 weeks ago with new or recurrent disease and under treatment in ambulatory services at a Swiss cantonal hospital were recruited for the study. They were provided with validated French and German paper and pencil version of the Connor-Davidson-Resilience Scale with 25 items (CD-RISC) and the Supportive Care Needs Survey 34 item (SCNS SF 34) version. Cantonal ethics committee approved the study. Descriptive and correlational statistics were applied.
Results: 30 female and 38 male cancer patients with a mean age of 63.12 (sd 11.3) and of which 20 (29%) had a recurrent disease were included in the study. The highest level of unmet needs, as measured by the SCNS SF 34 (range 0–100), were observed in the psychological (md = 30; IQR = 10), health system and information (md = 27.27; IQR = 14) and physical domains (md = 25; IQR = 17). Resilience scores, measured CD-RISC 25 were significantly lower compared to general population (m = 74.35 SD = 12.612 vs. m = 80.4 SD = 12.80; p = 0.0002). A multiple regression analysis showed resilience decreased with age (−0.295; CI −0.546, 0.43, p = 0.022) and was substantially higher in patients with a recurrent disease (+7.985, CI 1.72, = 14.07, p = 0.013). Low resilience scores were significantly and strongly associated with higher levels of unmet psychological needs (Rho = −0.68, p < 0.001), supportive care needs (Rho = −0.49, p < 0.001) and information needs (Rho = −0.42, p = 0.001), as well as marginally with higher physical needs (Rho = −0.31, p = 0.010).
Conclusion: Our results suggest that patients with higher resilience express lower unmet needs. A longitudinal design would allow the clarification of causal patterns between resilience and supportive care needs. This could be a starting point for developing interventions to enhance resilience and thereby improve patient engagement via self-management.
No conflict of interest.

1722 ORAL

Patients with cancer fall too: What the evidence tells us about assessing and preventing falls in patients with cancer

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Background: Falls with injury are common in patients with advanced cancer. It is estimated that approximately 50% of patients with advanced cancer will experience a fall with a high risk of physical injury every year. Moreover, patients with cancer are at a higher risk of falls than patients treated in other acute or settings. Often falls include injuries such as soft tissue, fractures (hip, facial), cranial bleeds, and other detrimental injuries. Falls can result in decreased quality of life, tremendous cost to the health care system, and unfortunately on some occasions, death of the patient. Researchers have estimated that a patient experiencing a fall can cost approximately $13,000 in operating costs and extend a patients hospital stay by over 6 days. Fortunately, there are research studies which suggest effective ways to assess fall risk and provide evidence based interventions which may prevent patients from falling more often.
Material and Methods: This presentation will accomplish the purpose by presenting the current literature in the areas of assessment and intervention in patient falls. Participants will be able to 1) Summarize important variables to assessing patients at risk for falls, 2) Identify falls assessment tools with established validity and reliability and 3) Interpret evidence based patient centered interventions which may prevent patients from falling. This presentation will have two focuses: 1) On the demographic and other factors such as ambulation issues, medications, and prior falls history that should be included in assessment of falls along with an overview of the major falls assessment tools and their respective strengths and limitations 2) On the nurse sensitive patient outcome interventions based in research that may be effective in preventing or lessening patient falls.
Results: The clinical practice outcomes from this evidence based-practice presentation are tremendously important for oncology nurses because of the risk that our patients with cancer face on a daily basis.
Conclusions: Given that patient falls are so significant to those with cancer this presentation will be one of the few which focuses on both the assessment tools and evidenced based interventions which might keep patients with cancer more safe from falls with injury. Participants will be able to translate information from this presentation into their individual practices, creating a safer environment for their patients with cancer.
No conflict of interest.

1723 ORAL

Experiences of the older person with cancer: A qualitative study of two ward settings

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Background: This paper reports on the final stage of a qualitative study that seeks to compare patient and health care professionals' perspectives and experiences of cancer care for the older person. This study seeks to illuminate the experiences of both patients and health care professionals in two hospital wards (a specialist cancer ward and a general medical ward in a general hospital) selected to allow comparisons to be made in terms of the potentially different emphasis given, depending on whether the focus is on cancer treatment or care of the older person.
Material and Methods: The research design, employing focus groups, dissemination focus groups and semi-structured interviews, centres around comparison of a medical and a specialist ward in one hospital − exploring the challenges involved, depending on whether the focus is on the older person or the disease (cancer patient). It also highlights the tensions that may arise − both for patients and professional carers, as they negotiate the potentially contradictory demands of the 'social' and the 'clinical', the 'system' and the patients' life worlds.
Results: Findings were organized around the following themes: 'the ward as a half way house', 'etiquette', 'emotion work' and 'hope'. Dissemination focus group sessions served as dual purpose: to inform participants and to generate further data to establish whether these findings have relevance for them.
Importantly this allowed for the original sample to be augmented (by including new categories of staff and individuals with a remit to work across both wards, who were not involved in the first set of focus groups and interviews).

Integrating analysis of original study transcripts and data generated in dissemination sessions also allows for further interrogation of theoretical frameworks that seek to elaborate the intersection of the older person with cancer.
Conclusion: This study shows the complex and potentially conflicting perspectives of this heterogeneous group of patients and their professional carers, as they respond to the challenges raised by the conjunction of cancer and old age. The implications for health care delivery and professional training for gero-oncology will be considered.
No conflict of interest.

Proffered Papers Session (Mon, 30 Sep)
Nursing − Supportive and Palliative Care/ Survivorship and Rehabilitation

1724 ORAL

Return to work following cancer: perspectives of survivors, employers, and insurance agencies

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Background: The number of individuals who are living after a diagnosis of cancer is growing steadily. Unfortunately, cancer survivorship does not come without cost. It is increasingly evident that there are late and long-term effects that cancer survivors experience. These physical and psychosocial effects can compromise quality of life and increase the burden of suffering. In particular, survivors can experience challenges in returning to work after their treatment.
Objective: The purpose of this work is to explore the perspectives of cancer survivors (employees), employers, and insuring agencies about the challenges of returning to work after cancer treatment.
Methods: An environmental scan was undertaken to identify existing programs and resources to assist survivors in their return to work. A literature review and on-line survey were undertaken to document the perspectives of cancer survivors and their family caregivers about the challenges in returning to work after cancer treatment. Focus groups were held with employers, human resource representatives, and insuring agencies to gather their perspectives about employees returning to work after cancer.
Results: 8,385 websites were scanned for relevant materials and 90 were identified with resources to support patients as they return to work following cancer or other chronic illness episodes. Most programs were developed in the last decade. There are a broad range of program delivery modalities making it difficult to identify best practices. Patients (N = 410) described reduction in income, a range of positive and negative experiences in returning to work, and work-related issues dealing with side-effects (fatigue and loss of energy, cognitive changes). Caregivers (N = 60) described their own work-related challenges including reduction in income, loss of concentration and productivity, stress and lack of support from colleagues. Employers, human resource experts, and insuring agency representatives acknowledged the issues related to return to work. They reported that there are very few employees at any one point in time who are returning to work after cancer and this makes it challenging for managers to know how best to support these individuals.
Conclusion: With the increasing number of cancer survivors, return to work is a growing concern. Individuals clearly experience challenges in making this transition. There is a need for resources to be developed to help survivors, health care professionals, and employing agencies become more aware of the challenges survivors experience and be able to deal more effectively with the situation.
No conflict of interest.

1725 ORAL

Joint Aches Cohort Study (JACS): The impact of joint pain in women on adjuvant therapy for primary breast cancer

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Background: Joint pains and stiffness have been clearly demonstrated to be a problem for women following treatment for primary breast cancer, and appear to be associated with both hormone therapies, particularly aromatase inhibitors, and chemotherapy (particularly taxanes)(Fenlon et al 2013). However, there is less work available on the impact that this has on women's lives. This study set out to provide detailed information on the extent of the problem in the first year following cancer diagnosis.
Methods: A cohort of 578 women was recruited from hospitals across South England and Wales. Women were asked to complete questionnaires at baseline, three, six, nine, and twelve months. Alongside several validated survey measures, women were invited to write free text on whether they had new joint pain since their breast cancer treatment and the impact of this pain on their lives. The free text comments of a subset of 233 of these from one hospital were analysed using content analysis. The coding process allowed the initial codes to emerge from the data, and these were verified by a second researcher. Emerging themes showed clear parallels to the Brief Pain Inventory (BPI), and hence, subsequent coding used the BPI as a framework, as well as new themes emerging from the data.
Results: Early results suggest that all aspects of quality of life, including mobility, mood, ability to work, enjoyment of life and sleep, are affected by joint pain associated with adjuvant treatment for breast cancer. Additionally, it is clear that further factors like patients' perception of their pain and attitude to it, their ability to manage their own pain, and the ability to manage change and a changing identity, also influences how the patient experiences their quality of life as a survivor of cancer. Full data will be presented at the conference presentation.
Conclusions: Our initial results suggest that joint pain associated with adjuvant treatment can have a profound impact on the lives of women following breast cancer. This may lead to decreased drug compliance or cessation of treatment, despite the known life-lengthening benefits of adjuvant treatment.
No conflict of interest.

1726 ORAL

Support group for lung cancer patients

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Background: Early palliative care among patients with metastatic lung cancer can lead to improvements in both quality of life and mood. Support group for oncology patients provide a place to share common concerns and emotional support, teach coping skills and provide important information. In Israel, there is approximately 1600 newly diagnosed lung cancer patients every year, 370 of them were treated at Sheba Medical Center during 2012. Through 2011–2012 3 time-limited support groups were established for lung cancer patients.
Material and Methods: 34 patients participated in 3 different support groups. One group included stage I+II lung cancer patients and the other two groups included stage III+ IV. Each group met for 2.5 hours session every 2 weeks for 10 sessions. Former to each meeting participants could practice Yoga exercise for 45 minutes with yoga trainer. Topics addressed in the groups were those of concern to the participants and included informational topics such as social rights, medical information of treatment, side effects and symptom management, psychology aspects of disease, intimacy and emotional caregivers support. All groups were led by oncology nurse coordinator from the lung cancer unit, onco- psychologist and a physician who recovered from lung cancer. After each meeting participants were asked to fill in satisfaction questioner.
Results: Participants of all groups claimed that being part of the group made it easier for them to deal with their emotional, medical and social problems concerning their illness. Patients with stage I+II lung cancer showed higher attendance and claimed to be more satisfied from the meetings compering stage III+IV patients. Participants also pointed that yoga exercise helped them to reduce stress. Topics for future improvement pointed by participant were that session being held at the hospital setting.
Conclusions: Support groups for cancer patients are necessary for dealing with their life threatening disease. It is important for nurses to lead such groups and be involved in educating patients and support them at this critical time. Support group for cancer patients provides a place to share common concerns and learn coping skills at a non-judgmental environment and should be an integrative part of the oncology nurse responsibility.
No conflict of interest.

1727 ORAL

Guilt and shame in end of life care − the next of kin's perspective

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Background: Being next of kin to someone in the final phase of life can be complicated. There can be a will to support the dying person and to make the time for him/her as comfortable as possible. To choose how to be involved can make the situation easier but there is also a responsibility to make a good choice. Choices can create anxiety and feelings of guilt and shame can occur if perceived obligations are not fulfilled. The aim of

the studies have been to explore and describe next of kin's feelings of guilt and shame in end of life care.
Material and Methods: Hermeneutic, and secondary analysis of qualitative interviews. Semantic concept analysis of the concepts guilt and shame.
Result: The result shows categories where guilt is felt: such as not having done/talked enough, being absent at important events, making errors in judgement. Categories where shame is felt: such as feelings of inferiority, being ashamed on behalf of the dying person, family conflicts becoming apparent.
Conclusion: It is important that health professionals are perceptive to next of kin's experiences of guilt and shame in end of life care. To have knowledge about these experiences and to be able to perceive these experiences can be seen as tools that help health professionals to be better able to encounter the next of kin. Identifying next of kin's experiences of guilt and/or shame might also contribute to facilitating a bereavement process, which in turn could be beneficial to public welfare and reduce sick-leave. The findings also have a potential to help next of kin see that experiences of guilt and/or shame are normal and understandable reactions when spending time with and taking care of a loved one in end of life care. It is of uttermost importance to improve end of life care as a whole.
No conflict of interest.

1728 ORAL

Why do they still hope? A qualitative study to explore how caregivers interpret hopefulness in palliative patients

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Background: Studies on experiences of advanced cancer patients shows that patients do not lose hope, even not hope for a cure and that this hope has positive effects on their mood and quality of life. In the American oncology literature hope is seen as a positive power. Caregivers are taught to encourage the hope. The Dutch oncology literature, however, describes hope rather as a problem about which doctors should do something.
The aim of this study was to explore the opinions of professionals about how to deal with hope in palliative patients.
Methods: Three focus group discussions (a multidisciplinary group, a nursing group and a group with community nurses) of six to ten caregivers were held. Data collection and data analysis took place in a cyclical process. All focus group discussions were recorded and transcribed verbatim. Data analysis used constant comparison between and within interview transcript of the coded material. Researcher triangulation was enhanced validity and reliability.
Results: *Telling the truth* is the central theme. It is seen as countering 'false hope' by information. False hope is hope that is stronger than the medical facts allow. False hope is seen as an impediment to proper dying. False hope is considered an information problem (the patient has not understood the doctor's message), informing the patient (again) as the obvious intervention. Hope is sometimes confused with denial. In their opinion, hope should evolve from hope for cure or longer life to hope for a good death. Situations that do not match this deal are experienced as difficult. This is for instance the case when the patient and his/her relative(s) feel different about whether or not to continue the treatment.
Conclusions: To oncology professionals, hope that does not match the medical facts is seen as a problem in need of remediation. The participants feel they need to make the patient (and his/her family members) see that death is unavoidable and they attribute hope to a lack of understanding of one's situation. This interpretation of the place of hope in terminal palliative care is at odds with the reports of patients about hope and with the findings of North American studies about interventions fostering hope.
No conflict of interest.

1729 ORAL

The impact of a rehabilitation programme for cancer patients − a story of patients looking back and ahead

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Background: Cancer related fatigue, fear of cancer recurrence, long term side effects, changed inter-personal relationships are often major themes in the follow up period after the treatment of cancer. Rehabilitation programmes can help cancer survivors to cope with these problems. It is unclear how patients experience the period after a rehabilitation programme and to which extent they incorporate the lifestyle instructions in their daily lives.
Method: A qualitative study was performed to explore the experiences of breast cancer survivors after following a three month rehabilitation programme and to explore reasons for (non-) adherence to relevant lifestyle instructions for breast cancer survivors. Fifteen breast cancer survivors, treated in a university hospital, were interviewed. A phenomenological approach was used. The interviews were transcribed and coded (NVivo 7) and constant comparison was used to analyse the data.
Results: After ending the programme, patients are confronted with mixed feelings. Patients still experience a lot of symptoms affecting their quality of life (fatigue, cognitive dysfunction, side effects of the endocrine therapy, fear, sleep disturbance). Patients also experience a second 'black period' in which they feel alone and in which the supportive group has often partially disappeared. However, the rehabilitation programme still means a lot for the patient. The programme helps them to get grip on their life, to live in a better (healthier) way to cope with their fears and to handle their daily problems. They are so focussed to survive the cancer. The provided lifestyle instructions enhance being in control of the symptoms that patients experience. For patients it is difficult to adhere to the lifestyle instructions when they have started working again and when social support is scarce.
Conclusion: After a rehabilitation programme, the breast cancer patients experience the rehabilitation programme still as meaningful. They have learned many skills coping with their problems after the cancer treatment. However, they are still searching for answers. Follow up sessions are recommended and a clear survivorship care plan can help to prevent these experienced loneliness.
No conflict of interest.

1730 ORAL

Supportive self-care strategies during chemotherapy treatment: A longitudinal qualitative exploration of the experiences of patients with breast or colorectal cancer

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Background: The Advanced Symptom Management System (ASyMS) is a mobile phone based system to remotely monitor and manage the toxicities of cancer treatment in the home care setting. ASyMS is being evaluated in a three-phase, multi-site complex intervention study, with a before and after study design. The study is exploring the impact of ASyMS on care delivered to people with breast/colorectal cancer receiving adjuvant chemotherapy. The shift of chemotherapy administration into the ambulatory setting requires patients to engage in self-care activities to prevent or reduce the severity of numerous and possible complex side effects. Phase I of the study is now complete. This paper will present the experiences of patients interviewed longitudinally throughout Phase I in relation to the supportive self-care behaviours and strategies they engaged in during their chemotherapy treatment.
Material and Methods: A total of 141 patients were recruited to Phase I. Of these 141 patients, 23 individuals from across all eight study sites participated in up to seven longitudinal semi-structured interviews each over the course of their entire chemotherapy treatment. The symptom experiences of patients, the role of supportive self-care behaviours and self-care strategies to manage these symptoms, and patients' experiences and perceptions of their care pathways, were explored longitudinally in all patient interviews.
Results: Patients discussed the importance of self-care in the context of their chemotherapy-related symptom experiences. Patients' indicated that adopted self-care behaviours and strategies tended to be triadic in nature: information was provided by health care professional staff, independently sourced from alternative sources, or informed by previous experiential knowledge. For many patients, there were notable changes in the extent to which adopted self-care strategies were embedded in their day-to-day and cycle-by-cycle symptom experiences over the course of their chemotherapy treatment. Often patients elected to self-manage their symptoms at home, rather than report them to health care professional staff.
Conclusions: The findings indicate that patients commonly adopt supportive self-care strategies to manage their chemotherapy-related symptoms whilst at home. As patients' chemotherapy treatment progressed, experiential self-care knowledge was equally important in the management of these symptoms as advice from health care professionals.
No conflict of interest.

1731 ORAL

Effects of an exercise intervention in early palliative phase for advanced lung cancer patients

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Background: Lung cancer is the leading cause of cancer-related death worldwide. The majority of lung cancer patients present with advanced,

incurable disease resulting in a median survival of only 9−12 months. In this context, the aim of anti-cancer treatment is to improve or maintain quality of life (QOL), anxiety and depression in addition to prolonging survival. The benefits of physical exercise for cancer patients are described in a series of studies, most of which included patients with breast cancer and haematological neoplasias. Few studies have examined exercise interventions on advanced lung cancer patients although other studies (Jones et al 2011 and Kasymjanova et al 2009) have found a correlation between an increased aerobic capacity (VO_{2peak}), functional capacity and increased survival. Based on these results this study seeks to examine the effect the effect of a 6-week exercise intervention for advanced lung cancer patients.
Material and Methods: Patients with inoperable NSCLC (IIIb-IV) and SCLC (ED) were screened for eligibility. Aerobic capacity (VO_{2peak}), muscle strength (1RM), functional capacity (6MWD), lung capacity (FEV1), HRQOL, cancer related symptoms (FACT-L) and anxiety and depression (HADS) were measured at baseline and 6 weeks.
Results: One-hundred-two patients were included and 72 patients undergoing concurrent systemic treatment were eligible for analysis. There was a significant increase in aerobic capacity − VO_{2peak} ($p = 0.014$) and functional capacity- 6 MWD ($p = 0.006$). There was significant improvement in strength ($P<0.001$). There was a significant change in the parameter for 'emotional wellbeing' ($p = 0.000$) with a moderate effect size of 0.30 and 'social well-being' ($p = 0.000$) with a small effect size of 0.23. However, there was no significant improvement or decline in general QOL. Theere was a significant reduction in anxiety (HADS-A) ($p = 0.008$) a significant change in Psychological Morbidity (HADS-T) ($p = 0.023$). However, there was no significant change in Depression (HADS-D) ($p = 0.124$).
Conclusion: The results from this study shows that it is beneficial for advanced lung cancer patients to participate in a 6 weeks exercise intervention. The significant reduction in anxiety has not been found in other studies with advanced lung cancer patients, further research will show the clinical relevance of these findings.
No conflict of interest.

Proffered Papers Session (Tue, 1 Oct)
Nursing − Symptom Management

1732 ORAL

Cognitive changes following cancer treatment

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Background: Reports suggest that patients with cancer can experience cognitive changes following chemotherapy treatment − the socalled 'chemo brain'. Changes such as memory loss, concentration problems, difficulty in organizing information and ability to work have been reported. The changes are often subtle, but can have a major impact on the quality of life and cause a lot of distress for patients and their relatives.
Healthcare professionals disagree on the causes of the cognitive changes and whether they are the result of chemotherapy or other factors. Patients often complain of the lack of acknowledgement by healthcare professionals concerning their experienced cognitive changes, and lack of information and educational tools.
Purpose: To investigate the knowledge of cognitive changes in connection with cancer and cancer treatment among healthcare professionals at a department of oncology. In adition to investigate the daily practice related to assessment, information and interventions related to cognitive changes.
Method: A total of 308 nurses and doctors from the same oncology department received an electronic questionnaire about patients experiencing cognitive changes in connection with cancer and cancer treatment. The questionnaire included a total of 18 items related to knowledge and awareness of cognitive changes, practice regarding assessment and education of patients and families, and demographic information about participants. Data was categorized into different themes and divided into different profession groups, wards, education and length of employment.
Results and relevance to clinical practice: Cognitive changes during and after chemotherapy were well-known symptoms among the majority of nurses and doctors. Only a minority assessed, informed and intervened to prevent or act, when patients and relatives reported symptoms.
In spite of the healthcare professionals' assessment of the extent and the impact of the problem, this knowledge had no influence on clinical practice. There was an obvious difference between knowledge, awareness and actions in daily clinical practice.
No conflict of interest.

1739 ORAL

The effect of a pain consult combined with a patient pain education program on patient adherence to analgesics

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Background: Optimal pain management is hindered by professional-related barriers, e.g. knowledge deficits resulting in inadequate prescriptions of analgesics, as well as patient-related barriers, e.g. reluctance to report pain or use analgesics. Pain Consult (PC) and Pain Education Programs (PEP) have been studied to overcome these barriers in cancer pain management. PEP had been suggested to improve medication adherence, but only 3/18 previous PEP studies found a significant effect. In the primary analysis of a randomised controlled trial (RCT), we found the combination of PC&PEP to be more effective in decreasing pain than Standard Care (SC). In this secondary analysis of the RCT, we evaluated the effect of PC&PEP to improve oncology outpatients' adherence to their analgesic regimen.
Methods: PEP consisted of patient-tailored pain education and weekly monitoring of pain and side effects. Adherence was measured using a Medication Event Monitoring System (MEMS). The MEMS consists of a medicine container with an electronic circuitry that registers when the lid is opened. Adherence was measured in the time intervals: week 1&2; week 3&4; and week 7&8 after randomization. Between-group differences per time interval were analysed using non-parametric tests. 72 Patients were planned (α=0.029, β=0.80, one-sided t-test). The study protocol was approved by the Institutional Review Board of the Erasmus MC (NTR613). All patients gave written informed consent.
Results: In 54 of the 72 included patients data about adherence were available (SC n = 26; PC&PEP n = 28). Of these 54 patients, 80% had metastatic cancer. At baseline, patients' worst pain was 8.1 (sd=1.2) and average pain intensity was 6.0 (sd=1.5). All but one patients had a prescription for WHO step 1 analgesics and over 60% had a prescription for strong opioids. At week 7&8, adherence increased in PC&PEP group compared to baseline (from 91% to 96%) and decreased in SC group (from 85% to 78%)($P<0.05$). At week 7&8, more patients in the intervention group took their analgesics with the right intervals (78%) compared to SC (64%, $P<0.05$). During the study, patients were more adherent to opioids than to non-opioids.
Conclusions: PC&PEP can increase both taking adherence and timing adherence. Strategies directed at further increasing patient adherence may improve cancer pain treatment.
Study is closed.
This work was supported by the Erasmus MC Health Care Research and the Erasmus MC Revolving Fund.
No conflict of interest.

1734 ORAL

The development and testing of a PROM to measure symptoms associated with chemotherapy in people with breast and colorectal cancer: The Chemotherapy Toxicity Self-Assessment Questionnaire (CTAQ)

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Background: In 2008 3.2 million people were newly diagnosed with cancer in Europe for which chemotherapy is a core treatment. Definite advances in survival have been observed as a result of the use of cytotoxic agents, but are associated with significant toxicities that impact negatively on patient outcomes and can lead to death. Toxicities not only occur during the acute phase of treatment but can also persist into survivorship. Poor assessment and management of treatment-related symptoms can have a sustained negative effect on patient outcomes post-treatment and increase supportive care needs, reduce quality of life (QoL) and impede rehabilitation. Patient-reported outcome measures (PROMs) provide an effective way to optimise standard practice and improve the assessment and management of chemotherapy related symptoms. The aim of this study was to develop and measure the reliability of a PROM (Chemotherapy Toxicity self-Assessment Questionnaire − CTAQ) to assess chemotherapy related symptoms in people with breast and colorectal cancer.
Materials and Methods: The CTAQ was developed via two systematic reviews of the literature on the symptoms associated with chemotherapy in people with breast and colorectal cancer and via expert consensus from patient and clinician groups based in 8 hospitals in the UK. People with breast (n = 26) and colorectal cancer (n = 26) completed the CTAQ on paper on two occasions one hour apart. Reliability of the CTAQ was assessed by comparisons of the participants' responses using Cohen's kappa statistic in SPSS v.18.

Results: A total of 52 people with breast (n = 26) and colorectal cancer (n = 26) completed the CTAQ. Agreement was high with many questions having perfect agreement. The lowest Kappas tended to be for questions related to tingling and pain and redness with hands or feet.
Conclusion: The CTAQ is a reliable method for measuring the symptoms associated with chemotherapy in people with breast and colorectal cancer.
No conflict of interest.

1735 ORAL

Use of the rocket IPC in palliative care

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Background: Although the Rocket IPC (indwelling pleural catheter) is more often used to release symptomatic malignant pleural effusion (MPE), little is known about the clinical outcome, patient satisfaction and complications. Insufficient information can lead to ignorance of this alternative palliative intervention to evacuate malignant pleural effusion. Purpose of this presentation is to increase knowledge and awareness about the Rocket IPC in palliative care.
Method: Between October 2009 and March 2013 all patients in the Antoni van Leeuwenhoek hospital in Amsterdam treated with a Rocket IPC, were included in this prospective observational study. Registered are primary malignancy, date of IPC insertion, use of supplies, complications and patient satisfaction.
Results: Sixty-eight patients were included: 31% non-small cell lung cancer, 30% breast cancer, 14% urogenital cancers, 9% mesothelioma, 9% gastrointestinal cancers and 7% other cancers. The mean overall survival after IPC insertion was 4 months (1−28). Mean monthly use of supplies was 11 bottles (2−65). Patient satisfaction: 76% didn't need home care. Complications: 7% obstruction/dysfunction drain; 3% empyema; 3% infection; 3% pain during effusion; 1.5% pneumothorax and 1.5% metastasis.
Conclusion: In this population the mean use of supplies was low, hardly any serious complications were seen and patient satisfaction was high. The Rocket IPC seems a good palliative intervention for MPE. Furthermore study is needed in patient reported outcome, cost effectiveness and clinical factors to predict treatment outcome.
No conflict of interest.

1736 ORAL

Symptom management pathways for patients undergoing adjuvant chemotherapy for breast and colorectal cancer: The application of process maps

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Background: Management of symptoms is an important aspect of care delivery for patients undergoing chemotherapy treatment. Symptoms associated with chemotherapy can be wide ranging, complex, and, if incorrectly managed, life-threatening. The Advanced Symptom Management System (ASyMS) − III study is investigating the impact of ASyMS on the care delivered to people with breast and colorectal cancer receiving adjuvant chemotherapy. Part of this research involves understanding the different models of care employed by different hospitals across the UK in order to evaluate the impact ASyMS has on current care delivery. In this presentation we describe the use of process of care mapping to elicit symptom management care pathways in 8 cancer settings across the UK.
Material and Methods: Hospitals across Scotland, England and Northern Ireland were mapped in a series of dynamic, practical workshops in order to define the series of steps or actions performed in the management of chemotherapy related symptoms. The workshops were conducted with a range of clinicians involved in the delivery of chemotherapy for breast or colorectal cancer. Participant numbers ranged from 3−15 attendees, and involved practitioners such as chemotherapy nurses, consultants, pharmacists and specialist cancer nurses. Maps created in the workshop were digitised using the Microsoft Visio Software.
Results: Process of care mapping proved a useful tool for representing the complexities of chemotherapy symptom management and in providing contextual information for analysing pathways across the NHS. Feedback from participants was positive in terms of the value of the workshop session and all could be involved in the construction of the maps as there were no technological barriers.
Conclusions: The use of Microsoft Visio offered a number of technical benefits which allowed ease of dissemination and modification. The challenge now lies with interpreting the data gathered in the maps, and identifying how we can best evaluate the impact of ASyMS on the process of care pathway.
No conflict of interest.

1737 ORAL

Aftercare following allogeneic stem cell transplantation: Adjustment to individual needs

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Background: Allogeneic stem cell transplantation (alloSCT) is an important treatment modality for patients with haematological malignancies. Increased long-term disease free survival forces health care professionals to pay more attention to quality of life after alloSCT.
However, little is known about the problems patients are confronted with following transplantation and the need for support.
Material and Method: In a retrospective qualitative study, patients with a haematological malignancy were interviewed one year post alloSCT in the Erasmus MC Cancer Institute. The interviews were transcribed verbatim and analysed using qualitative content analysis, according to the constant comparative method from the Grounded Theory. Several measures were used to ensure the methodological quality and trustworthiness of the study.
Results: After 10 patients saturation (of the data) was reached. Although fatigue was the most striking problem posttransplant, patients experienced many more changes and problems regarding their physical, psychological, social and spiritual well-being. Although patients went through an individual process of recovery and rehabilitation, a common pattern of five phases could be distinguished: *1) survive*, in which intense fatigue and frequent visits to the outpatient clinic are most prominent; *2) on the receiving end,* when the patient is confronted with additional side effects and complications of the therapy; *3) bring under control,* the phase in which the physical condition starts to improve; *4) start recuperation,* when the patient starts to pick up his roles in daily life; *5) retrospection,* the phase in which the patient starts to look backwards and is able to give a meaning to the experiences. The length of the phases and the severity of problems patients experienced varied, mostly due to differences in the severity of graft-versus-host disease. Although the need of support showed some individual variation, all patients followed the five-phased pattern of recovery and rehabilitation.
Conclusion: Recovery and rehabilitation after alloSCT is an intense process, showing individual variation in a fived-phased common pattern. Posttransplant care can be improved by adjusting care to the need of support within the distinct phases the patient is going through.
No conflict of interest.

1738 ORAL

Dyadic sleep/wake assessments in cancer care: New insight from a longitudinal study among women with breast cancer and their informal caregivers during adjuvant chemotherapy

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Background: Alterations in habitual sleep/wake patterns (SWP) of women with breast cancer and their informal caregivers may be concurrently exacerbated and co-vary during the patient's treatment. Taking into consideration the complexity of mechanisms interfering with a care dyad's sleep, the current study set out to longitudinally explore SWP of patient-caregiver dyads in the context of adjuvant chemotherapy (CTh) for breast cancer.
Material and Methods: In this descriptive, observational, repeated-measures dyadic study, 48 newly diagnosed women receiving outpatient adjuvant CTh for early stage breast cancer (stage I−IIIA), and their nominated primary informal caregiver completed self-reported sleep measures at pre-treatment (week prior to CTh), post-CTh cycle 1, post-CTh cycle 4, and approximately 30 days after CTh (total of $\geqslant$6 cycles received). Multivariate hierarchical linear modelling (MHLM) techniques were implemented to analyse dyadic sleep data.
Results: Prior to CTh, 65% of dyads consisted of at least one poor sleeper, a rate further increasing to approximately 88% at CThC4. MHLM revealed curvilinear trajectories for most of dyads' sleep/wake parameters that nevertheless reached significance (p <. 05) only for patients. In both groups, sleep/wake impairment reached its peak at mid-treatment (CThC4); yet, patients consistently reported significantly more sleep problems than their carers. Partial convergence also emerged as suggested by positive correlations and no between-groups differences in daily disturbance, daytime napping duration (NAPTIME), total sleep time, and overall sleep/wake disruption at pre-treatment. At CThC4, rates of change in sleep latency and NAPTIME were also similar.
Conclusions: The current study is one of the first studies to show that a dyadic approach in the assessment of SWP in patients with breast cancer

and their carers is a promising method to enhance exploration of potentially concurrent sleep-impairment. Replication of the current findings in future dyadic sleep research is an absolute priority. Meanwhile, clinicians will need to engage in concurrent systematic and on-going sleep assessments that synthesise and contrast data to establish a care dyad's level of sleep quality.
No conflict of interest.

1733 ORAL

To be in pain (or not); a computer enables outpatients to inform their physician

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Background: In the outpatient oncology clinic, pain management is inadequate. Incorporating systematic pain management into visits is likely to improve this. In 2009, we started an innovative program, including structured computerized assessment of outpatients' pain intensity, with the aim of improving pain management. In this study, we investigated whether this program improved pain control.
Material and Methods: At eight oncology outpatient clinics, patients were asked to register their pain intensity on a touch screen computer. These scores were automatically copied into their electronic medical records. Additionally, a hospital-wide multidimensional cancer-related pain treatment protocol and web-based patient education were developed. A data warehouse system enabled us to extract patient data from the electronic medical record anonymously and to use them for analysis. The main outcome was the adequacy of pain management; expressed as the percentage of patients with moderate to severe pain (current pain intensity, NRS>4) during the first two weeks and after six months after implementation of the program.
Results: During the first six months after implementation, 4.454 of the 5.989 patients (74%) registered their pain intensity on the touch screen computer. The mean age was 54 years (sd=14) and 53% was male. Fifty-two percent reported to be in pain (NRS>0). During the first two weeks of the implementation, 13.3% scored their pain as moderate to severe. After six months, the prevalence of moderate to severe pain decreased with 30% compared to the start (9% NRS>4).
Conclusion: Although it was difficult to convince patients to adhere, pain registration by patients themselves is feasible, provides insight into patients' pain and may serve as a basis for improved integration of pain treatment into daily oncology care. For both physicians and nurses, the program provides direct insight into patients pain intensity, so that pain treatment can be tailored individually.
No conflict of interest.

Poster Session (Sat, 28 Sep − Mon, 30 Sep)
Nursing − Advanced Nursing Roles

1740 POSTER

Nutrition issues in oncological nursing practice: The experience of a focus group

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Background: Nurses are responsible for promoting and supporting standards of care and being able to track the results of their assistance to achieve quality outcomes and that is especially newsworthy in the field of nutrition's problems of hospitalised cancer patients. The use of heuristic approaches to answer as best as possible to current patient needs emphasises the many aspects of care that are often overlooked, both under a clinical point of view and also in terms of organization and management of oncological nursing practice. Focus group methodology is one of several tools that nurse can use to generate valid information important to the advancement of programs and organisations to best assess what are the cultural and organisational weaknesses regarding the nutritional care of hospitalised cancer patients.
Material and Methods: We used the focus group methodology in which took part nurses involved in the struggle against cancer under different profiles. Incentive for using this approach was given by the discussion of clinical cases, personal experiences and a literature review about nutritional problems of hospitalised cancer patients. The moderator of the Focus group was a nurse with relevant experience in cancer nursing, and the focus members were six nurses coming from different clinical areas and with different experiences. The focus group session and conversation among participants was recorded, transcribed and analysed. The group explored issues that were analysed and categorised according to the Focus group qualitative method analysis.
Results: The end result is a report, featuring graphs and tables, in which arises seven major categories that summarise the main problems felt by members of the focus:
1. most urgent priorities and activities
2. with so much work there is something you miss
3. intimate need
4. lack of communication
5. poor care planning
6. improper assessment
7. incorrect data collection

It is evident that these categories identified encompass both clinical and organisational aspects of nursing practice. Aspects, such as not giving importance to the nutritional needs or failing in organise activities, were deeply felt by the participants.
Conclusions: All qualitative approaches share control of the research experience with participants and take advantage of spontaneous and unexpected elements. This focus group has produced high quality data, suggestions and proposals, which can and should be used in trying to respond as adequately as possible to the needs of our patients and increase nursing knowledge with more research.
No conflict of interest.

1741 POSTER

The multidisciplinary approach to elder cancer patients: Geriatric assessment and nursing decision making

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Background: Geriatric assessment in oncology settings has different implications compared with geriatric settings. While in the literature there is general agreement on the importance of a comprehensive geriatric assessment (CGA) in the oncology medical practice, mostly to tailor treatments, the CGA employment and utility for oncology nursing practice is still less explored.
In 2012 in the Oncology Institute of Southern Switzerland (IOSI) within a multidisciplinary project for elder care, a pilot qualitative study exploring how nurses used the CGA in their decision-making, pointed out the use of CGA perceived as not substantially influencing nursing decision-making and elder patient care planning.
The purpose of this project is to promote the correlation between geriatric assessment, as a multidisciplinary instrument, and nursing decision-making process and practice in two oncology outpatient settings.
Methods: The project has involved two IOSI outpatients units. An initial literature review has been done to explore nursing implications of CGA in oncology settings.
Two Group discussions have been set up with nurse teams to lead them to reflect upon their usual decision making process for aged patients and which kind of decisions and interventions a CGA could help them to take and do.
Before instrument implementation, data collected from the Group Discussions and from literature have been shared in an educational meeting with all nurses involved.
Results: Decisions that nurses usually take for elder patients are mainly related to psychosocial aspects, organizational matters, symptoms-side effects and technical aspects on the basis of the initial assessment and individual expertise. CGA can be useful giving additional objective structured data to guide practice, but it's important it's perceived consistent with the decisional order, also avoiding instrument complexity and data repetitiveness. Multidisciplinary collaboration is essential for the utility of collected data.
Conclusions: Nurses have a key role in the multidisciplinary approach to elder cancer patient and the correlation between data collected by geriatric assessment and interventions can lead nurses to more effective and comprehensive decisions but consistent with the specific context in balance between patient needs, professional competences and decisional and organizing framework. From this assumption a work to create conditions promoting nursing decision making orientation is being done in our Institution.
No conflict of interest.

1742 POSTER

Importance of combination therapy in patients with lymphedema

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Aim: This study aims to present the level of lymphedema prevention education in breast cancer patients in Romania, to evaluate present physical and psychological signs at the time of lymphedema onset, and highlight the results obtained by combining several therapeutic methods.
Method: Retrospective study on 50 patients who attended the Hospice 'Casa Sperantei' lymphedema service, weekly or every fortnight, between June2011 and December 2011; data analysis was carried out in SPSS 10. Every patient was interviewed and information was recorded in the patients' files. Assessment of lymphedema evolution was done from medical files, taking into account the measurement done before and 6 months after interventions.
Results: Analyzing data, the moment of lymphedema onset was 1−3 years from surgery in 36% of cases, 4−6 years in 24%, up to 1 year in 18%, over 6 years in 4%, immediately after surgery in 16% and before surgery in 2% of cases. After surgery 46% of patients did exercise; only 8% of them received information on how to prevent lymphedema.
Signs at onset: the modification of limbsize in 26%, and, in addition 28% experienced pain; discomfort and the modification of limb size occurred in 32% of cases and pain with complications in 14%. These patients had combined symptoms of pain, loss of mobility and complications such as infections and thrombophlebitis. The lymphedema location was: hand and forearm 34%, upper limb 32%, arm-forearm 20%, forearm-elbow 4%, arm 2%, hand 2% and thorax and upper limb region 6%.
Regarding the psycho-emotional aspects, patients accepted the situation at a rate of 18%, the rest experienced various feelings and negative emotions. The evolution was favorable for 76% of patients; the correlation between types of interventions and evolution after therapy was: 66% of the patients with exercise − manual lymphatic drainage − elastic sleeve having contraindications for pump, had favorable evolution and 34% of these were stable. Patients with added pneumatic pump treatment evolved favorably in 78% and were stable in 22%.
Conclusions: In Romania post-surgical education of patients regarding lymphedema prevention is still inadequate: there is considerable need of raising the medical staff awareness about the importance of prevention. Considering that lymphedema associate with cancer can't be cured, the aim of the treatment should target the maximum long-term improvement. A combined and sustained therapy brings real benefits to the patients.
No conflict of interest.

1743 POSTER

Competence review of the MANP at the Netherlands Cancer Institute: The position and function of the nurse practitioner in a specialized cancer hospital

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Background: The first Master of Advanced Nursing Practice (MANP), also called nurse practitioner, was introduced in 2001 at the Netherlands Cancer Institute (Amsterdam). Currently, over forty nurse practitioners are appointed in this specialized cancer hospital. They work at 14 different specializations. Within Dutch law the MANP has been accepted as an independent profession since 2010. The MANP roles are, similar to other medical professions, described according to the CanMED competences.
After more than 10 years of settlement the MANP group is now reviewing their function as a basis for future development. The aim of this study is therefore to evaluate the position and function of the nurse practitioner per specialization.
Material and Methods: In June 2013, the 41 nurse practitioners, stemming form 14 specializations, will be invited to complete a questionnaire. In addition, 70 medical specialists (5 per specialization), 70 nurses (5 per specialization), and 300 patients (20 per specialization) will be invited to complete a questionnaire. An adapted version of the Multi Source Feedback questionnaire (a valid instrument to evaluate medical professionals in the Netherlands) will be used to assess competences of the MANP. This questionnaire is based on the CanMED competences, and will be used to assemble 360º feedback.
Results: We expect a minimum response rate of 65% of the colleagues (n = 91/140) and of 75% of the patients (n = 225/300). The results of the questionnaires will be evaluated for the total group, and per specialization. The opinions of the medical specialists, nurses, nurse practitioners and patients about the different CanMeD competences will be compared for each specialization.
Conclusions: The results of this study will give insight in the position and the functioning of the nurse practitioner as a group, and per specialization, in a specialized cancer hospital. The different perspectives from the medical specialists, nurses, nurse practitioners and patients about the current position and functioning of the MANP group will show the strengths and limitations of the CanMED competences of the nurse practitioners in the Netherlands Cancer Institute. These results can be helpful to improve the competences of the nurse practitioners in this hospital, and the results can serve as a model for other hospitals that have introduced this relatively new position in the care for their cancer patients.
No conflict of interest.

1744 POSTER

Education of patients and their families before specific cancer outpatient treatment at the institute of oncology Ljubljana

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Background: Today's patients are aware of their rights and demand a partnership with healthcare professionals. On the other hand increasing of rights and participation brings greater responsibility. To become an equal partner in decision-making an individual should have the information and knowledge. Therefore the priority of the Division of Nursing and Care for Patients at the Institute of Oncology (OI) was to upgrade services of the Oncology nursing consultancy (Consultancy). Consultancy services have been in operation at the OI for about 12 years but some education areas had developed rapidly during this time and they became nowadays independent and essential activities for high-quality treatment and care of cancer patients. On the other hand some education areas diminished for various reasons.
Material and Methods: In January 2012 individual counseling primarily for the patients treated in outpatient units was organized at the OI. These patients were informed about their treatment and care in order to reduce side effects of specific cancer treatment, to solve their individual problems, and to improve the quality of life during the treatment. In 2012 the Consultancy was attended by 169 patients and 134 patients were asked to complete an evaluation questionnaire. Seventy one questionnaires were filled out and returned.
The most important aim of this evaluation was to explore the satisfaction or dissatisfaction with the newly organized Consultancy visit, to identify reasons for the Consultancy visit and to define a standard way of appointments for patients in the Consultancy.
Results: Of those patients who had submitted the questionnaire, 25% highlighted the positive feelings about the Consultancy. Majority of patients required more information about rehabilitation and time after treatment. Patients visited the Consultancy because they were referred (almost 65%) and/or they needed more information about treatment and care (almost 41%). Ninety one percent of those who responded to questionnaire were referred to the Consultancy by nurses and doctors in specialist clinics.
Conclusions: Findings showed that there was necessary to encourage the appointments of patients to the Consultancy and that a standard way of preparing cancer patients for the specific cancer treatment needs to be established, and that nurses who were working in the Consultancy needed additional trainings in area of cancer patient's education.
No conflict of interest.

1745 POSTER

Prognostic factors for mortality within 90 days in phase I oncology trial

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Background: A selection criteria for cancer patients with advanced malignancies whom will participate in a phase I trial is an expected survival for more than 90 days that in spite of the difficulty of predicting the overall survival of these patients.
Methods: The data used for this analysis were retrospectively abstracted from 371 medical records of patients enrolled in a phase 1 clinical trial at the Nederlandse Kanker Institute (NKI) in the Netherlands between October 1st 2009 and February 29th 2012. The cohort consisted of 179 men and 192 women aged between 18 and 86 years all with a solid tumor. We used univariate and multivariate logistic regression analysis to validate exciting prognostic factors and prognostic scores.
Results: Analysis of our cohort suggests that the five prognostic factors: hemoglobin, Eastern Cooperative Oncology Group performance status,

albumin, lactate dehydrogenase and number of metastatic sites of disease, should all be included in a prognostic score. These five prognostic factors showed a significant association with mortality. The score from the Princess Margaret hospital in Canada predicted the best the mortality in our dataset with a AIC of 0 compared to the Royal Marsden (AIC 16.2), MD Anderson Cancer Center (AIC 16) and Centre Léon Bérard (AIC 25.1). We produced a new 5 level prognostic score which in our dataset has a greater prognostic value than those previously published.
Conclusion: Our results suggest that patients with a score 4 or more should not be entered into phase I trials as their 90 days survival estimate is only 37% (23%-62%). Similarly patients with a score of 3 may be considered for exclusion, as their 90 days survival is also low, 65% (51% − 82%). Prospective validation of the NKI prognostic score is warranted.
No conflict of interest.

1746 POSTER

Russia's oncological nurses promote prevention and early intervention

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Cost-effective and affordable measures to prevent many cancers and alleviate suffering of those already diagnosed can be implemented irrespective of the level of resources in any country in every stage of the fight against cancer (prevention, early detection, treatment and palliative care).
This presentation will describe initial changes being implemented in the role of nurses in four primary care clinics in Russia's Saratov Oblast. The project, funded by the Bristol-Myers Squibb Foundation, is exploring the effectiveness of enhancing the role of nurses in prevention and early detection through the following approaches:
– New programs of postgraduate education 'Primary health and prophylactic assistance to the population'
– 'Primary health care for the adult population' − education for nurses working in primary care clinics which also incorporates new standards
– Adaptation of the 'medical home' patient care model which maximizes the application of nursing skills and knowledge to improve patient care.
Changes in practice and the education of nurses are being made by faculty of the Balakovo Secondary Medical College with the support of the Ministry of Health of the Saratov region, and in cooperation with the Committees of health and municipal clinics in the cities of Balakovo and Saratov.
Results: In the pilot clinics nurses provide routine patient education intended to reduce common risk factors: smoking, alcohol, weight, exercise, and other lifestyle factors. To prepare and support nurses in assuming expanded roles and responsibilities in the primary care setting, education and in-service programs have been implemented which include:
– leadership skills, best practices in prevention, screening and patient education;
– procedures to ensure the continuity of treatment between the institutions of primary health care and specialized agencies; and
– nurses as cancer patient advocates.
Conclusions: This project is seeking to implement significant changes in patient care for patients in the primary care setting, with the desired goal of preventing cancers by enhanced patient education, and improving outcomes for those patients diagnosed with cancer by early detection and effective referral for prompt treatment.
Progress in meeting this goal will be monitored by audit of nursing notes to ensure that patient education and screening is being provided according to new standards and the expanded scope of nursing practice. These audits will also document the percentage of patients initiating self care as a result of nursing interventions (i.e. breast self exam, smoking cessation, etc.).
Initial response from patients, physicians and nurses has been promising. A proposal is being developed for consideration by federal education authorities to incorporate expanded nursing practice into the secondary college system's standards.
No conflict of interest.

1747 POSTER

Introducing the nurse practitioner role to Australian regional oncology patients

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Background: For some time in Australia, it has been recognised that the Nurse Practitioner Role offers feasible and cost effective alternatives in the redesign of health care delivery. To improve outcomes for Oncology patients across all health settings, it is paramount for the Oncology Nurse Practitioner (ONP) to have formal collaboration and partnerships with other health care providers.
Methods: A mixed methods design – Gap analysis and Literature Review – was employed by the Oncology Nurse Practitioner; to undertake a needs analysis in the development of the ONP Model of Care.
Results: This study identified gaps in oncology care delivery from Oncologists, General Practitioners and supportive care staff perspectives. Collaborative engagement with internal and external partner and other health care providers determined the ONP model and scope of practice within rural/regional Victoria and Southern New South Wales with the primary aim of improving Oncology patient outcomes.
Conclusions: This ONP model reflects a key strategic objective: To promote access to Quality Specialist Supportive Care for Oncology Patients in regional Australia.
No conflict of interest.

1748 POSTER

Patient education and competence in the oral cancer therapy as a key factor for patient's adherence and safety − aims and results of a cross-sectional survey among medical oncology practices

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Introduction: Oral agents for cancer treatment are increasingly prescribed throughout the world, also in Germany. Regardless the benefits of oral agents regarding the convenience of administration for the patient, oral cancer medications have considerable potential for side effects, toxicity and interactions with other drugs. Inadequate use of medication may therefore lead to effect reduction or ineffectiveness of medication and in some cases to premature breakup of therapy. Against this background and because oral agents are usually self-administered or administered by lay caregiver, our analysis assumes that the provision of adequate information to the clinical picture, treatment options, side effects, and the proper handling of medications is crucial for therapy adherence and therefore for therapeutic success. Due to the lack of data on this issue in the context of outpatient care with oral cancer agents in Germany, we conducted a systematic explorative survey on the handling of oral cancer care in oncology practices.
Methods: The study consisted of a representative cross-sectional survey among medical oncology practices (n = 220) in order to systematically describe a) the ambulant care of patients receiving oral cancer agents, and b) the current therapy management and education measures from the point of view of medical oncology practices. Information was collected via questionnaire from nearly 90 oncologists and hematologists.
Results: Data collection took place in the first quarter of 2013. The majority of respondents (74%) have the opinion that nurses should be more involved in the training and guidance of orally treated patients, especially if they have acquired an oncology qualification. Surveyed oncologists consider mainly educative and informative approaches or methods as crucial to ensure treatment adherence. Further details will be presented.
Conclusions: The results confirm the study's assumptions and indicate a need for action regarding the degree of involvement of oncology nurses and the use of systematic education tools for patients receiving oral cancer agents. These findings will be the focus in a new interventional study starting this year.
No conflict of interest.

1749 POSTER

Development and psychometric validation and sensitivity of an evaluation instrument for a breast cancer nursing consult

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Background: A breast cancer consult refers to the meetings in which support is given by the breast care nurse (BCN) attuned to the specific care demands of breast cancer patients. It is essential to assess patients' experiences and perspectives with these nursing consultations in breast cancer care. No validated instrument to evaluate breast cancer nursing consultations is available. The aim of the study is to develop and validate an instrument to evaluate breast cancer nursing consultations.
Methods: *Phase 1: Identification of topics of the instrument.* A review was performed to identify cancer patients' expectations about nursing consultations and to explore their preferred support by healthcare professionals. In addition, data of 4 qualitative studies were integrated: 45 semi-structured patient interviews about breast cancer patients' experiences and 4 focus group interviews with BCN about their perspectives on breast care).
Phase 2: Psychometric validation and sensitivity. Face validity of the instrument was assessed by breast cancer patients, BCN and clinical nurse specialists (CNS), multicentric. Comprehensibility and phrasing of each question was assessed by 8 breast cancer patients. Psychometric validity (internal consistency, stability and construct validity) of the instrument was evaluated in a convenience sample of 104 breast cancer patients.

Sensitivity of the instrument was assessed. 56 breast cancer patients completed the instrument and 19 patients were interviewed using the Q-sort method.
Results: A 78-item instrument was developed based on the review and qualitative data. The items were categorized in 9 topics. The relevance of each item was assessed by 15 BCN. The final instrument consisted of 71 items. The internal consistency (Chronbach alpha) of the 9 topics was between 0.77 and 0.98. Stability was demonstrated for 7 of 9 topics and 2/3 of the items. Ceiling effects of the instrument were apparent. The sensitivity study indicated that 14 items were sensitive for evaluating a breast cancer nursing consultation. One third of the items were interpreted differently or were less or not understood.
Conclusion: This study is the first step in the development of a validated instrument to evaluate breast cancer nursing consultations. The instrument shows a strong internal consistency and a high content validity. This instrument could be used by BCN to optimize their nursing consultations.
No conflict of interest.

1750 POSTER

Implementation of nurse consultations in psychosocial cancer care: Experiences of advanced nurse practitioners

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Background: Successful implementation of the role of advanced nurse practitioners (ANPs) is challenging. Less attention is given to the mechanisms used by ANPs to enact their professional role within the multi-professional team, caring for patients with cancer. The aim of this study is to elicit barriers, facilitators and underlying processes in implementing these ANP roles in cancer care.
Methods: A qualitative study was performed to explore experiences and underlying processes in the implementation of a nurse consultation in psychosocial care for patients with cancer and their relatives. Fifteen advanced nurse practitioners involved in psychosocial cancer care working in a university hospital or working in a general hospital were interviewed. A grounded theory approach was used. Interviews were transcribed verbatim. Data collection and analysis took place iteratively and analysis was validated by means of researcher triangulation.
Results: ANPs are often confronted with ambiguity about the role description and role clarity. Resistance from other healthcare professionals is experienced because of unclear role boundaries. Acceptance, especially by physicians, was a main problem when implementing an ANP role. Physicians also extensively influence the ANP role development. ANP's often experience insufficient organizational support for their role and a shortcoming of coaching. To enhance successful implementation, ANPs indicate building relationships with other healthcare professionals as essential. The results indicate an evolution of provider oriented care ('I focus') when starting as an ANP towards a team-oriented care ('my team focus') after several years.
Conclusions: Future approaches should focus on the use of frameworks to facilitate successful implementation of ANP roles in patient cancer care. Support from nurse managers and clinical nurse specialists could also facilitate role clarity, role implementation and role development.
No conflict of interest.

1751 POSTER

Reflections on the position of nurse practitioner breast cancer care in the Netherlands

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Title: Reflections on the position of Nurse Practitioner breast cancer care: a survey in the Netherlands and a comparison to the role of a Nurse Practitioner in an tertiary referral institute.
Background: Every year about a million women are diagnosed with breast cancer worldwide. In The Netherlands 1 out of 8 women will be confronted with this disease.
In 2002 the Antoni van Leeuwenhoek Hospital incorporated the position of Nurse Practitioner in the clinic for diagnostic work-up, treatment and follow-up of breast cancer patients.
In the last 10 years a lot of the Dutch hospitals have adopted Nurse Practitioners in their breast clinics.
Within Dutch law the Nurse Practitioner has been accepted as an independent profession since 2010.
However, no clear data exist concerning the nationwide variability of working activities of nurse practitioners in the Netherlands. Therefore, we performed a survey studying the current role of the nurse practitioner breast cancer care in the Netherlands.
Method: A questionnaire was sent to all hospitals in the Netherlands. Questions about the content of the position of the Nurse Practitioner and which tasks are performed, were included. The results were collected, and analysed and subsequently compared with the role of the Nurse Practitioner in a tertiary referral institute.
Results: Of the addressed hospitals actively participated in the survey in 68.5% of these hospitals, Nurse Practitioners play a vital role in the outpatient clinic activities of the breast clinic, compared to the situation in a specialized center.
Conclusion: By 2010 the position of Nurse Practitioner was fully integrated into the majority of Dutch hospitals. Compared to other hospitals in the Netherlands the Nurse Practitioners in the Netherlands Cancer Institute have a broad spectrum of activities.
No conflict of interest.

Poster Session (Sat, 28 Sep − Mon, 30 Sep)
Nursing − Impact of Cancer on Patients and Families

1752 POSTER

Experience of Iranian men in living with a spouse with breast cancer

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Introduction: Breast cancer is the most common cancer among women. In Iran, breast cancer is in the first rank in malignant cancers among Iranian women and has the highest prevalence. Although cancer is a stressful event for all family members, one of the most important social and familial consequences of breast cancer is its effect on the spouses of these patients. Spouses' trust and support are crucial for a patient in stages of diagnosis and treatment of cancer. As patients' spouses often accept the role of a caregiver with the lowest preparation and support, if their concerns, remain unknown, the problems will not be solved, so exploration of men's adaption process to their spouses' cancer can be helpful in provision of care and manner of their dealing with their spouses' disease.
Methods: This is a qualitative study conducted based on grounded theory. Participant comprised the men whose spouses had breast cancer and selected from various social and economic classes and interviewed. Sampling continued until data saturation and ended with total of 26 participants. Constant comparative method was used to analyze the data in this study.
Results: Results of the present study showed that men's adaptation with their spouses' breast cancer is a process which starts from the moment of disease diagnosis and occurs in three stages of *exposure to crisis*, *insertion of life-course disruption* and *struggle to modify disruption in life*. The first stage of men's exposure to their spouses' disease is the exposure to crisis. The happenings in this stage indicate the fact that cancer leaves the spouse in a sudden shock and is accompanied with unpleasant psychological and mental reactions. *Family disruption*, *heavy shadow of disease on marital relationship*, *concerns associated to disease management*, and *resistance against disruption in life* are the main categories which formed the second stage of men's exposure to their spouses' disease. '*Revising the relationship with the relatives*', '*emotional and functional support to the spouse*', '*trying to improve marital relationship*' and '*seeking support to modify disruption in life*' formed the third stage of men's exposure to their wives' breast cancer as 'struggle to modify disruption in life'. Men gradually found out that they could not live in the way before their spouses' disease and had to revise many aspects of their life. Therefore, a struggle to modify disruption in life was administered and they constantly tried to compensate the defects.
Conclusion: Results declared the necessity for these men's support and conduct toward use of efficient coping strategies. Nurses can plan to facilitate the men's adaptation to the conditions by supporting and helping them through an accurate primary and comprehensive assessment of their psychological status, experiences and investigation of their used strategies. Nurses should support men's struggle to modify the disruption in life and facilitate their adaption to the disease of their spouses through appropriate interventions.
No conflict of interest.

1753 POSTER

How to meet the needs and wishes of relatives to cancer patients at an oncology ward − an intervention study by nurses

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Background: A survey in 2010 of relatives (n = 157) to Danish cancer patients at the Oncology ward of Copenhagen University Hospital, Rigshospitalet, revealed a need for an enhanced focus on their needs. The survey showed that 21% of the relatives believed that they were responsible for the coordination of the patient's treatments and examinations, 58% experienced that the staff only a few times or never had asked to their wellbeing as relatives, and 36% had not been informed about possible offers of support. An intervention study was initiated in 2011 as a part of nurses' focus on cancer patients' daily lives. The aim was to investigate whether an optimized effort from the clinic and their nurses could improve the relatives' experiences and meet their needs.
Materials and Methods: The study was designed as a quality improvement study and goals for the relatives' experiences were set as 80 % know who the patient's devoted nurse/doctor is, 90% experience that the staff is interested in their wellbeing, 80% feel that they are involved in the patients treatment and care at the hospital in the way they prefer, 80% are well informed about how they support the patient and finally 90% have got information about where they can get and seek help as relatives.The model PDSA (Plan − Do − Study − Act) was used for the intervention.The above presented data are baseline data, and the intervention is based on: Evidence-based interventions for relatives to cancer patients, the recommendations and guidelines regarding relatives to seriously ill patients from the Danish National Board of Health, and recommendations from the patient organisation Danske Patienter ('Danish Patients'). The nursing management and the cancer rehabilitation nurse of the hospital are responsible for the intervention.
The intervention included: Inviting and welcoming the relatives to the first contact with the hospital and continuously during treatment and follow-up; Information about supportive services for relatives, Information about the patients' illness and treatment and presumed side effects and complications; Agreements about the relatives' involvement; And presenting the offer of meeting other relatives/peers. Researcher from the Research Unit at the Department of Palliative Medicine at Bispebjerg Hospital collect and analyze the data from a follow-up in the spring of 2013 showing whether the goals are met.
Results: Data collected from relatives in 2013 will be compared with baseline data. We expect to present preliminary results at ECCO, including evaluation from the information meetings for relatives held at the hospital.
Conclusions: This study's impact on clinical nursing practice is to meet not only the patients' needs and wishes but also those of the relatives. However, the evaluation of the intervention has to be based on research data and not just assumptions or subjective experiences. No evidence based intervention for relatives at an oncology ward has previously been tested.
No conflict of interest.

1754 POSTER

Patients' self-assessed knowledge about cancer

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Background: Patients' need for information to manage everyday life is increasing. Studies show that especially women retrieves information related to disease and health on the Internet. In addition, this information influences the choices they subsequently make.
This study distinguishes between examining the patient's desire for knowledge held up against the self-assessed current knowledge.
Purpose was to investigate:
- How much knowledge do cancer patients *want to have* about disease and treatment?
- How much knowledge do cancer patients *currently have* about disease and treatment?
- Is there a gender difference in the need of knowledge?

Methods: In total 84 cancer patients (38 men, 46 women) with a median age of 59 years (range 36−83) completed a questionnaire. On a scale from 0−10, patients ranked knowledge about disease and treatment.
Results: In average, women want to have knowledge about *disease* equivalent to 9.3, and men 9.2 ($p = 0.762$). Women actually have knowledge about *disease* equivalent to 8.0, and men 7.2 ($p = 0.006$).
In average, women want to have knowledge about *treatment* equivalent to 9.5, and men 9.8 ($p = 0.094$). Women actually have knowledge about *treatment* equivalent to 8.4, and men 7.5 ($p = 0.002$).
Conclusion: Both male and female patients want to have a high level of knowledge about disease and treatment and no significance difference is found between genders in these wishes.
In this study, the female patients had a significantly higher self-assessed level of knowledge about both disease and treatment than men.
It is relevant to examine what this difference in level of knowledge causes and means.
No conflict of interest.

1755 POSTER

The experience of the changing nature of coping with nodal relapse of malignant melanoma

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Background: Currently, approximately 132,000 malignant melanoma skin cancers occur globally each year (World Health Organisation, 2012). The incidence of malignant melanoma is now four times higher than 30 years ago, and is predicted to continue to increase.
Despite the significant increase in patients with melanoma there appeared to be no research on the specific needs of patients with nodal relapse. Due to the current gap in the literature this study aimed to provide an essential insight into patients' specific needs when they developed nodal relapse of malignant melanoma. It explored how the patients' experience a transition from curative to nodal relapse and potentially palliative care.This transition was described through the use of an emerging middle-range theory of transitions described by Meleis *et al.*(2000).
Material and Methods: Using a descriptive qualitative design the target population was patients with nodal relapse of malignant melanoma, who had a surgical block dissection of lymph glands in the neck, axilla or groin within the last two years. The sample size was six participants.Interviews were conducted and transcribed verbatim.
The data analysis was based on the constant comparative method (Glaser and Strauss 1967) and was conducted by two researchers.
Results: The participants appeared to have an unpredictable emotional reaction in that they were less shocked at nodal relapse when compared to their reaction to the initial diagnosis. Information gaps were identified which related to the physical effects following surgery, review arrangements such as the format and the language used by health professionals were also identified as well as treatment dilemmas pertaining to Interferon treatment. Hope was the main strategy expressed by the participants. The participants acquired new coping skills from their initial diagnosis of melanoma to nodal relapse and beyond. They continued to develop their coping resources which pre-empted the next transition process regarding their cancer. Nonetheless they had an acceptance and understanding of the threat of even further spread of their disease. Despite this they had a palpable awareness of life and an overriding sense of hope and positivity.
Conclusion: This unique patient group experience a transition from their initial diagnosis of malignant melanoma to nodal relapse and adopt coping mechanisms to respond to their situation. Through identification of the specific information and support needs this provides health care professionals with an in-depth description of the specific physical and psychological impact of nodal relapse of malignant melanoma.
No conflict of interest.

1756 POSTER

Attitude of family caregivers of Egyptian patients with cancer towards cancer diagnosis disclosure

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Background: Little is known about the communication preferences among Egyptians in the cancer care setting, especially those related to cancer diagnosis disclosure. Family caregivers in Egypt are seen frequently by oncologists as a barrier to effective communication with cancer patients. This study was performed to explore the disclosure preferences of Egyptian family caregivers of patients with cancer.
Materials and Methods: We conducted a structured interview with 288 family caregivers accompanying cancer patients in the outpatient or the inpatient setting in Cairo and Port Said. Caregivers were asked about their preferences regarding cancer diagnosis disclosure to their related patient and their preferences in case they themselves developed cancer.
Results: The median age of caregivers was 35 years (range: 18−70), 58% were females, 51% were offspring of patients, 87% were literate and 70% were living with the patient.
According to the interviewed caregivers, the majority (85%) of patients were aware of their cancer diagnosis. The majority (81%) of caregivers

preferred cancer diagnosis to the patient. Factors associated significantly with the caregiver's preference not to disclose cancer diagnosis to patients were illiteracy of patients, urban residence of patients and having a lung or hematological malignancies ($p = 0.005$, <0.001 and <0.001; respectively). Furthermore, caregivers who preferred not to know their own cancer diagnosis and not to tell their families in case they themselves developed cancer, were more likely to be against disclosure to their related patients ($p < 0.001$). In case they themselves developed cancer, 92% of caregivers wanted to know their cancer diagnosis and 88% wanted to tell their families.
Conclusions: Unlike the impression of oncologists in Egypt and according to the report of interviewed caregivers, the majority of Egyptian patients are aware of their cancer diagnosis and their informal caregivers are not against disclosing diagnosis to them. The results suggest that, in general, informal caregivers of Egyptian cancer patients do not represent a barrier to honest communication with patients. For the group of caregivers who are against disclosure, effective strategies are needed to overcome their negative attitude noting that they may be reflecting their own fears of cancer. Communication with patients with cancer and their informal caregivers in the Egyptian culture is an area that needs further exploration in future studies.
No conflict of interest.

1757 POSTER

Nurse care and resilience in women with breast cancer in adjuvant chemotherapy

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Background: Breast cancer is the second most common type of cancer worldwide and the most common among women. Resilience is explained as 'processes that explain the 'overcoming' of crisis and adversity in individuals, groups and organizations.' The importance of analyzing the resilience in women with breast cancer can help them and assist them during the treatment. This project discuss about resilience as an element for recovery of women with breast cancer undergoing chemotherapy. Its objectives are to characterize the resilience in women with breast cancer to adjuvant chemotherapy treatment; analyze the risk factors and protective resilience expressed and to discuss the expression of resilience in these women.
Material and Methods: This was a descriptive study with a qualitative approach. We collected data from the interview and there also was used Resilience Scale, and the Wagnild Young, validated by Pesce in Brazil. For data analysis, there was performed interpretative elaboration of subcategories derived from observation, interviews and analysis of the information collected based on the theoretical framework.
Results: The data were collected from fifteen women with breast cancer in adjuvant chemotherapy. Resilience was measured using the Resilience Scale (Wagnild and Young). We considered scores lower than 125 low resilience, from 125 to 145 moderate and higher resilience than 145 high resilience. None was classified as low resilience. Findings were four women with moderate resilience, equivalent to 26.67% and eleven women with high resilience, tabulating 73.33% of them. The treatment was rated as strenuous and as something that takes a long time. Hair loss is also a major downside in cancer treatment. The protection factor was 'Faith in God.' According to these women, faith that moves them to continue and complete the treatment. The family was also cited by many. Mothers, children, grandchildren, make a difference in the lives of these women. Individual willpower makes them go on.
Conclusions: This study contribute to the awareness that nurses can, knowing the concept of resilience associated with nurse care, enlarge the see and do in nurse care or the managerial practice. The perception was evident that women felt victorious to be alive and able to give her account. Risk factors and protective were: chemotherapy, fatigue, sick, time spent in hospital, hair loss, feeling sick, addiction, lack of family support; to hide feelings and 'nothing weakens me'. The contribution for nurse care is that we can take care of our customers in a comprehensive way. A woman with breast cancer undergoing chemotherapy experience unique experiences such as fear, physical pain and the will to live touched on, so people with high chances of being resilient.
No conflict of interest.

1758 POSTER

Everyday life with prostate cancer − female spouses' experiences

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Background: Spouses or partners play an important role in how well patients with prostate cancer manage their illness. Whereas earlier studies mostly included both patients and spouses, this study focuses on the spouses' experiences during the illness trajectory. The objective of the study was to illuminate the daily life experiences of female spouses living with husbands with prostate cancer to determine the spouses' needs for support and improve care for the patients.
Material and Methods: Qualitative interviews were conducted with nine spouses of men receiving potential curative treatment for prostate cancer, i.e., radical prostatectomy or radiation therapy.
Results: Illness was an event that the spouses experienced as part of a couple and as a challenge with significant emotional and practical demands. Spouses suppressed their own anxieties and needs for support and felt overlooked by health care providers. Those spouses living in the situation over a period of years expressed tiredness and a shift in focus from their husbands' needs to their own needs.
Conclusion: Being a spouse to a man with prostate cancer is emotionally and practically demanding. There is a danger of the spouses erasing themselves in the process of supporting their husbands. Spouses may also need support after a prostate cancer diagnosis.
Health care providers should provide support for spouses during a prostate cancer illness trajectory, encourage spouses to participate in spouse-only rehabilitation courses, and be aware of the potential for situational fatigue in spouses after years of dealing with a husband's illness.
No conflict of interest.

1759 POSTER

Reasons for patients' preferences for subcutaneous or intravenous trastuzumab in the PrefHer study

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Background: Subcutaneous (SC) trastuzumab, administered via single-use injection device (SID), was overwhelmingly preferred to intravenous (IV) infusion by patients in the ongoing PrefHer study (NCT01401166, F. Hoffmann-La Roche Ltd). Reasons for patients' preferences were assessed in an exploratory analysis.
Materials and Methods: After completing (neo)adjuvant chemotherapy, patients with HER2-positive early breast cancer were randomised to receive 4 cycles of SC trastuzumab (600 mg fixed dose via the SID) followed by 4 cycles of standard IV or the reverse sequence as part of their adjuvant trastuzumab therapy.
Prior to randomisation and at the end of the cross-over period, patients were interviewed at home by phone by experienced interviewers. Factors potentially influencing preferences, including type of venous access device used and experiences during administration, were collected. After the cross-over period, patients' final preferences, reasons for these and strength of preferences were elicited. Interviews were quality-controlled to ensure impartial questioning.
Four researchers independently coded from verbatim quotes the two primary reasons patients gave for their preferences. These were reconciled and grouped into 10 categories for descriptive analyses.
Results: Of the 236 patients, 216 (92%) preferred SC delivery, 16 (7%) preferred IV and four (2%) had no preference.[1]
The top three categories for SC preference were: (i) time-saving (195/216),[1] e.g. '*It does affect me being there so many hours. With this it was 'Hello' and 'Bye' without having to spend hours with patients,*' (ii) less pain/discomfort (88/216),[1] e.g. '*The SC method was a lot less painful to me and my bruises faded faster than in the case of the IV method,*' and (iii) convenience (35/216),[1] e.g. '*Busy mum with four young children − want to get on with life.*'
The primary reason given by the 16 patients with an IV preference was fewer reactions (pain, bruising, irritation, etc.) (11/16),[1] e.g. '*Irritation due to the SC.*'.
Irrespective of preference, 64% of patients (152/236) said that SC caused least anxiety, 94% (222) found SC to be most convenient and 84% (199) thought that staff usually found SC easiest to administer.
Conclusions: The overwhelming preference expressed by patients for SC delivery of trastuzumab using an SID was mainly due to perceptions that it saved time, caused less pain/discomfort and was more convenient than IV administration.
Conflict of interest: *Advisory board: Xavier Pivot: F. Hoffmann-La Roche Ltd, Novartis, GlaxoSmithKline. Other substantive relationships: Nicole Fitzpatrick: Employee of F. Hoffmann-La Roche Ltd with ownership of non-voting company shares.Stuart Osborne: Employee of F. Hoffmann-La Roche Ltd.Xavier Pivot: Honoraria from F. Hoffmann-La Roche Ltd and Sanofi-Aventis.*

Poster Session (Sat, 28 Sep − Mon, 30 Sep)
Nursing − New Developments

1760 POSTER

Urology oncology nurses take on the challenge

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Background: The urology outpatients department in St. Franciscus Gasthuis, Rotterdam, has had to deal with a fast increasing amount of urology oncology patients in the past 4−5 years. These patients require more guidance, counselling and psychosocial care. Both factors have contributed to increasing the workload of the urologists. By educating urology nurses in urology oncology and implementing a nurse led clinic, quality urology oncology care can effectively be provided and hopefully decrease the workload of the urologists.
Material and Methods: A literature study was conducted in order to determine exactly what the needs of the urology oncology patient are.
A literature study was conducted to determine if there is a 'right moment' when to discuss sexuality.
A nurse led clinic was implemented based on the needs of the urology oncology patient and evidenced based practice.
A patient survey was conducted to evaluate if our nurse led clinic can provide the necessary urology oncology nursing care, required by this patient group.
Results: 60 questionnaires were handed out to patients who attended the nurse led clinic. 50 were returned and analysed. 75% of the patients who filled out the questionnaire were age 60−80 and 25% of the patients were age 40−60. A score of 8.5 out of 10 was given for the overall appreciation of the nurse led clinic.
The questionnaire was divided into the following themes:
– The expertise of the urology oncology nurse
– Adequate information given
– The quality of information given
– The telephonic availability of urology oncology nurse
– Enough time to ask questions
– The impact of emotions and sexuality
Conclusion: A nurse led clinic can certainly contribute to providing quality urology oncology care and decrease the workload of the urologists.
The psychosocial impact of urology oncology is great and the extra time available for these patients to be able to discuss their diagnosis, information and psychosocial issues, is very much appreciated by the patients.
No conflict of interest.

1761 POSTER

Personalized choice of experience

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Background: It is difficult for patients, relatives and even health care professionals to navigate the Danish health care system obtaining information of where cancer patients are treated and at what level of quality. The management of health care is split in 5 regions in Denmark and there is no central overview.
The purpose of this project is to enable patients and relatives to see where treatments are offered throughout the country, at what level of quality and to which level of satisfaction.
Methods: The Danish Cancer Society has built a website to provide easily accessible information on cancer treatment in Denmark. The Danish Cancer Society is responsible for updating data. The project involves all Danish hospital departments treating cancer patients. 98 departments have contributed to the information on the website.
The authors personally contacted every hospital in Denmark to find out, where cancer patients are treated and what treatments are offered. Each department has appointed a contact person responsible for the project to assure continuous update of the most recent data.
Focus-groups of patients and relatives have participated in interviews on their needs and the usefulness of the website.
Results: The website www.cancer.dk/gps gives an overview of the cancer treatments throughout Denmark. Treatment sites are mapped for each of 33 cancer diagnoses. The website contains information *for each department*, on:
- Treatment offered (surgery, radiotherapy, chemotherapy, medical treatment).
- Available counseling (patient counselor, social worker, priest, psychologist)
- Patient satisfaction surveys (The Nationwide Survey of Patient Experiences).
- Pathways (pathways, waiting times)
- Contact information

In this early version of the website there are approximately 15,000 users per year. Half of them are unique new users. (5 million inhabitants in Denmark.)
Conclusion: The website has proven to help cancer patients get a simple accessible overview of where to receive treatment, which medical facilities are available for the particular cancer diagnosis and at what level of quality (patient satisfaction). It allows cancer patients in a simple way to navigate on-line for information in the complex healthcare system offered, to quickly get in touch with the individual departments and to compare departments. This is an important empowerment of patients, and often during their acute crisis after the initial diagnosis.
No conflict of interest.

1762 POSTER

Bringing patients' intimate cancer experiences closer to nursing students with a new educational approach

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Background: Perceptions and personal experiences of patients with cancer about their illness, health care and health care system are important sources of learning for nursing students. In the year 2012 at the Institute of Oncology Ljubljana (IOL) in collaboration with the College of Nursing Jesenice we started to develop an education approach for nursing students. The aim was to bring patients' intimate cancer experiences closer to students.
Material and Methods: In the first part of the project second year nursing students were assigned to read a book written by a cancer patient and to write a reflection on its content. This was a part of the individual work during clinical practice at the IOL. The research instrument for the data collection was students' reflections on the read books. The data analysis was based on the content analysis method with which the categories of content and the frequency of occurrence were analyzed. The first results showed a need for a more focused, question-oriented assignment approach. We upgraded the reflection tool and executed the second part of the project with different student group in year 2013.
Results: The main theme 'Reflection of cancer patients' stories' was studied from the perspective of four different categories: patient's perceptions of the illness, communication, complementary therapies, and students' experiences. In the table are presented and compared the results of both parts of the project.
Conclusions: In comparison with the research from last year, we came to the conclusion that the greater number of students in 2013 experienced positive emotions and thus deeply identified themselves with patients and their experience of illness and the process of healing themselves. As observed in the table, there was a greater gap in the category 'communication' due to a perception of experience working relationships.

Table 1 (abstract 1762). Comparison of the main frequencies of occurrence in the year 2012 and 2013

Year 2012 (105 analysed reflections)		Year 2013 (28 analysed reflections)	
Theme	%	Theme	%
Category 'The patient's perception on the illness'			
Emotional field	57%	Emotional field	46%
Category 'Communication'			
Negative experience between medical staff and patients	50%	Positive experience between medical staff and patients	68%
Category 'Complementary medical treatment'			
Change of lifestyle	52%	Complementary methods of treatment	43%
Category 'Students' experiences'			
Positive emotions	52%	Positive emotions	79%

The results showed that the vast majority of students responded positively to the new educational approach.
No conflict of interest.

1763 POSTER

The importance of nurses in the process of patient care with cutaneous melanoma (SECA-GEMM project)

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Introduction: Cutaneous melanoma is a malignant tumor that, due to its increasing incidence, mortality and risk factors, currently represents a public health problem. It also involves a wide variety of clinical-care setting from the primary diagnosis to the possible development of mestastases. The purpose of the SECA-GEMM project is to increase awareness of this disease and the involvement of each of the health professionals. In order to carry out a multidisciplinary approach for patiens with melanoma, nursing represents and important role by providing an appropiate response to the needs os each patient.
Objective: To determine, according to the methodology of process managment, the involvement of each of the health professionals involved in the managment of the disease as well as the essential nursing work.
Methodology: The project has been developed by health professionals with experience and knowledge in pathology − dermatologists, oncologists, nurses, hospital pharmacists, plastic surgeons and primary care physicians − who have worked with professionals in the field de process management and sanitary quality. In the methodology, the nursing role is crucial. In the first phase, works with the physician in order to properly asses, care and evaluate the patient. At the beginning of the surgical treatment, the nurse checks both the procedure to be preformed and the control of medication. During follow up treatment, it is essential to make use of the nurse's expertise in the magnament of chemotherapy, immunotherapy or radiotherapy and in the identification and management of potential adverse effects.
Conclusions: The involvement of the nurse in the care of patients with melanoma is crucial from the first contact of the patient throughout the process to completion. Recently, there have been major advances in the treatment of melanoma, with addition to the array of innovate drugs. These developments require that the nurse performs the necessary procedure for the proper monitoring and care patients with melanoma.
No conflict of interest.

1764 POSTER

Improving the practices of nurse leaders with systematic training

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Background: Healthcare environment is constantly changing and produces new situations with which a nurse leader must be able to cope. If we want to have in the organization changes in leadership for the better it is essential to invest in the education for effective leadership. In the Division of Nursing and Care at the Institute of Oncology Ljubljana (IOL) we were very much aware of the later so we took a systematic approach toward it. Our previous experiences thought us that models from others could not be simply transferred to our environment, and that to be successful we had to find a way that was right for us.
Material and Methods: In 2011 we started with a two year project on raising the level of nursing leadership. The overall aim of the project was to empower nurse leaders so that they would be able to facilitate the transition from a largely surveillance to leadership roles. The main focus of the training was on learning about the tools and approaches that managers can use in their work.
The project was conducted in two phases: the first phase was carried out in 2011 and the second phase in 2012–2013. The training was executed in the form of intensive interactive workshops, individual coaching, telephone and e-counseling.
Results: Training was based on the Relationship Awareness Theory and Strength Deployment Inventory® (SDI). Through this approach we got to know our profile, our strengths and excessive virtues, and delved into how this affected our approaches of management and leadership, creating relationships with co-workers and the working atmosphere in the team. We looked at the SDI profile of our leadership group and analyzed strengths and drawbacks of our team. We also created competence profile of us as leaders, and performed interactive work on our everyday examples. We learned about and tried out different management tools: conflict resolution strategy, giving feedback, motivating employees and ourselves, taking care of ourselves, what and how to delegate, how to set priorities, development of employees, and the use of a principled approach that was soft to people and hard to the problem.
Conclusions: Only well organized and managed nursing care can lead to a successful meeting of the patients needs. With a good implementation of the project, the nurse leaders gained a sense of how important the role they had as key holders was and that with their approach, activities and acting as role models they shaped the image and success of the organization.
No conflict of interest.

1765 POSTER

The impact of Breast Cancer Patient Pathway (BCPP) to patient's anxiety

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Background: The BCPP is an Internet-based patient education tool describing a flow chart of the patient pathway during the breast treatment process, from breast cancer diagnostic tests to the follow-up after treatments. The ultimate goal of this study was to evaluate the effect of the BCPP to the breast cancer patient's empowerment by using the patient pathway as a patient education tool. The essential part of empower process is knowledge. In the model of empowerment by Leino-Kilpi et al. the knowledge is the basic element to empower. As an outcome of empowering patient education patients can have less anxiety. The purpose of this study is to report the results of RCT study that evaluated the effect of BCPP to breast cancer patients' anxiety during treatment process.
Material and Methods: The BCPP program was piloted with 10 breast cancer patients. After that patients were randomised to an intervention group (n = 50) and control group (n = 48) between years 2008–2010 in South-Western health District of Finland. State of anxiety was measured at baseline, before and after surgery, before and after chemotherapy and before and after radiotherapy to indicate the effectiveness of the intervention. Anxiety was assessed with the State Anxiety Inventory (STAI).
Results: Anxiety level was highest (mean 2.53, from scale 1 to 4) at baseline in the intervention group and before surgery in the control group (means 2.41). No statistical differences were found between the groups in anxiety. However, anxiety decreased faster in the intervention group when looking at internal differences between the groups at different measurement times.
Conclusions: Based on the results we can say that the BCPP programme did not decrease anxiety level when compared to controls. However, in the intervention group anxiety level was decreasing during treatment time, while in the control group anxiety level increased before surgery and chemotherapy, and remained at same level during chemotherapy. Further research is needed to find the effect of Internet based patient education to breast cancer patient's anxiety.
No conflict of interest.

Poster Session (Sat, 28 Sep − Mon, 30 Sep)
Nursing − Other

1766 POSTER

Frozen gloves − do they work? For patients with breast cancer being treated with docetaxel

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Background: Nail changes and neuropathy are widespread problems in connection with treatment with docetaxel. 85.7% of patients experience first to second degree nail changes (second degree being the highest level of toxicity), and 51 % of patients experience first to fourth degree neuropathy (fourth degree being the highest level of toxicity). Studies have been made, that describe the extent of the problem, but only few studies have considered solutions to the problem. The biggest problem with nail changes and neuropathy occur in patients with breast cancer relapses, where long term treatment with docetaxel is frequently used. The side effect often impair the patients' daily lives, and reduce their quality of life.
Objective: To investigate whether the use of frozen gloves reduces the occurrence and degree of nail changes and neuropathy in connetion with docetaxel treatment in patient with disseminated breast cancer.
Method: 28 patients were included in the study, and they were all treated with docetaxel every third week. Frozen gloves (gel gloves, which are frozen down to −25 degree Celcius) were placed on the patients hands 15 minutes prior to docetxel infusion, during the one hour infusion, and 15 minutes after completion of the infusion. At each treatment a nurse filled out an evaluation form together with the patient. CTC-criteria were

used to evaluate the degree of side effects of nail changes and neuropathy respectively. The results are compared to an earlier study, where the focus was on the extent of the problem.

Results and conclusion:

- Nail changes are significantly reduced by using frozen gloves.
- There are fewer second degree nail changes.
- Longer time elapses before the occurrence of second degree nail changes.
- The occurrence of neuropathy seems to be delayed by the use of frozen gloves, but the effect stops after long term − i.e. 5−6 courses − docetaxel treatment.

Frozen gloves should be offered to disseminated breast cancer patients being treated with docetaxel, because they are often given many treatments and are therefore at greater risk of suffering from nail changes and neuropathy.

No conflict of interest.

1767 POSTER

Moving clinical nursing practice forward − a model developed in the Department of Oncology, Aarhus University Hospital, Denmark

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Background: In the Oncology Department Aahus University Hospital we have developed a model: 'The Umbrella Model'. Under the same theme nurses in all units are involved in development during three years.

Purpose:

- To generate new knowledge and learning strategies to develop nursing care in close collaboration with local needs and to do so in partnership with clinical nurses, nursing leaders and academic nurses.
- To support the development of nurses' competences in using research based knowledge in practice.

Purpose of the current project from 2012–2015: To generate new knowledge and nursing interventions which are practicable in future cancer care characterised by shorter contacts with patients and their relatives.

Material and Methods: Participant oriented learning and practice research, acknowledging that changes are more likely to happen if practice is able to join the research process − from producing research questions, through data collection and analysis to the information and transformation of findings into new methods in practice.

Activities during the three years: 1st year: Preparation; 2nd year: Implementation of projects; 3rd year: Completion.

Workshop days:

- All members of the organisation meet ×4/year
- Sharing processes and experiences
- Theoretical inputs

Continuously:

- Planned time of practice for working with all projects
- Concurrent supervision
- Involvement of colleagues

Termination:

- Writing up projects for publication
- Presenting at local symposia
- Implementation plan

Results: Two projects completed and published in Danish:

1. *Young people with cancer* 2005–2008.
2. *Relatives and the cancer patient's social network* 2009–2012.

Conclusions: The Umbrella Model:

– Helps to organise projects in a large organisation
– Focuses the resources spent
– Engages clinical nurses, nursing leaders and academic nurses in shared projects
– Supports development of new clinical services and interventions
– Contributes with new knowledge
– Develops the nurses' competences
– Other departments seek to implement the model

No conflict of interest.

1768 POSTER

Factors influencing HPV vaccine acceptability among young female college students in Thailand

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Objectives: To determine knowledge of Human Papillomavirus (HPV) and cervical cancer, beliefs toward HPV cervical cancer and vaccination, acceptance of the HPV vaccine, and to identify independent predictors associated with the acceptance of the HPV vaccine among young women in upper northern Thailand.

Methods: A convenience sample of young women aged 18−24 years (n = 747) recruited from universities/colleges located in upper northern Thailand. An online questionnaire was carried out to obtain demographics, HPV and cervical cancer-related health characteristics, as well as knowledge and beliefs toward HPV and cervical cancer. Logistic regression analysis was used to determine significant independent predictors of HPV vaccine acceptability.

Results: Knowledge about HPV and cervical cancer was moderate. The mean total knowledge score was 7.5±3.8. HPV vaccine acceptability was significantly associated with having received a recommendation for vaccination (OR 2.12; 95% CI 1.22–3.68), perceived susceptibility to disease (OR 1.37; 95% CI 1.22–1.52), perceived benefits of vaccination (OR 1.33; 95% CI 1.19–1.49), and perceived seriousness of disease (OR 0.90; 95% CI 0.81–1.00).

Conclusion: Understanding variables associated with HPV vaccine acceptability from this study may guide immunization initiatives in increasing the uptake rate of HPV vaccine among young women.

No conflict of interest.

1769 POSTER

Clinical nurse specialist: a key link to manage patients using targeted therapies − experience of Centre Eugene Marquis from Rennes (France)

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Background: Cancer targeted therapies are widely used, most of them are oral treatments. Their adverse events are specifics and often unfamiliar to health professionals. Their prescription requires personalized information. In this setting, a new nursing job was established in our center in 2012 complementary to the oncologist consultation.

Patients and Method: Two clinical nurses (with University Degree in Clinical Oncology) offer consultations. They also provide a 'hot line' phone and email address so that patients and their G.P. could reach them easily at office hours. They collaborate with patients' referent oncologist, attending physician, pharmacist and the whole multidisciplinary team. For very patient: (i) An initial consultation allows the nurse to recap with him terms of his treatment and how to prevent side effects. (ii) A weekly telephone appointment, during 2 to 3 months, allows to assess compliance to treatment and to remind preventive care measures. (iii) A follow-up visit, just before the medical consultation for treatment renewal, provides updates on treatment tolerance and compliance. A systematic prospective collection of side effect was initiated in July 2012 (according to NCI CTCAE-VERSION 3.0).

Results: In 2012, nurses followed 148 patients. Mean age was 63 years (21−83), women 42%, men 58%. All have advanced disease: kidney cancer (54), hepatocellular carcinoma (36), breast cancer (24) and melanoma (22).

– Targeted therapies were: sorafenib (50), sunitinib (40), everolimus (32), vemurafenib (22) and lapatinib (8).
– 444 consultations were done, 91 initial consultations and 353 follow-up consultations. They had 1474 phone calls 81.3% of pre-planned calls and 18.7% of calls initiated by the patients
– Among 118 patients followed, 21% presented G3−4 toxicity: asthenia (8.2%), hand–foot syndrome (3.3%), pain (2.2%), diarrhea (2.2%), nausea (2.2%), rash (1.1%), dyspnea (1.1%), hypertension (0.55%), 7 patients (3.8%) were hospitalized because of severe toxicity.

Conclusion: The development of this new activity in our center is relevant. It allows a better follow up of patients, better observance, better knowledge of the treatment by health care professionals.

Despite regular monitoring, some preventive measures remain difficult to adopt by the patients. Therapeutic education seems to hold its full meaning here. The impact of clinical nurse intervention on treatment efficacy and cost effectiveness should be assessed.

No conflict of interest.

1770 POSTER

Oncology nurses' caring behaviours in Hellas

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Background: Caring is an elusive concept, that encompasses a range of behaviours. Perceptions and expressions of caring behaviours are context dependent. The life threatening character of cancer and the far-reaching consequences of the medical treatments make cancer nursing very demanding. Nursing behaviours recognized as caring remain a challenging issue for oncology nurses.
Aim of the study: To identify caring behaviors as perceived by nurses working in cancer care in Hellas.
Method: Methodological triangulation applied separately, by regarding both quantitative and qualitative methods as equally valuable. At first, a descriptive, quantitative study consisted by a convenience sample of 72 nurses, from three oncology centres in Attica area. Data were collected using the validated in Greek language Caring Behaviour Inventory (CBI) consisted of 24 items scored in a six point Likert scale.CBI-24 has four subscales: F1 Assurance of human presence, F2 Knowledge and skill, F3 Respectful deference to others, and F4 Positive connectedness. Collected data were analyzed using SPSS software version 17.0. Level of statistical significance was set at $p < 0.05$.
The second phase was a qualitative descriptive study. A purposive sample of 18 oncology nurses participated in three focus groups. Researchers triangulation was used to analyze the data. Through careful data preparation, coding, and interpretation trustworthiness of the study was achieved.
Results: Subscale F2: knowledge and skill was perceived as the most important (5 ± 0.7) followed by F1 Assurance of human presence (4.8 ± 0.7), F3 Respectful deference to others (4.5 ± 0.8), and F4 Positive connectedness (4.3 ± 0.9). Deductive Content analysis emerged the following categories: Caring as a value, Respect for the person, Creating a therapeutic relationship, being empathetic, communication and information support, the fear of cancer and perception of their role as oncology nurse.
Conclusion: Research into care is possible using quantitative methodology, but qualitative data provide a rich source of individual detail into what care is. As quantitave data has shown oncology nurses value most highly technical skills, however qualitative data shows a plethora of information concerning nurses perceptions of the humanistic and emotional aspects of care. In addition personal beliefs for their role tends to influence their caring behaviors.
No conflict of interest.

1771 POSTER

Peripheral venous catheter-associated complications of patients with solid tumours in a general and oncological hospital in Greece

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Background: Several studies suggest that the peripheral venous catheter (PVC)-associated complications are the most common adverse events affecting cancer patients. A prospective study was carried out to investigate the incidence of PVC-associated complications in patients with solid tumours at General and Oncological Hospital of Kifissia 'Oi Agioi Anargiroi' in Athens, Greece from October 2012 to November 2012.
Material and Methods: Peripheral venous catheter-associated complications were grouped as phlebitis, infiltration and extravasation. The definitions of PVC-associated complications were in accordance with the Infusion Nurses Society and Oncology Nursing Society criteria. Neutropenia and anaemia were defined by the National Cancer Institute, Common Toxicity Criteria.
Results: During the study period 14 of 134 patients developed 14 complications (10.4%). The mean age of patients was 63.60 ± 13.16 (range 18−85) years. There were 91 males (67.9%). The most common underlying malignancy was lung cancer in 36 patients (26.9%) followed by colorectal in 25 (18.7%), head and neck in 17 (12.7%) and urinary tract in 16 (11.9%). Recent chemotherapy had been administered in 88 patients (65.8%) and neutropenia was present in 32 patients (23.9%), being grade 4 in 2 of 14 episodes (14.2%). Anaemia stage 4 was present in 1of 14 episodes. The Phlebitis incidence was 7.5% (5 phlebitis grade1; 50% and 5 phlebitis grade 2; 50%), the infiltration incidence was 1.5%, infiltration grade 2 in all episodes (100%) and the extravasation incidence was 1.5%, extravasation grade 4 of infiltration scale in all episodes (100%). Crude mortality in patients with and without complications was 35.7% and 22.5% ($p = 0.280$), respectively. There was significant difference in length of stay between patients with and without complications (9.79 ± 8.28 vs 3.08 ± 3.6% days, $P = 0.001$).
Conclusions: Early identification of the first signs and symptoms and the strict adherence with peripheral vascular catheter care bundle are critical for improving safety and quality of care in patients with solid tumours.
No conflict of interest.

1772 POSTER

Surveillance of infections in patients with solid tumours at a general and oncological hospital in Greece

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Background: Cancer patients are at an increased risk of infections, since a weakened immune system during chemotherapy treatments increase susceptibility to infections and can result in hospitalizations and even death. The aim of this study was to investigate the incidence of infections in patients with solid tumours at General and Oncological Hospital of Kifissia 'Oi Agioi Anargyroi' in Athens, Greece from October 2012 to November 2012.
Material and Methods: A standardized survey record form has been used, according to the Healthcare Associated Infections (HAIs) definitions provided by the CDC's National Healthcare Safety Network (NHSN). HAI was defined as the episode developing at the time of hospital admission if the patient had been hospitalized during the preceding 30 days.
Results: During 789 patient-days, 12 out of 163 patients acquired 20 infections (7.4%) or 15.2 infections per 1,000 patient-days. The mean age of patients was 62.43 ± 10.79 (range 30−84) years. There were 104 males (63.8%). The most common underlying malignancy was colorectal cancer (33.7%), followed by head and neck (15.9%) and lung (9.8%). Ten out of 20 infections (50%) were healthcare-associated and 10 (50%) hospital acquired. The incidence rate of wound infection was (5.2%), for urinary tract infections was 3.7%, for bloodstream infection was 2.45% and pneumonia 0.6%. Crude mortality in patients with and without infections was 25,% and 6% ($p = 0.015$), respectively. Furthermore, there was significant difference in length of stay between patients with and without complications (14.42 ± 813.7 vs 4.11 ± 5.57% days, $P = 0.001$). Gram-negative bacteria were isolated in 16 (80 %), with E coli (7 out of 16; 43.7%) and klebsiella pneumonia (41;25%) being the most frequent. Gram-positiveorganisms were isolated in 4 episodes (20%) with St aureus being the most common (50%).
Conclusions: Infections in patients with solid tumours increase the duration of hospitalization and the mortality. Early diagnosis and the early intervention with emphasis to adherence with hand hygiene are optimal for preventing life-threatening infections.
No conflict of interest.

1773 POSTER

Burnout in health caregivers: Experience of a Moroccan anti cancer center

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Background: The burnout syndrome or the Professional exhaustion syndrome has become the topic of the day in the world. The burnout can be defined as an emotional exhaustion, a depersonalization of the relations with others, and a decrease in the personal accomplishment.
The aim of this work is to assess the prevalence of burnout syndrome among medical and paramedical staff in the center of hematology-oncology at the University Hospital Mohammed VI Marrakech.
Patients and Methods: A self-administered questionnaire was distributed to 43 persons in the center of hematology and oncology, including Maslach burnout inventory (MBI), sociodemographic and professional features.
Results: Forty three questionnary was correctely completed. The staff participation was: 23.25% physicians and 76.75% nurses. Average age was 27.62 years (23 years − 35 years). According to the criteria of the MBI: about half of the affected professionals had a high level of emotional distress, 30% had a high level of depersonalization and 25% had a low

level of professional fulfillment. The analysis showed that age did not affect the occurrence of burnout. The female is a protective factor of depersonalization, leisure and sporting activities decreased significantly increasing emotional exhaustion and personal accomplishment. Our results corroborate partially with those of the literature and illustrate some parameters that can be the cause of burnout, such as working conditions, role ambiguity, and lack of expérience among the new staff. We also have some heterogeneous conclusion according to literature, this can be explained by various reasons: the average age of the population, workload, socio religious and quality of life.
Conclusion: Any person engaged daily in a helping relationship with others and subjected to chronic stress may one day be achieved from a burnout staff and caregivers should be informed by disseminating information programs to prevent this scourge.
No conflict of interest.

1774 POSTER

Cultural adaptation and validation of spiritual distress scale

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Objective: To adapt and validate the Spiritual Distress Scale for Brazilian culture.
Methodology: A methodological study conducted in 2012, with 150 cancer patients treated in a general hospital. The Spiritual Distress Scale, created in Taiwan, consists of 30 items divided into four domains (individual's relationship with himself, with others, with God and facing death). His response options are presented on a Likert scale of six points. The sum of the items may vary from 30 to 180 points, so that higher values indicate higher level of spiritual distress. The process of cultural adaptation of the scale has the following steps: translation (English-Portuguese) and reverse translation (Portuguese-English), review by committee of judges, cultural equivalence assessment and pre-test. To construct validity divergent applied to Scale Spiritual Well-Being, considered the gold standard in this type of validity. For statistical analysis we used the kappa coefficient, the Cronbach's alpha coefficient and Spearman correlation. Analyses were performed in the application Statistical Package for Social Sciences (SPSS).
Results: Among the items on the scale only 4 had difficulty understanding by patients in the evaluation phase of cultural equivalence, which were modified after review by a panel of judges. The intra-and inter analyzes were satisfactory, since 60% of the items presented kappa coefficient above 0.75. We observed satisfactory internal consistency with a Cronbach's alpha of 0.87. Correlation analysis between the scales has revealed an inverse correlation ($r = -0.468$, $p < 0.001$) there between.
Conclusion: This study has been able to adapt and validate the Spiritual Distress Scale, an instrument capable of identifying the presence of the phenomenon that purports to measure (spiritual distress), as demonstrated validity and reliability.
No conflict of interest.

1775 POSTER

Why bothering? Experience-based co-design makes 1 + 1 = 3

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Background: For continuous improvement of the service level in hospital care, we use many methods to get feedback from patients. But next, in the requested actions for improvement, the patient is often neglected. In a Dutch teaching hospital we started a project based on EBCD ("experience-based co-design"), developed by the King's Fund/National Health Service, United Kingdom.
Method: EBCD focuses primary on experiences and emotions instead of opinions and views. EBCD involves gathering experiences from patients and staff through in/depth interviewing, observations and group dicussions; identifying key 'touch points' (emotionally significant points) and assigning positive or negative feelings. In an impactful series of photos the service to patients is made perceptible. Staff and patients together identify areas for redesign, and work together to make improvements to the service and to the pathway of care.
Participating patients: Hemato-oncologic patients chronically treated with (immuno-)chemotherapy.
Workingplan: 4 groups were formed (patients; sounding board group and focus group, caregivers and external observators). These 4 groups selected the most important and urgent actions of improvement, based on the jointed experiences. Next 4 newly mixed co-design groups tackled the chosen issues. The patient sounding board group monitored the progression and the results of the actions taken.
Results: With 4 co-design groups, we worked on; (a) a better information regarding visiting the dentist before and during treatment, (b) better communication between family doctor an specialist/hospital, (c) guidance of waiting time during visits, (d) a more pleasant atmosphere and ambience on the out patient department and short stay unit.
Conclusions: The EBCD method offered an effective tool to work on the service level as experienced by our hematology-oncology patients and caregivers together. In a stimulating and valuable cooperation important results have been achieved. Moreover, EBCD offers the opportunity to verify with patients that actions performed indeed succed in improving patients experiences.
No conflict of interest.

1776 POSTER

The effectiveness of integrating oncosexology into cancer care: Changes in attitudes and practices of healthcare professionals

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Background: Sexuality problems are experienced by 40–100% of cancer patients but healthcare professionals rarely address these issues. In 2012 a two year project was completed integrating oncosexology by training professionals in communication about sexuality issues. The purpose of the study was to evaluate the effectiveness of the intervention by assessing the attitudes and practices of nurses and physicians towards cancer-related sexual health issues.
Material and Methods: The intervention included two workshops for 40 key-staff members from 10 units in one hospital, staff-educational meetings, staff-pocket guides, patient education material, a web-site on sexuality and cancer, and services of a sexuality counselor. A questionnaire assessing common practices, attitudes, and possible barriers to discussing sexuality-related issues in daily work (Hautamäki etal, 2007) was mailed electronically to all nurses and physicians working in medical, surgical, and gynecological oncology, pre-intervention (T1, $N = 206$), after 11 months (T2, $N = 216$), and after 17 months (T3, $N = 210$).
Results: The response rate was 66% at T1, 45% at T2 and 38% at T3. No differences were found between the three time points with regard to background variables. At all time points the majority regarded discussions on sexuality-related issues with patients as a part of their job. Scores on having enough knowledge and training increased both significantly ($p < 0.05$) over time, more for those who attended the workshops. Significant improvements were reported in six of eight practice issues and more by those who attended the training ($p < 0.05$). A total of 10−16% reported discussing sexuality-related issues with more than 50% of patients and the prevalence was higher among trainees (19%) than non-trainees (9%) ($p < 0.001$). The main barriers for discussing sexual issues were lack of time (40%) and privacy (27%) among those who attended the workshops, but lack of training (30%) and not important to discuss (30%) were reported by those who did not attend the training.
Conclusions: The results indicate improvements in both knowledge and practices, but probably for a minority of patients.
No conflict of interest.

1777 POSTER

Determining communication skills and empowerment perceptions of pediatric oncology nurses

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Background: Cancer and cancer treatment is a challenging situation for children and their families. For this reason, commutation is especially

important in pediatric oncology nursing. Empowerment of nurses in communication and interaction affects the quality of care in the patients.
Material and Methods: This descriptive study was conducted to determine the communication skills and empowerment perceptions of nurses in a pediatric hematology-oncology hospital, Ankara, Turkey in 2012. Totally 55 pediatric oncology staff nurses worked in the hospital and 48 nurses accepted to participate in the study. Data were collected with a descriptive form for nurses, empowerment perception scale (EPS) (min-max score=0−60) with the four dimensions of empowerment related to meaningful work, competence, self-determination and impact. Communication skills asessment scale (CSAS) scores between 45–225. High points in both scales indicate well perception and good communication skills. Data were analyzed by Pearson test.
Results: Nurses' mean age was 29.06±4.1 and their mean working year as a pediatric oncology nurse was 2.22±1.98. Most of them were women (89.6%). Mean total EPS score was 47.0±5.4. When dimensions of EPS analyzed, meaningful work scores mean was 14.00±1.22; competence scores mean was 12.27±1.84, self determination mean was 11.04±2.03 and impact scores mean was 9.68±2.20.
Mean CSES score was found 185.7±14.7. Low- moderate correlation was found statistically significant between scales of EPS and CSES. ($r = 0.382$, $p = 0.007$). Moderate correlation was found statistically significant between scales of meaningful work ($r = 0.441$, $p = 0.007$), competence($r = 0.336$, $p = 0.01$) and impact ($r = 0.334$, $p = 0.02$) with CSES.
Conclusion: According to the results of the study, it has found that nurses had good communication skills and have positive empowerment perception. Nurses feel mostly empowerment in the meaning of the work and feel less in being able to influence major decisions in an organization. If they have good communication skills, they feel empowerment in meaning of work and reflect confidence in one's ability to perform a job well, and being able to influence major decisions in an organization.
No conflict of interest.

1778 POSTER

How the pluridisciplinary team take care of melanoma: Evaluation, analyse and benefits

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Context: The oncological context in which we are has evolved and is constantly changing. More and more patients with specific expectations have longer and more complex treatments that are supported by different professional teams with various more or less impacts.
Pioneer regarding multidisciplinary consultations at the cancer center of Cliniques Universitaires Saint-Luc, and concerned to improve the quality of the taking care for its patients, the melanoma clinic wanted to know its patients' opinion.
Objectives: Benefits of the multidisciplinary consultation and evaluation of information tools created.
We created a questionnaire for patients suffering from a melanoma stage 1b needing a sentinel lymph node search. Those patients have seen a dermatologist, an oncologist, a plastic surgeon and a coordinating care nurse during consultations. We were also willing to evaluate the communication tools given to the patients: personalised care planning, treatment monitoring and explanatory brochures.
Finally we wanted to know the consistency of our information.
- Qualitative evaluation concerned each contributor and each tool used.
- The study allowed us to find the patient's entrance, to highlight the relevance of each contributor and for the very first time the role of the coordinating care nurse
- The coordinating nurse gave the questionnaire to 80 patients for a period of 3 months.

Results: The multidisciplinary consultation presents a real advantage for the patients and their family, this kind of consultation reassures them and allows them to feel better supported.
The communication tools are a great help for the patients and help them to feel themselves actors of their own treatment.
This study showed us that 91% of the patients or their family kept in touch with the coordinating care nurse and that this contact was very helpful for them.
Conclusion: That kind of consultation energizes the care team; each one has his own place in such a transversal and multidisciplinary organization to the patient's benefit.
Moreover, it allows a better internal coordination and saves time.
Those results confirm us the real benefit of a multidisciplinary consultation as well as the communication tools put at the patient's service.
The patient's clinical itinerary is clarified.
The study illustrates the complementarity of each contributor.
The profession of the coordinating care nurse in oncology appears to be primordial and shows us how much that person is the privileged one.
No conflict of interest.

1779 POSTER

Sense of coherence − a measurement of successful coping remains stable during the first year after breast cancer surgery

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Background: Some women with breast cancer have symptoms attributed to treatment which affects quality of life. Sense of Coherence (SOC) can be measured by a health-related quality of life questionnaire with 13 items that reflect the individual's ability to manage difficulties according to the salutogenesis theory model by Antonovsky. High scoring levels of SOC indicate a better coping strategy to the illness. Preliminary results have shown that SOC was stable over time in a subsample of breast cancer patients. The purpose of the study was to evaluate SOC for stability over time in a large multicenter cohort of women that underwent breast cancer surgery.
Material and Methods: At four Swedish hospitals 567 women were included between 1999–2004 and 417 (74%) completed the SOC questionnaires preoperatively and one year postoperatively. The reliability was tested using Cronbach's alpha reliability coefficient. The intra class correlation (ICC) was measured to evaluate the correlation between SOC pre- and postoperatively. Cohen's effect size was calculated to evaluate the magnitude of mean differences of SOC.
Results: SOC scores did not change during the first yearly assessment, neither individually nor on group level. The internal consistency was adequate. Cronbach's alpha was at T 1 0.816 and at T 2 0.841. The ICC between SOC preoperative and one year postoperative was 0.68 ($p < 0.001$). Cohen's effect size was 0.06 indicating a minimal change over time. The surgical and adjuvant treatment did not affect SOC levels.
Conclusions: This longitudinal prospective study shows that SOC is stable the first 12 months after breast cancer surgery.
No conflict of interest.

1780 POSTER

Use of internet to access health-related information: Perspectives from patients with cancer and other chronic diseases, their relatives and nurses

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Background: Internet is used commonly in the world as a powerful communication and information resource. As indicated in the literature, individuals have used internet to get information about their or loved ones' health problems. Especially patient with cancer and other chronic diseases may seek more information due to complexity of the treatment regimens and disease trajectory. It is as simple as to touch a few keys to access the desired information on the internet; however it can be quite difficult to reach accurate, up to date, evidence-based information. Patients and their relatives can easily get confused and this may influence their compliance. Since increased use of internet and availability of the information resources, nurses need to assess whether patients and their relatives seeking information on the internet and provide evidence-based and reliable information resources. We aimed to investigate opinions and experiences towards internet usage for access to health related information from the perspectives of the patient with cancer and other chronic diseases, their relatives and nurses who caring for them.
Material and Methods: This descriptive study is conducted in medical departments and oncology clinics in a University Hospital located in Ankara, Turkey. Following the pilot study, the sample has been calculated as 216 patients and 216 relatives; besides all nurses working in these departments were included. The data has been collected with questionnaires for patients, their relatives and nurses which were developed by the researchers based on the literature. Independent variables of this study include socio-demographic characteristics, disease duration, having

internet access and skills; dependent variables are mean duration of internet usage, the opinions about reliability of the resources and use of internet.
Results: Until now, we have reached 35 cancer patients and their relatives; 40 patients with other chronic diseases and 71 nurses. The study is continued and data will be analysed with descriptive statistics and chi-square tests in SPSS 17.0 program.
Conclusions: This study will contribute to raising awareness about internet usage among patients and their relatives, and provide insights to nurses about current practices. Results from this study will also guide to develop web based educational resources.
No conflict of interest.

Poster Session (Sat, 28 Sep − Mon, 30 Sep)
Nursing − Supportive and Palliative Care

1781 POSTER

Patients attitudes towards follow up

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Background: The increasing of long survivor's patients (pts) is creating some planning and economical difficulties in Oncology Departments.'Who' and 'how' manage follow-up (FU) is an open discussion, but pts preferences are rarely taken into consideration. With this aim, we started our study.
Material and Methods: We investigated pts feelings before check up, main worries and fears, meaning given to the FU, their relationship with the oncologist and the level of satisfaction about FU procedures. From February 2012 to March 2013, 450 pts in FU (63.3% female; average age 62 -range 34−85; prevailing pathologies: 46.2% gastrointestinal, 42.6% breast) were interviewed using an anonymous structured questionnaire, before the visit with the oncologist.
Pts were divided into three groups, regarding the number of years of their check up: a) less than 5 years (53.5%) b) between 5 and 10 years (33.6%) c) more than 10 years (12.8%).
Results: 62.2% pts feel trust and serenity, 21% feel anxiety and 15% fear and worry. Prevailing worries are linked to disease recurrence (44.9%), 15.3% about surgery and 9.8% chemotherapy. A high percentage is not worried (29.8%).
Most important clinical meanings given to FU are: evaluation of health situation(37.8%) and early detection of disease's relapse (22.4%); 25.5% of pts gives FU a psychological meaning (44% from groups b and c): mantain the relationship with the oncologist and reassure themself. This aspect is confirmed by the choice to consider the oncologist as reference point for every health problems from more than 74% pts of the c group. 72% pts are satisfied about FU procedures, 9.8% would prefer to undergo fewer examinations and 11.6% ask for more meetings with the oncologist.
Conclusions: Our data suggest a deep relationship between pts and oncologist, but also pts' fear to be abandoned. The necessity to move FU to different clinical professionists (pratictioner or trained nurses) should pass throught a strong cohoperations of this figures since the first taking care of pts so to create the feeling of a multidisciplinary equipe.
No conflict of interest.

1782 POSTER

The introduction of an art-therapy program for oncological patients at the Oncology Institute of Southern Switzerland: A pilot study

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Background: Several studies confirm that art-therapy can give a better psychophysical well-being to patient suffering from different pathologies, oncological patients included.
The various ways of communication of art-therapy (such as drawing, painting, music) stir the creative abilities that every person has and that keeps existing even during difficult and apparently unmanageable moments. In Autumn 2010, it was decided to start a similar program at the Oncology Institute of Southern Switzerland (IOSI), addressed to in-patients and to consider its effects.
Material and Methods: In order to consider the acceptability and the possible benefits expressed by patients, a pilot study was realized from May 23rd until December 18th 2011 with all the new patients in care for more than five days at IOSI. Two questionnaires were created: one given to all new patients in hospital during that period and the other given only to patients that had participated at least at one art-therapy session. A thematic analysis of the drawings had then been made by an art-therapist.
Results: On a sample of 315 patients (481 admissions), 168 had a stay longer than five days and 51 answered the first questionnaire (30.4%). Some of them (28 out of 51) didn't take part in the art-therapy sessions because of different reasons (they didn't like drawing, they thought it was not useful for them, they didn't have time, etc). 23 patients out of 168 participated in art-therapy and the most were women (17), with an average age of 61.4 (range 24−90). The reasons why they took sessions of art-therapy were curiosity (7), to express moods (6) and/or to feel better (6). Practicing art-therapy gave them peace and quiet (6), helped them in communication and relationship with relatives (7) and/or gave them a sense of release (5). All of them would have done it again and some would have kept doing it (13), especially at home (9).
Conclusions: Participants have considered useful art-therapy sessions, because they helped them feeling personally better. The small number of attendances is probably due to context characteristics, both organizational (several admissions of short duration) and cultural (approximate knowledge and patients not used to these kinds of expressive forms).
With the future mind, this projects seems to be indicated only to limited targets of patients, with a long stay in hospital. Due to the study limits, the program wasn't continued after the patients discharge from hospital, despite some wishes expressed.
No conflict of interest.

1783 POSTER

Highly frequent and serious cases of injection site reaction induced by peripheral venous injection of fosaprepitant in anthracycline-treated patients

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Background: Fosaprepitant-associated injection site reaction (ISR) was evaluated in some patients treated with an irritant drug such as cisplatin. Anthracyclines are vesicant drugs that cause severe surrounding tissue damage and necrosis by extravasation. Although little is known about this effect in patients treated with vesicant drugs such as anthracyclines. Therefore, We conducted this retrospective study to clarify the incidence and symptoms of fosaprepitant-associated ISR in patients treated with anthracycline.
Patients and Methods: Incidence and symptoms of ISR were compared between 24 patients with 61 injections of fosaprepitant through peripheral vein (fosaprepitant group) and 40 patients with 98 injections without fosaprepitant (historical control group) before undergoing FEC, AC or (R-)CHOP regimen. We also compared between 16 patients with 28 injections with fosaprepitant and 15 patients with 31 injections of without fosaprepitant before undergoing non-anthracycline regimens such as those containing cisplatin or carboplatin.
Results: There were no statistically significant differences between the fosaprepitant and the historical control groups with regard to background clinical variables (gender, age, BMI, number of prior chemotherapy regimen, chemotherapy regimen used in the present study, and injection site). Both ISR incidence rates per patient and per injection were significantly higher in the fosaprepitant group than in the historical control group (67% *vs.* 15%; *P<0.0001,* 34% *vs.* 8.2%; *P<0.0001*, respectively). By multivariate analysis, fosaprepitant injection was found to be a significant independent variable correlated with ISR risk. Symptoms of ISR observed in 61 injections of fosaprepitant were pain in 14 (23%), redness in 10 (16%), swelling in 6 (10%), and decreased infusion rate in 6 (10%). After an observation period, no ISR occurred when the administration route was changed to central venous injection or oral aprepitant despite continuation of chemotherapy. In the non-anthracycline regimen group, both ISR incidence rates per patient and per injection were no significant differences between the fosaprepitant group and the without fosaprepitant group (31.3% *vs.* 13.3%; *P = 0.3944,* 17.9% *vs.* 6.5%; *P = 0.2398*, respectively).
Conclusion: ISR was induced at high frequency and seriously when fosaprepitant was injected through peripheral vein in patients who received anthracycline. Accordingly, peripheral vein injection of fosaprepitant should be avoided in patients receiving anthracycline-containing chemotherapy.
No conflict of interest.

1784 POSTER

Manual nutrition in cancer

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Background: In order to give the best nutritional care to cancer patients, dietetic counselling should be based on scientific evidence and best practice. It is important that dieticians, doctors and nurses not only have practical nutritional knowledge of cancer in general, but also have tumour-specific nutritional knowledge and are able to cope with problems that could develop during the different stages and treatment of cancer. Therefore we have developed the Manual for Nutrition in Cancer.
Methods: Thirty-two experienced Dutch dieticians, specialized in oncology, were invited to write a chapter about their field of expertise (expert opinion). To guarantee best evidence, results from the systematic literature search performed for the evidence based Dutch guideline 'Malnutrition in cancer patients' were incorporated and some additional literature searches were executed. The guidelines within the manual have also been approved by the Dutch Dieticians Oncology Group in cooperation with the Surgical Association Dieticians Academic Hospitals and the Dutch Dieticians Haematology and Stem Cell Transplants Group.
Results: The first part of the Manual deals with the role of nutrition during cancer treatment in general. Specific attention is given to (screening for) malnutrition, sarcopenia, energy and nutrient requirements, nutritional complaints and dietetic counselling, clinical nutrition, comorbidity, cancer in the elderly, paediatric oncology, nutritional targets in the period of rehabilitation and in the palliative stage of the disease. The second part of the Manual includes the nutritional problems commonly occurring in 20 tumour types together with the corresponding nutritional advices.
Conclusion: Nutritional care is an important task for dieticians, doctors and nurses. These multidisciplinary guidelines combined in a manual and as a digital guide (www.oncoline.nl) are a very practical tool for all caregivers in the treatment of cancer patients.
No conflict of interest.

1785 POSTER

Recommendation of areas of expertise for nurses in palliative care, at an under-graduate and post-graduate level development of a curriculum, entitled 'Competences for Nurses in Palliative Care' in Denmark

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Background: Surveys carried out by the Danish Knowledge Center for Palliative Care (PAVI) confirm a large variation in education standards in palliative care and medicine in nursing training across Denmark.
Objective: To ensure that palliative patients have equal access to high quality care the Danish Multi-Disciplinary Cancer Group for Palliative Care (DMCG-PAL) prepared a standarised curriculum in order to provide opportunities for nurses to obtain and develop a standardised set of skills in palliative care.
Design and setting: The standardised curriculum of required skills were created, based on a range of national and international palliative care training curricula. The CanMEDS 7-Roles Framework has been adapted to the nursing profession. The required skills have been separated into 4 domains − empirical, ethical, personal and psychosocial. The learning outcomes (knowledge, skills and attitudes) were specified in three levels, in order to show the progression from undergraduate-to postgraduate level of nursing training. The suggested standardised curriculum has been circulated amongst the clinical and educational professional groups in Denmark.
Main outcome measures: The standardised curriculum provides a framework for current and future training of nurses in palliative care and creates a foundation for development and evaluation of professional skills.
Results: 'National Recommendations of Competences for Nurses in Palliative Care' was compiled and published in 2012 with financial support from the Danish Nursing Organisation.
Conclusion: Nursing training in Denmark has been offered a standardised curriculum of required skills in palliative care.
Acknowledgements: The authors are grateful to the Danish Nursing Organisation for their financial support
No conflict of interest.

1786 POSTER

Developing oncology nursing role in palliative care in Serbia

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Palliative care is a relatively new specialty that focuses on promoting the best possible quality of life for patients and family members facing serious, life-threatening illness, through optimal management of physical, psychosocial, emotional and spiritual symptoms. This specialty grew out of the hospice movement and is continuing to evolve as more palliative care teams are integrated into health care systems, more palliative care content is taught in schools of medicine and nursing, and more research is conducted to support an evidence base for palliative interventions. Palliative care of cancer patients is directed to improving quality of life for patients and family members through optimal management of cancer symptoms and complications, adverse effects of its treatment as well as psychosocial, emotional and spiritual problems. Modern oncology advocates the integration of palliative care into specific oncology approach from the time of the cancer diagnosis and continued throughout the course of the illness, across all levels of care and care settings, including inpatients units, ambulatory care clinics, intensive care units, emergency departments, home care, nursing homes, hospices. Nevertheless, comprehensive palliative care of cancer patients requires interdisciplinary approach − the expertise of medicine − oncology, oncology nursing, social work, psychology, counseling, nutrition, special education and rehabilitation, pharmacy, therapists and other health team professionals, to meet the multidimensional needs of patients and their families who are facing serious, life-threatening illnesses. Oncology nursing is the core discipline of palliative care of cancer patients and includes three key elements − working directly with patients and families, working with other health and social care professionals to network and co-ordinate services, and working at an organizational level to plan, develop and manage service provision in local, regional and national settings. Oncology nurse, as a member of palliative care team, must have both basic and very specific knowledge and clinical skills in palliative care in order to be able to meet the needs of patients with chronic and advanced disease improving quality of life for patients and families throughout the experience of illness. Integration of palliative care into the health-care system of the Republic of Serbia is ongoing process and nurses have an important role in supporting that process. Strategy for palliative care (2009–2015) is adopted in accordance with the recommendations from the WHO and Council of Europe, Committee of Ministers 'REC 24 (2003)' regarding organization of palliative care. Palliative care is also included into the National Program "Serbia against Cancer".
No conflict of interest.

1787 POSTER

Unmet supportive care needs in lung and breast cancer: differences by tumour site and by clinical pathways

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Background: Supportive care needs assessment aims to identify individuals and subgroups of oncology patients with high levels of unmet needs. This allows targeting appropriate interventions as well as screening and prioritizing specific needs. To date, little is known about differences in supportive care needs of patients with different tumour sites and clinical pathways. Our aim was to explore potential differences in unmet supportive care needs between two of the most common cancers, namely lung and breast cancer.
Material and Methods: This abstract reports a secondary analysis of data collected in two descriptive studies. Both studies recruited a convenience sample of patients in the oncological department of a University Hospital in Switzerland during the chemotherapy phase. Both studies focused on lung (n = 37) or breast (n = 33) cancer patients during the early treatment phase. Unmet needs were measured with the Supportive Care Needs Survey Short Form 34 with 34 items categorised in five domains (psychological, health system and information, physical and daily living, patient care and support, and sexuality needs), measured on a 5-point Likert scale (no need, not applicable=1; satisfied=2; low need=3; moderate need=4; high need=5). The differences between breast and lung cancer patients were tested with Wilcoxon test for the dimensions and with Chi-square test for each dichotomized item (1−2=no need; 3−4−5=need).
Results: Lung cancer patients expressed significantly higher unmet supportive care needs than breast cancer patients on 18 out of 34 items, mostly pertaining to the health system and information ($p = 0.0009$),

psychological (p = 0.0015) and patient care and support (p = 0.0055) domains. Comparing the institution care pathways, breast cancer patients were typically followed in a standardized pathway by a multidisciplinary team (MDTs) composed of specialist physicians and a breast care nurse, while lung cancer patients received unstandardized specialized care without specialised nursing care.
Conclusions: The differences in unmet supportive care needs found in this study could be explained by the differences in tumour site, prognosis and treatment, but also by the differences in clinical pathways. More research is necessary in order to understand the respective role of these factors. Further intervention studies should test whether the counselling by specialized nurses may help reducing unmet supportive care needs.
No conflict of interest.

Poster Session (Sat, 28 Sep − Mon, 30 Sep)
Nursing − Survivorship and Rehabilitation

1788 POSTER

Implementing a national agenda to achieve person-centered care: the need for multiple strategies

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Background: Evidence from patient satisfaction surveys, needs assessments, and stakeholder forums provide a clear picture that cancer patients are not receiving the full range of supportive care services that could be of benefit to them. The cancer system needs to undergo a shift toward person-centered care. Such a cultural shift requires concerted effort and multiple strategies to be successful.
Objective: The purpose of the Cancer Journey Action Group of the Canadian Partnership Against Cancer is to provide leadership to achieve person-centered care in the Canadian cancer care system.
Methods: The Cancer Journey Action Group has developed and implemented several initiatives to demonstrate how person-centered care can be achieved. The initiatives include programs in screening for distress (6^{th} vital sign), patient navigation, on-line support groups, survivorship care plans projects, cancer transition education, and palliative care/end-of-life education. Tools to support this work have been designed including evidence-based practice guidelines, algorithms, and on-line education modules. Evaluation has focused on program uptake, educational effectiveness, inter-professional teamwork and patient satisfaction.
Results: All initiatives have been evaluated by patients/survivors as helpful. Issues of importance to patients/survivors are the focus of conversations with, and assessments by, health care professionals. Critical success factors across the respective programs for achieving person-centered care include clarity of a shared vision, leadership, persistent and concerted effort, and consistent messaging in communications.
Conclusions: Demonstration projects undertaken for each topic area have provided an excellent opportunity to learn about best practices to implement the respective approaches. Guiding principles for implementation and relevant tools/resources have been developed as a result. Although progress toward person-centered care is evident, intentional and concerted efforts are necessary to sustain momentum of these efforts in routine clinical practice.
No conflict of interest.

1789 POSTER

A survivorship screening tool to help identify cancer survivors' needs

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Background: There are more than 12 million cancer survivors in the United States and they comprise at least 4% of the U.S. population. Cancer survivors report more mental health needs and greater psychological distress compared to the general population, yet many oncologists underestimate distress in their patients' lives and fail to link them to appropriate services when needs are identified. Roswell Park Cancer Institute developed a Survivorship Screening Tool (SST) to identify a cancer survivor's psychosocial, rehabilitative and nutritional concerns.
Methods: The SST was developed by a multidisciplinary team across a range of supportive services, and includes empirically-validated and clinically-relevant questions. Questions are answered using a Likert-type scale, with 0 = No problem and 4 = Severe problem. Two questions elicited feedback regarding the clarity of the instructions and questions, as well as three open-ended questions for patients to share areas that were not addressed, length of time to fill out the measure, and any additional comments. Cutoffs for clinical interventions were developed by each discipline based on research literature.
Results: The SST was piloted in the outpatient Bone Marrow Transplantation Annual Clinic. One hundred and five patients at least 1 year post-transplant were assessed with the SST over a 9-month period. Sixty percent of patients reached the threshold for clinical intervention in at least one area, with 60% of consults triggered for psychosocial oncology. 33% declined consults. Primary concerns identified to trigger clinical intervention included: worry about the future, fatigue, finances, managing work/school/home life, and sexuality/intimacy. Subscales were created to examine concerns related to Physical, Emotional, Practical, and ADL issues. Of note, many patients identified 3+ concerns in each of these areas. The majority of patients (80%) reported <5 minutes to complete the SST and 97% felt that the SST addressed their concerns.
Conclusions: The SST helps identify a cancer survivor's issues. Furthermore, it may allow more efficient use of the patient visit time and will add to the growing literature examining how best to measure and intervene in cancer survivorship.
No conflict of interest.

1790 POSTER

Education − integral part of adult tumour of young adolescents services?

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Introduction: A patient survey done [CLIC Sargent, (2008), More Than My Illness: Delivering Quality Care for Children with Cancer] among 119 young people with cancer and 91 carers showed that 64% of 16−18 year olds fell behind with studies or did not do as well as they thought they could have, 29% had to leave education and 65% said it was important to get education and training support. Children with cancer rated disruption to education as the second most devastating impact of cancer on them after physical heath [CLIC Sargent (2010), The impact of cancer on a child's world]. Approximately 75% of young people unemployed for more than six months have GCSE qualifications below Level 2 and employment rate of adults with a Level 2 qualification is twice that of those without qualifications [Department of Education, UK, (2011), Building Engagement, Building Futures].
In this study we evaluated the benefits of providing in house educational services offered as an integral part of the adult Tumour and Young Adolescents (TYA) services. To the best of our knowledge, we are the only adult TYA principle treatment centre that provides in house educational services in the UK.
Methodology: Educational services were offered by a qualified teacher to all patients in the TYA unit at the Queen Elizabeth Hospital, Birmingham, UK, as per GCSE syllabus. A total of 52 patients accessed the services (Year 2012–2013) for giving GCSE's or equivalent (functional skills at level 2; n = 34) and for unit accreditation (n = 18). Of the 34 patients who accessed the services for GCSE or equivalent, 29 patients had either left full time education or had level 1 or below qualification. Among the 18 patients who accessed the services for unit accreditation 9 did course work and were assessed by an exam board and 9 of them were teacher assessed.
Results: Among the 29 patients who had left full time education or had level 1 or below qualification, 14 went back to full time education. Fifteen patients sat the GCSE examination or equivalent in the TYA unit. Thirteen patients (86%) achieved level 2 qualifications. All patients who did unit accreditation passed their assessments.
Conclusion: This study demonstrates that providing educational input to patients who are undergoing significant life changing events is possible and an important aspect of the successful patient's rehabilitation and survivorship. The Level 2 Qualification of the TYA students was higher than the national average of 64% (2011–2012).
No conflict of interest.

1791 POSTER

How to endure life during treatment for colorectal cancer

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This study explores the post-diagnosis period as experienced by patients with colorectal cancer, who have undergone surgery and/ or medical treatment in outpatient clinics.
The aim was to explore what challenges the patients experienced during treatment and how they coped with their situation. The study was carried

out using a descriptive phenomenological approach. Data were collected from semistructured interviews. Ten patients were interviewed.
The findings showed that the patients' life was characterised by endurance. The patients struggled to endure the omgoing treatment, unpleasant side effects and changes in everyday life related to the disease. Four themes were revealed:coping with bodily changes; reorganisation of everyday life; getting support from close relatives; seeing lift from a different perspective. Daily diarrhoea forced the patients to reorganise everyday life and challanged their body image. Further, every day had to be planned according to the scheduled treatment and prescribed medication. The patients also experienced that the diagnosis involved existential struggling that took great effort and care from close relatives played a sifnificant role for patients'ability to endure treatment and maintain a positive attitude towards life.
Rehabilitative care for patients with colorectal cancer need to be initiated from beginning to end of a treatment course. This includes dialogues about the challenges faced by the patients as supporting the patient in coping with them.
No conflict of interest.

1792 POSTER

The establishment of an oncologic rehabilitation network

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Background: It is now recognised that rehabilitation should be part of the oncologic treatment program.New multimodal treatment modalities including surgery, radiotherapy and systemic treatments significantly improved the overall survival, but often at the cost of higher toxicity. This creates new needs of dealing with increased difficulties in professional, social and family life, during and after treatment. We aimed at creating of a network of professionals, which could follow patients from diagnosis to prevent or limit the difficulties due to cancer and its treatment.
Material and Methods: We established a rehabilitation program in one of the IOSI outpatient clinics(Lugano)including prevention, information and support from the initial phase of the illness. We gradually constructed a network of professionals, including specialized nurses, physicians, physiotherapists, ergotherapist, logopedist, nutritionist, psychologist, psychiatrist, social worker, spiritual assistant, stoma therapist, esthetician, hairdresser, stop smocking consultant, volunteers. The coordinating nurse selects the patients, administers a self evaluation form, performs an assessment discussion and organizes the different consultations as needed, tailored to the needs of each single patient and its family. A final evaluation is performed at the end of the treatment.
Results: In 2011, 292 new patients were treated in Lugano, 168 were eligible for the rehabilitation program, and 69 were effectively enrolled in the program. Median age of patients was 64.5 years. The consultations were distributed among the specialists as follows: 25 nutritionist, 25 social worker, 19 physiotherapist, 6 psychologist, 6 esthetician. 28 patients presented a compromised nutritional status at diagnosis and entered a nutrition counseling program, with several benefitting with a weight improvement. The social assistant interventions addressed the economical, organizational or professional reinsertion field. Physiotherapy benefited the physical activities, as demonstrated by measurable performance tests before and after the program. Fatigue was a major limitation to the inclusion in the rehabilitation program.
Conclusions: Despite the limited number of patients and some missing pre- or post-treatment data, we evaluate that this type of multidisciplinary approach is useful for patients and allows an improvement in their quality of life.
No conflict of interest.

1793 POSTER

Age differences in patients salient beliefs about cancer

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Background: The number of elderly cancer patients is increasing significantly due to the aging population and the increasing incidence of cancer in general. Our knowledge of elderly cancer patients' thoughts and experiences are sparse.
This project compares two groups of adults and examine whether their thoughts about cancer are identical.
Purpose: To investigate whether there is an age difference in patients' salient beliefs about cancer.
Method: In total 121 patients with different diagnoses in curative cancer therapy completed a self-administered questionnaire. 65 patients <60 years with an average age of 45 years [range 39−59] and 56 patients ⩾60 years with an average age of 69 years [range 60−81].
Only one question was asked: *'What are your thoughts when you hear the word Cancer?'*
The method is based on Salient Belief Assessment (SBA). According to SBA these answers were divided in topics and rated. The first answer on the questionnaire got 10 points, the second 9 points etcetera. The total score was added for each response.
Results: Responses from patients <60 years of age generated in average 4.9 expressions.
Total scores:
Death (7.8)
Disease/Treatment (7.1)
Uncertainty/Insecurity (6.4)
Psychological reactions (5.4)
Hope/fighting spirit (3.7)
Family/Children (3.4)
Loss of control/Powerlessness (2.6)
Responses from patients ⩾60 years of age generated in average 3.5 expressions.
Total scores:
Hope/fighting spirit (7.2)
Psychological reactions (5.1)
Death (4.6)
Uncertainty/Insecurity (4.4)
Disease/Treatment (3.4)
Family/Children (3.1)
Loss of control/Powerlessness (0.7)
Conclusions: Regardless of age, patients' salient beliefs about cancer coincide.
Themes of family/children and psychological reactions have roughly the same score in the two age groups.
Noteworthy is the highest score in patients <60 years is *death*, while the highest score in patients ⩾60 years is *hope/fighting spirit*. In principle, two opposing approaches to cancer.
Salient Belief Assessment requires that clinicians address patients' salient beliefs.
No conflict of interest.

1794 POSTER

Developing and evaluating a self-management psychosocial intervention for men with prostate cancer and their partners: A feasibility study

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Background: The number of men living with prostate cancer and its associated psycho-social problems is rising. Little is known about interventions to help men and their partners cope with the after effects of prostate cancer treatment. This feasibility study aims to develop and pilot a supportive education intervention for men with prostate cancer and their partners.
Methods and Design: This nine week intervention commences on completion of treatment and takes the form of three group and two telephone sessions. The intervention focuses on symptom management, sexual dysfunction, uncertainty management, positive thinking and couple communication. The telephone sessions provide the opportunity for the intervention to be individualised. Twenty Five couples will be assigned to either the intervention or a control group receiving usual care. Participants will be assessed at baseline (on completion of treatment), immediately post-intervention and at one and six months post-intervention. Outcome measures include: self-efficacy (primary outcome), quality of life, symptom distress, uncertainty in illness, benefits of illness, health behaviour and measures of couple communication and support. A caregiver assessment will be completed by the partner. The intervention will also be assessed in terms of structure (cost of the intervention recruitment) and process (experiences and perceptions of facilitators, participants and non-participants).
Conclusion: The feasibility study will provide valuable information on the development and implementation of the intervention. Data on access, recruitment and participation by men and their partners, their views and experience of the different aspects of the intervention and its cost will also be collected. This information will be used to inform a future larger randomised controlled trial with this population.
No conflict of interest.

1795 POSTER

Nurse led rehabilitation consultation

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Background: These years in Denmark there is a huge focus on rehabilitation for cancer patients. In oncology outpatient clinic for women with breast cancer, an increasing portion of our patients receive adjuvant chemotherapy. After completion of chemotherapy women with HER2-positive tumours receive trastuzumab in a group, where rehabilitation needs are addressed. This has gained our interest for investigating the need for rehabilitations among other patients: How they were dealing with side effects in their everyday life, if they had returned to work etc.
Material and Methods: We explored weather patients with HER2-negative tumours would benefit from a nurse led rehabilitation consultation, when they had completed chemotherapy. At June 2012, a pilot project was initiated. A total of 10 women, who had received adjuvant chemotherapy for breast cancer, were invited to tree rehabilitation consultations. The first consultation took place tree weeks after ending chemotherapy and continued after three months and six months respectively. The nurse led rehabilitation consultation was performed by the primary nurse.
The consultations were planned for duration of 30 minutes. Approximately 14 days after each meeting, the women were invited to participate in a phone interview about their experience and outcome of the rehabilitation consultation.
Results: The preliminary results and response from the telephone interviews indicate an immense satisfaction with the rehabilitation consultation. The women have improved their empowerment and they knew where to look for help and support. The rehabilitation consultation increased their feeling of being safe and they felt highly taken care of in the time after the chemotherapy. The women highly recommend that it was their primary nurse, who had followed them through their adjuvant chemotherapy, who led these consultations.
The pilot project is still in process. Updated results will be available in August 2013. The final results will be presented on a poster at ECCO 2013.
Conclusions: If the promising results from the pilot-study are confirmed, we will implement these nurse led rehabilitation consultations in the future as a nursing routine program in our breast cancer oncology outpatient clinic. As a benefit to the nurses, they will be qualified to have a goal-oriented dialog with the patients, about how they are coping with their everyday life and their needs of rehabilitation.
No conflict of interest.

1796 POSTER

Conversations with cancer patients about daily life and rehabilitation needs

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Background: Implementing rehabilitation conversations with cancer patients is a prioritized area at the Oncology Clinic at Copenhagen University Hospital, Rigshospitalet. Our work is based on the assumption that formalized conversations between nurses, patients and relatives about problems, resources and the possibilities for support in everyday life following cancer and cancer treatment, would uncover rehabilitation needs as well as empower the patients and their relatives. By the end of 2012, 56 rehabilitation conversations had been conducted across the six integrated teams at the clinic.
The conversations processes have been different from team to team in terms of patient category, the times at which the conversations were held, informing patients and relatives, the use of interwievguides and the evaluation of the conversations.
The conversations have all been conducted by nurses with extensive oncological experience and training in rehabilitation and communication skills.
The purpose of this study is to describe and evaluate the perceived experience with rehabilitation conversations across the clinic, from three perspectives:
- Nurses' perspective.
- Patients' perspective
- Managerial and organizational perspective

Materials and Methods: The survey was conducted in early 2013 based on four semi-structured focus group interviews, with:
- 11 nurses, who have carried out the conversations about rehabilitation.
- 6 head nurses from each individual team
- 6 nurses who have interviewed patients after completion of the conversations

For all interviews, each lasting one and a half hours, and an interview guide was used.
Other data comprise transcriptions from patient interviews, conducted by phone with patients who have completed the conversations in the individual teams.
Results and Conclusions: The results are preliminary and are being processed; final results and conclusions will be available at the conference. The expected use of our results is:
- Planning future rehabilitation conversations and projects at the Oncology Clinic.
- Asking new questions and creating a foundation for relevant, focused development activities aimed at optimising the rehabilitation effort (hypothesis generating).

No conflict of interest.

1797 POSTER

Sexuality and cancer: information and counselling needs among cancer patients and their significant others

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Background: Sexuality problems among cancer patients are well known as well as the need for information and open communication about sexual issues. Cancer patients and significant others are provided with wealth of information and multidisciplinary services, but little is known about how sexuality needs are met. In 2012 a two year project was completed to train professionals in communication about sexuality issues. The purpose of the study was to examine whether cancer patients and their significant others receive too little, adequate or too much information about the effects of cancer/treatment on sexuality; satisfaction with resources offered for sexual problems, and their need for sexuality counseling.
Material and Methods: Patients attending chemotherapy- or radiation outpatient clinics and their significant others were offered to participate in a survey on how information and support needs were met. A self-report questionnaire designed for this study was administered. Data were collected before the initiation of the project (T1, N = 145), after 11 months (T2, N = 134) and after 17 months (T3, N = 166).
Results: 363 patients and 65 significant others participated. Overall almost equal numbers of patients and significant others reported having received adequate information about the effects on physical appearance (80%), fertility issues (70%), sexual functioning (65%) and the effects on relationships/marriage (50%). No difference was found between time points. A total of 60% of patients were satisfied with resources offered for sexuality problems with a 20% increase from T1-T3. The number of patients in need for the service of a sexuality counselor decreased significantly from 69% at T1 to 42% at T3.
Conclusions: The issue of sexuality is as important as other psychosocial needs and should be integrated into daily care. Unmet needs for sexuality-related information and resources ranged from 20−50% for both patients and significant others and did not change over time. Interest in sexuality counseling was expressed by half of patients and decreased significantly over time which may indicate improvements by clinical staff in addressing sexual issues during the project.
No conflict of interest.

Poster Session (Sat, 28 Sep − Mon, 30 Sep)
Nursing − Symptom Management

1799 POSTER

The influence of prayer on the vital signs of patients with cancer undergoing chemotherapy

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Background: To investigate the influence of prayer on the vital signs of cancer patients undergoing chemotherapy.

Material and Methods: A quasi-experimental study of pre and post-intervention, conducted from February to December 2012, in hospital oncology ward of a general hospital in the south of Minas Gerais. The study population was of 50 patients, the sample selection was done for convenience accounting for 25 subjects. We applied a questionnaire on sociodemographic information and related to spirituality/religiosity, then vital signs were measured − pulse frequency (PF) and respiration (FR), temperature (T) and blood pressure (BP). The intervention was applied for 11 minutes and again the questionnaires were administered and vital signs were measured. Intervention refers to a prayer heard by the patient for a headset. Data were analyzed using the statistical program BioEstat 5.0. The study was approved by the Research Ethics Committee under protocol 063/2011.
Results: Significant differences were observed between the samples before and after intervention for FR ($p = 0.04$) and BP ($P < 0.001$), so that the means of RR and BP before intervention were 20.43 bpm, 122.08 mmHg (systolic) and 80.83 mmHg (diastolic), respectively, after the intervention averages for the same variables were 18.2 bpm, 115.33 mmHg (systolic) and 76.50 mmHg (diastolic).
Conclusions: Prayer has been shown effective in reducing RF and BP. Prayer is a simple practice that provides benefits to the patient and can be used by nurses in providing holistic care.
No conflict of interest.

1800 POSTER

Daily walking during adjuvant chemotherapy for patients with breast and colorectal cancer − a randomized pilot study

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Background: Previous studies have been shown that physical activity during chemotherapy can reduce fatigue, improve symptoms and impact health related quality of life (HRQoL). Challenges associated with intervention studies on physical activity during cancer treatment, relates to good adherence. The aim was to study feasibility and adherence of and physical activity intervention among patients with cancer during adjuvant chemotherapy treatment and to investigate the effects of physical activity on health aspects including fatigue, quality of life and surrogate markers for cardiovascular disease.
Material and Methods: This randomized controlled trial included patients with breast cancer (BRCA) and colorectal cancer (CRC) during adjuvant chemotherapy. HRQoL was assessed using EORTC QLQ- C30 and the EORTC QLQ-BR 23 for specific HRQoL issues relevant to patient with BRCA and the EORTC QLQ − CR38 module for CRC patients. The intervention continued for 10 weeks and included daily walks of 10,000 steps and a weekly supervised group walk. Adherence was assessed by a pedometer and the number of participants who reported step every week and percentage of participants who achieved the target steps every week.
Results: The majority of participants achieved the target step goal every week and in total 76 % completed the exercise intervention. The most common cause of impaired adherence was illness, hassles with the pedometer and experiencing adverse reactions to treatment. The intervention group increases their daily physical activity and significant differences were found for some breast cancer specific symptoms (movement, swelling and pain). All participants gained weight during the intervention; however the weight gain was lower than expected.
Conclusion: Physical activity in the form of walking is a feasible intervention that patients adhere to during treatment. The physical activity increased in the intervention group during the study time, and had positive impact on HRQoL and symptoms.
No conflict of interest.

1801 POSTER

Addressing oral care in cancer: Presenting the work of the United Kingdom oral mucositis in cancer care group (UKOMIC)

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It is widely recognised that oral problems including oral mucositis (OM) can be a significant health burden for the individual, while making substantial demands on health care resources. Both these can be greatly reduced by the correct proactive care and treatment of oral problems.
This presentation will give an overview of the work and clinical guidance of the United Kingdom Oral Mucositis in Cancer Care Group (UKOMIC), a multi-professional group of oral care experts working in a variety of cancer and palliative care centres who have been working to raise awareness and address the often under reported impact of oral problems in cancer care.
Recognising that many clinical teams are unsure about the best way to prevent and treat oral problems and drawing upon their expertise and the most up to date evidence, the group developed guidance on the assessment, prevention, care and treatment of oral problems secondary to disease and treatments. These guidelines have been used to guide practice in a number of cancer settings and palliative care settings across the UK.
The development and the implementation of this expert guidance in multiple cancer settings supports the multi-professional team to anticipate, and attempt to minimise oral side effects in all patients undergoing care and treatment for cancer. Along with developing the guidance the group continues to highlight and address oral care in cancer and palliative care by supporting clinical teams through developing and delivering workshops, educational days, an interactive website, and on line teaching package.
No conflict of interest.

1802 POSTER

Platelet lysate mucoadhesive formulation to treat oral mucositis: A multidisciplinary approach

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Background: Mucositis is an inflammatory-like process of the mucous membranes lining any part of the digestive tract, not only oral and esophageal but also intestinal and rectal tracts, and the clinical aspects of oral mucositis are often dramatic. Typical examples are ulcerative mucositis of the cheek and of the tongue caused by radiotherapy (neck and head cancer) or mieloablative chemotherapy.
Recently platelet lysate (PL), a hemoderivative obtained by platelet destruction by freeze-thawing of a platelet rich plasma (PRP) sample in the presence of an anticoagulant agent, has proved capable of promoting the healing of buccal lesions.
Material and Methods: The present work focuses on the development and testing of few such formulations, in particular a mucoadhesive gel for the treatment of oral mucositis in haematological patients.
Results: The production of the gel is relatively recent in our hospital, but we have obtained a high organizational improvement. In particular, because our patients are strongly immunosuppressed we use an allogenic PL and the whole procedure of PRP is performed under a laminar flow hood with sterile handling techniques. The PRP was transported in sterile conditions and it was directly applied with sterile techniques.
The PRP produced in this way not only provides a very good quality for the high platelets number but also a sterility condition guaranteed by microbiological control and methods of sterilization 'Evidence Based'.
All treated patients have been found an important benefit with pain reduction and newfound sense of taste with a significant improvement in quality of life.
Conclusions: At the present state of knowledge, PL in mucoadhesive formulations opens a simple and economic option to cure mucosal damages otherwise very difficult to treat. At least on the bases of the formulative work performed, it is possible to provide medical doctors with appropriate vehicles for platelet lysate, easily prepared according to good preparation practices, safe and stable in use conditions.
No conflict of interest.

1803 POSTER

Swedish Emesis Registry (SER) − a web-based quality assurance tool for prevention and treatment of nausea and vomiting associated with chemotherapy

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Background: Chemotherapy-induced nausea and vomiting (CINV) is still a common side-effect and have a major impact on patients' well-being. Opportunities to prevent CINV has increased, but despite this, many patients still have problems especially with delayed nausea and vomiting from a few days up to several weeks after treatment.
Patients often receive chemotherapy as outpatients which mean that they need recommendations on how to perform self-care after treatment. International consensus guidelines are available for how nausea and vomiting should be treated, but they are difficult to follow in everyday clinical use. Also, individual risk-modifying factors are not always accounted for in the guidelines. The aim of the SER is to offer patients evidence-based antiemetic guidelines, taking into account individual risk factors, and ensure the quality of antiemetic treatment by standardized monitoring. The goal is to minimize CINV and by that improving patients' well-being and thus quality of life.
Methods: SER is a web-based quality assurance tool for prevention and treatment of nausea and vomiting associated with chemotherapy. SER consists of evidence-based antiemetic guidelines for all common chemotherapy treatments.
Results: An assessment of the individual patient's risk for nausea is performed and the patient receive antiemetics according to the guidelines. A diary is printed from the register in which the patient register degrees of nausea, vomiting and level of wellbeing in the morning and evening for 10 days after chemotherapy. The diary also prescribes the recommended drugs for CINV for the patient to take when required.
The responses from the patient diary are entered into the database and a new diary is given to the patient. If necessary, i.e. if the patient had CINV despite antiemetics the antiemetic prescription is revised according to the guidelines. Each participating clinic can produce graphs in real-time over diary responses both for individual patients and groups of patients which makes reflections over necessary revisions to the guidelines possible. All participating clinics can also easily compare their own data with all participating clinics data. 31771 diaries from 9403 patients is entered into the register. SER is since 2012 a national quality register and there are currently fourteen oncology clinics in Sweden participating in the registry. The Swedish Emesis Group in Cancer Care have also produced a comprehensive course covering CINV, radiotherapy-induced nausea/vomiting and nausea in the palliative care setting.
Conclusion: By providing evidence-based and individual guidelines for prevention and treatment of nausea and vomiting and follow them up in a standarized way, the chances for an improved quality of life for patients increases. We anticipate that the cooperation within the registry will lead to the establishment of national consensus guidelines which would fully guarantee all patients an equal antiemetic treatment.
No conflict of interest.

1804 POSTER

Improving the patient safety of the Advanced Symptom Management System (ASyMS) using a risk analysis tool

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Background: The Advanced Symptom Management System (ASyMS) has been developed over the past 10 years and has been used in a number of different cancer care settings. In the latest study the system is being evaluated in a three-phase, multi-site complex intervention study, with a before and after study design. A risk analysis was undertaken to assess the safety features of the system. Failure Modes, Effects and Criticality Analysis (FMECA) is a risk analysis technique originally used in engineering but has recently been applied in a variety of different settings. It is an innovative approach to testing the safety of a new health technology. The aim of the analysis was to identify all of the potential failures in the system as early as possible in order to eliminate them or mitigate their effects in a timely manner. This paper will outline the methodology used to undertake this risk analysis.
Materials and Methods: FMECA is a prospective risk analysis tool. This method is used to identify and categorise all of the potential failures in a product or system and involves a number of pre-determined stages: 1. Define the elements and boundaries of the system. 2. Calculate the functions of the different elements and their acceptable performance levels. 3. Classify the functional failure modes (i.e. functions that fail to reach an acceptable level of performance), and their causes and effects. 4. Devise methods to detect failure modes. 5. Propose corrective actions to eliminate failures or mitigate the effects of failures. 6. Calculate scores for (a) the likelihood of failure occurrence, (b) the likelihood of failure detection and (c) the potential severity of failure. These three scores were multiplied to give a risk priority number (RPN). 7. RPNs were then used to rank failures modes in order of priority for action. 8. Responsibility was assigned to members of the ASyMS team to implement corrective actions by order of priority.
Results: The successful application of this methodology will be presented using some exemplars from the ASyMS study.
Conclusions: The FMECA method has the potential to be used in assessing the safety of future health technologies in a systematic manner that prioritises safety issues by their potential risk level. This analysis can be performed early in the design stage of a product or system, but can also be used throughout its life cycle to address on-going safety issues.
No conflict of interest.

Proffered Papers Session (Sat, 28 Sep)
Breast Cancer − Advanced Disease

1850 ORAL

In two independent randomized trials young high risk breast cancer patients with luminal A tumors had benefit from postmastectomy radiation therapy

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Background: Luminal A (LumA) tumors are associated with good prognosis, but with substantial risk for late loco-regional relapses. We aimed to test the predictive value of intrinsic subtypes as defined by research-based PAM50 classifier, for predicting adjuvant radiation therapy benefit among pre-menopausal women with node positive tumors from two independent postmastectomy randomized adjuvant radiation trials with more than 20 years follow-up.
Methods: Formalin fixed paraffin embedded (FFPE) tissues (n = 128) were collected from the British Columbia (BC) trial and fresh frozen (FF) samples (n = 87) were available from a similarly designed study by the Danish Breast Cancer Cooperative Group(DBCG 82b). Gene expression profiles were done using Nanostring nCounter® for FFPE samples and the Human Genome Survey Microarray version 2.0 (Applied Biosystem) for FF samples. Tumors were classified into subtypes (LumA, Luminal B (LumB), Her2-enriched (Her2-E), Basal-like (BLBC) and Normal-like) based on the PAM50 classifier. Kaplan–Meier analysis and log-rank test were used to test the differences in local-regional relapse free survival (LRFS) and Overall Survival (OS).

Table 1. LRFS at 20 years across intrinsic subtypes in BC and DBCG 82b-trials

		BC-trial		DBCG 82b	
		CMF	CMF+RT	CMF	CMF+RT
LumA	LRFS	66%	94%	25%	92%
	p:	0.05		0.01	
LumB	LRFS	40%	60%	89%	86%
	p:	0.66		0.82	
Her2-E	LRFS	69%	65%	76%	90%
	p:	0.70		0.42	
BLBC	LRFS	23%	92%	66%	54%
	p:	0.004		0.33	

Results: In both trials, patients received adjuvant CMF (cyclophosphamide, methotrexate, fluorouracil) and were randomized to postmastectomy radiation therapy (RT) or no RT. The BC trial had a second randomization. Patients with estrogen receptor positive tumor were randomized to receive oophorectomy and 42 of them were included in this correlative study. Table 1 summarized the 20-yr LRFS rate according to subtypes. In both studies, LumA tumors (N = 41 (BC) + 20 (DBCG)) had a significantly better LRFS with postmastectomy RT; however, no difference in OS was observed.

There were no statistical significant differences observed for LRFS for other subtypes.
Conclusion: Radiation appears to significantly decrease local recurrence in premenopausal women with node positive and LumA tumors based upon two small but independent series. Though not definitive, our study suggests that these slow growing tumors may obtain the greatest benefit for regional radiotherapy and thus radiation should not be omitted in young patients with high-risk tumors.
Conflict of interest: *Ownership: M Cheang and T Nielsen are Co-inventor for the patent of PAM50 intrinsic subtype classifier.*

1851 ORAL

Phase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer − final analysis LEA study

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Background: We designed the randomized phase III LEA study of bevacizumab (B) in combination with endocrine therapy (ET), to address the hypothesis that anti-VEGF treatment can prevent resistance to endocrine therapy.
Methods: A multicentre, randomised, open label, phase III study investigated the addition of B 15 mg/kg every 3 weeks to ET with either letrozole or fulvestrant (250 mg/4 weeks) as first-line therapy in advanced breast cancer. Postmenopausal pts with HER2-negative and hormone-receptor-positive breast cancer were randomized in a 1:1 ratio after being stratified for prior adjuvant therapy with an aromatase inhibitor (AI); number of involved sites (one/multiple); measurable lesions (yes/no) and country (Spain/Germany). The primary objective was to compare progression-free survival (PFS). Secondary objectives were overall survival (OS), overall response rate (ORR), response duration (RD), time to treatment failure (TTF), clinical benefit rate (CBR) and safety. The safety analysis (Loibl et al. ESMO2012) and the primary endpoint (Martin et al. SABCS 2012) have been reported previously. We here report the final updated analysis.
Results: From 11/2007 to 11/2011, 380 pts were randomised to ET±B (Spain 270; Germany110). Baseline characteristics were well balanced. Median age was 65 years (38−86). 48% had visceral metastases. 19.5% pts had a prior AI. 72% had a performance status ECOG 0 (86% in Germany and 66% in Spain; p = 0.001). 30% had prior chemotherapy in Germany and 52% in Spain (p = 0.001). All other baseline characteristics were well balanced between the countries.
The median PFS was 14.4 months in ET and 17.7 months in ET+B (HR 0.855 [95% CI 0.671–1.088], log-rank p = 0.202).
Addition of B to ET significantly improved PFS in Germany (HR 0.549 [95% CI 0.341–0.884] log-rank p = 0.0012; interaction test p = 0.733). There was no difference within any other predefined subgroup. ORR was 17% with ET and 32% with ET+B (p = 0.001). The CBR was 66% and 78% (p = 0.012), the RD was 47.9 and 30.7 months (p = 0.011), TTF was 13.8 and 14.0 months; p = 0.471 with ET and ET+B, respectively. The median OS was 51.8 months with ET and 52.1 months with ET+B (HR 1.133 [95% CI 0.753–1.703] p = 0.549).
Conclusions: The LEA study failed to demonstrate a statistically significant increase in PFS by adding bevacizumab to ET as first line therapy. OS was also not impacted.
No conflict of interest.

1852 ORAL

Complex tumor genomes inferred from plasma DNA of patients with metastatic breast cancer by whole-genome sequencing

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With the increasing number of available predictive biomarkers, clinical management of cancer is becoming more and more reliant on the accurate serial monitoring of tumor genotypes. Recent advances in the understanding of the molecular mechanisms of cancer highlight the need for personalized medicine for both diagnostic purposes and the prediction of prognosis. Serial monitoring of blood biomarkers may explain why some patients initially respond well to therapy, but ultimately relapse due to treatment resistance.
We addressed whether complex tumor genomes may be identified non-invasively from the peripheral blood samples of metastatic breast cancer patients. 71 plasma samples of 58 patients were enrolled in the evaluation including several samples from different time points for 8 patients. Plasma DNA concentration and size distribution was determined and followed by qualitative and quantitative analysis for subsequent whole-genome sequencing at a shallow sequencing depth using the Illumina MiSeq® platform to establish genome-wide copy number profiles. Furthermore we used the CellSearch system® (Veridex) for enumeration of circulation tumor cells (CTCs) from blood. For 3 selected cases we performed in addition whole-exome sequencing of serial plasma DNAs and different areas of the respective primary tumors employing the Illumina HiSeq2000® platform.
A subset of metastatic patients had a biphasic size distribution of plasma DNA fragments, which was associated with an increase of CTCs, elevated concentrations of plasma DNA, and a high percentage of mutated DNA fragments. We were able to identify tumor-specific copy number changes (CNVs) in the plasma DNA associated with breast cancer, such as ERBB2 gene amplification or amplified regions including the CCND1 gene. Furthermore, we identified CNVs, which were not observed in the respective primary tumor and which may reflect tumor evolution. Using exome sequencing we identified mutations in the plasma originating from different tumor sites indicating presence of predominant tumor clones.
The techniques used in this study allow serial monitoring of tumor genomes with a simple blood test. The results yield novel insights, which allow us to address basic research questions, such as processes underlying metastasis and tumor evolution. Furthermore, the use of plasma DNA as prognostic and predictive biomarker may lead to individualization of cancer therapies.
No conflict of interest.

1853 ORAL

Population based study investigating biopsy verifications of "breast cancer recurrences" and biomarker changes

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Background: Evidence indicates discordance of biomarkers between the primary breast cancer and the corresponding relapse however; only few studies have shown prognostic impact. In the present study, we wanted to investigate tumor related events (e.g. relapse, other malignancy, and benign condition) after primary breast cancer. Furthermore, for patients with confirmed relapse, to perform a comparative analysis of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 (HER2) and proliferation (Ki67) between the primary tumor and the relapse. Any discordance in hormonal receptor status was to be correlated to survival.
Patient and Methods: The cohort includes 2102 women with primary invasive breast cancer during 2000 to 2011 in Värmland County, Sweden. Immunhistochemical (IHC)/immunocytocheimcal (ICC) methods were used to determine biomarker status and confirmation of HER2 status by fluorescence in situ hybridization (FISH).
Results: 1060 out of 2102 patients have had a biopsy taken after the initial breast cancer diagnosis. 177 patients (8.4%) had biopsy verifications of breast cancer relapse, 93 (4.4%) second cancer, 40 (1.9%) cancer *in situ* and 857 (40.8%) benign lesions. For patients with relapse, ER (n = 127), PR (n = 101), HER2 (n = 73) and Ki67 (n = 55) status in both primary tumor and the corresponding relapse were determined. The discordance of receptor status was 14.2%, 39.6%, 9.6% and 29.1% respectively. A significant impact on overall survival for ER and PR discordances was shown. In fact, loss of ER in the relapse resulted in a significantly increased risk of death (HR 3.62; 95% CI, 1.65–7.94) compared with stable ER positive patients. In addition, loss of PR in the relapse resulted in a significantly increased risk of death from the time of relapse (HR 2.34; 95% CI, 1.01–5.47) compared with stable PR positive patients. Finally, the proportion of patients losing ER was bigger in the group treated with hormonal therapy alone or in combination with chemotherapy, 16.7% and 13.3%, compared

to the group treated with chemotherapy alone or that which received no treatment 4.3% and 7.7% respectively.
Conclusion: This study demonstrates a discordance of biomarkers between the primary tumor and the corresponding relapse in 10−40%. Patients with loss of ER or PR in relapse have poorer survival compared to patients with stable positive biomarkers. Indeed, adjuvant therapy may affect the loss of hormonal receptors.
No conflict of interest.

1854 ORAL

Circulating tumor cells before and during therapy in metastatic breast cancer: An individual patient data pooled analysis of European studies

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Background: CTCs (CellSearch®) counts before or during therapy have been assessed in metastatic breast cancer patients (MBC pts) in only small- to medium-sized studies, with limited statistical power. We aimed to pool all European studies to obtain high-level evidence on the prognostic value of CTCs, CEA & CA15−3 levels, and to investigate their effects across different MBC subtypes and therapies.
Material and Methods: In December 2012, we searched for eligible studies that accrued patients in 2003–2011 and predefined the methods in a protocol. All European laboratories using CellSearch® were contacted. We used likelihood ratio tests (LR) in Cox regression models stratified by study to assess the independent prognostic value of CTC+ (>= 5 CTCs/7.5 mL), CEA+ & CA15−3+ (normalized values) when added to a clinicopathological (CP) model for progression-free and overall survival (PFS and OS). Landmark analyses were used to assess the prognostic effect of early changes in CTC.
Results: We collected individual data of 1944 MBC pts, from 20 different studies (some unpublished), from 17 centers in 7 European countries. We observed 1507 PFS events and 929 deaths. Baseline CTC count was significantly associated with several patient characteristics, such as performance status (PS, $p<10^{-4}$), synchronous metastasis ($p<10^{-2}$) tumor subtype ($p<10^{-4}$), liver & bone metastases ($p<10^{-4}$), CEA & CA15−3 levels ($p<10^{-4}$). The CP model for OS included PS, MBC subtypes, number of previous lines of treatment, patient's age, metastasis-free interval, liver and brain metastases, and treatment modality ($p < 0.01$ for all). At multivariate analysis, baseline CTC+ was a significant independent predictor of OS (n = 1444, HR = 2.7, 95% CI [2.2−3.2], LR $p<10^{-4}$). CEA had a small added effect to the CP plus baseline CTC+ model for OS (n = 747, HR = 1.3 [1.0−1.6], LR p = 0.024). Finally, early changes in CTC+ status at week 3−5 significantly added prognostic information for OS to a model with CP factors and baseline CTC+ (n = 569, HR = 1.8 [2.2−3.2], LR $p < 0.001$). Additional results will be presented at the meeting.
Conclusions: This large pooled analysis has a previously unreached statistical power and provides level-of-evidence 1 on the independent prognostic value of CTCs before and during treatment in MBC.
Conflict of interest: *Advisory board: Veridex. Corporate-sponsored research: Veridex*

Proffered Papers Session (Sun, 29 Sep)
Breast Cancer − Early Disease

1855 ORAL

The 70-gene signature predicts the risk of locoregional recurrence after adequate breast surgery

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Background: The possibility of predicting the risk of ipsilateral locoregional recurrence (LRR) after adequate surgery will allow individually tailored treatment. With the 70-gene signature (70-GS) it is possible to predict the risk of distant metastases in breast cancer and select those patients who will have benefit in survival from adjuvant treatment. Given the strong association between LRR and distant metastases, we hypothesize that the 70-GS will also be predictive for LRR.
Methods: Follow-up and radiotherapy details were updated for 1053 individual breast cancer patients, diagnosed and treated at the Netherlands Cancer Institute between 1984 and 2006. All patients were part of various 70-GS studies and were primarily treated with breast-conserving treatment (BCT) or mastectomy (MST). Adjuvant treatment consisted of radiotherapy, chemotherapy and/or endocrine therapy as indicated by guidelines used at the time.
Results: After 10 years of follow-up (median FU: 8.91 years), 89 LRR events had occurred. 70-GS high risk patients had a significantly higher risk of LRR compared to 70-GS low risk patients ($p<0.001$; Table). The 70-GS had a similar prognostic value for patients treated with BCT or MST ($p = 0.002$; Table). When stratifying for nodal status (positive and negative), the significant difference in LRR risk between 70-GS high and low risk remains for lymph node-negative patients treated with BCT and lymph node-positive patients treated with MST. Among lymph node-negative patients treated with MST no difference in risk of LRR was seen. Multivariate analysis identified 70-GS high risk ($p = 0.021$), lack of adjuvant chemotherapy ($p = 0.032$) and young age ($p<0.001$) as predictors of LRR.
Conclusions: The 70-GS is able to predict the risk of LRR. Patients with 70-GS high risk breast cancers may benefit from more extensive adjuvant treatment to reduce the risk of LRR while patients with 70-GS low risk breast cancers may benefit from more limited treatment strategies.

	Cumulative absolute risk of LRR				
	70-GS high risk (n = 492)		70-GS low risk (n = 561)		*p*-value
	5 years	10 years	5 years	10 years	
Entire group (n = 1053)	9.5%	13.0%	2.7%	6.1%	<0.001
Breast-conserving treatment (n = 481)	7.7%	13.2%	1.6%	5.8%	0.002
Node positive (n = 211)	6.5%	11.6%	1.0%	6.6%	0.116
Node negative (n = 264)	9.0%	15.4%	2.0%	4.9%	0.006
Mastectomy (n = 567)	11.2%	13.0%	3.4%	6.0%	0.002
Node positive (n = 323)	13.8%	15.2%	0.6%	2.0%	<0.001
Node negative (n = 244)	7.5%	9.8%	6.8%	11.1%	0.895

Conflict of interest: *Advisory board: H. Bartelink is a non-stakeholding, non-remunerated member of the supervisory board of Agendia NV. Other substantive relationships: L.J. van 't Veer is listed inventor of 70-gene signature and stockholder, co-founder and employee Agendia NV.*

1856 ORAL

Development and validation of a gene profile predicting benefit of postmastectomy radiotherapy in high risk breast cancer − a study of gene expression in the DBCG82bc cohort

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Background: Postmastectomy radiation (PMRT) is primarily offered to patients estimated from clinico-pathological variables to have a high risk of local recurrence (LR). Large randomized trials, including the DBCG82 trials (Danish Breast Cancer Cooperative Group), have nevertheless shown a substantial overall survival benefit after PMRT in patients with low risk of LR. Our hypothesis is that a more refined selection of patients likely to benefit from PMRT can be established through identification of a molecular profile predictive of radiosensitivity in terms of local control.
Materials and Methods: The DBCG82bc cohort constitutes high risk patients (tumor size >5 cm and/or positive lymph nodes and/or invasion in skin or pectoral fascia) diagnosed between 1983−89, treated with mastectomy and partial axillary lymph nodes dissection and randomized to +/− PMRT. From 257 DBCG82bc patients, fresh frozen tumor samples were available. Gene expression was measured in 191/257 samples using whole genome arrays. Genes, whose expression levels interacted with PMRT on the association with LR, were identified through a two step Cox Proportional Hazard model with lasso penalty. In the training set, transfer to quantitative Real Time Polymerase Chain Reaction (qRT-PCR) and formalin fixed, paraffin embedded tissue (FFPE) was performed in order to validate the profile in 931 DBCG82bc patients with only FFPE available.
Results: Seven genes, whose expression interacted with the effect of PMRT, were identified and a weighted index was generated. By dividing the index at the upper quartile, the patients were classified into two groups: high index (25% of the patients) and low index (75%). Among patients not receiving PMRT, a low index was associated with a significantly lower local control rate compared to patients with a high index (31% vs. 90%, $p=3*10^{-5}$). PMRT significantly improved local control rate in patients with a low index (31% vs. 85%, $p=2.6*10^{-8}$); equalizing the rate to patients with a high index, who showed no additional benefit from PMRT in terms of local control (86% vs. 90%, $p = 0.93$). The predictive value was independent of known clinico-pathological parameters. In the training set, there was a significant correlation between risk classifications calculated from microarray and qRT-PCR data. Detection of all genes in the profile by qRT-PCR was successful in 116/931 FFPE validation samples, and the prognostic and predictive value was validated in these samples.
Conclusions: The study presents a gene profile consistently predicting local control and benefit from PMRT. The gene profile can be applied to FFPE, and does not require fresh frozen tissue. The gene profile may assist in identifying patients expected to benefit from PMRT.
Conflict of interest: *Other substantive relationships: Patent filed on the presented gene profile*

1857 ORAL

Can breast IMRT improve patient reported outcome measures? Results from Cambridge breast IMRT trial

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Background: The use of intensity-modulated radiotherapy (IMRT) in breast cancer reduces clinician-assessed breast tissue toxicity including fibrosis, telengiectasia and sub-optimal cosmesis. Patient reported outcome measures (PROMs) are also important as they provide the patient's perspective. This longitudinal study reports on the (a) effects of IMRT on PROMs compared to standard RT and (b) trend of PROMs over 5 years.
Materials and Methods: PROMs were assessed at baseline (pre-RT), 6, 24 and 60 months after completion of RT using global health and four breast symptom questions (BR23). Also, four breast RT-specific questions were included at 6, 24 and 60 months: change in skin appearance, firmness to touch, reduction in breast size and overall change in breast appearance since RT. The benefits of IMRT over standard RT were assessed using generalized estimating equations (GEE) for global health and logistic regression analysis to compare the proportion of moderate-severe changes for eight breast symptoms at 5 years. A repeated measure multivariate analysis using GEE investigated time trend.
Results: 727/815 (89%), 84%, 81% and 60% patients completed questionnaires at baseline, 6, 24 and 60 months respectively. At 5 years, PROMs assessments did not demonstrate a benefit for IMRT for global health ($p = 0.8$) and breast specific questions (table 1). Patients reported worse toxicity for all four BR23 breast symptoms at 6 months, which then improved over time ($p < 0.0001$). Patients reported improvement in skin appearance and breast hardness over time ($p < 0.0001$), with no significant change for breast shrinkage ($p = 0.47$) and overall breast appearance ($p = 0.13$).
Conclusions: Contrary to clinician assessed outcome, breast IMRT did not translate in to improved PROMs in this study. Only a small proportion of patients reported moderate-severe breast changes post radiotherapy with most PROMs improving over time. Patients' perception of toxicity may be influenced by other psycho-social factors, which requires further investigation. A combination of clinician assessment and PROMs appear optimal for evaluating breast toxicity.
No conflict of interest.

Table 1. PROMs comparing proportion of moderate-severe changes between IMRT and standard RT at 5 years

PROMs	Control (%)	IMRT (%)	p-value
Breast pain	5.2	5.8	0.8
Swollen breast	0	0.8	na
Oversensitive breast	4.8	5	0.9
Breast skin problems	4.4	4.2	0.9
Skin changes post RT	4.5	5.5	0.6
Overall breast changes post RT	13	17.7	0.2
Breast became smaller post RT	13.5	13.4	0.9
Breast became firmer post RT	9	6.4	0.2

1858 ORAL

Clinical and pathological response after neoadjuvant chemotherapy with or without zoledronic acid for patients with HER2-negative large resectable or stage II or III breast cancer

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Background: The role of bisphosphonates when added to the neoadjuvant treatment of BC in enhancing the clinical and pathological response of tumors is still unknown.
Methods: NEOZOTAC is a national, multicenter, randomized study comparing the efficacy of TAC (docetaxel, Adriamycin and cyclophosphamide i.v.) followed by G-CSF on day 2 with or without ZA 4 mg i.v. q 3 weeks in patients (pts) with stage II/III, measurable, HER2-negative BC and absence of prior bisphosphonate usage. Here we present the primary and secondary endpoints of pathological (pCR and Miller and Payne) and radiological (RECIST 1.1) response. Analysis was based on intent-to-treat. An unplanned subgroup analysis of postmenopausal women (PMW; FSH >20 and estradiol <110) was performed.
Results: From July 2010 to April 2012, 250 patients from 26 participating sites were randomized. Clinical and pathological response data of 213 and 237 pts are currently available. Complete clinical response rate was 23.1% for TAC+ZA and 16.5% for TAC only ($P = 0.21$). Overall clinical response (complete and partial response) did not differ between groups (75.9% for TAC+ZA vs. 75.7% for TAC only) pCR rate also was not different across the two study arms (16.2% vs. 17.5% with addition of ZA, $P = 0.80$). However, a numerical benefit in favor of ZA was observed in PMW (10.6% vs. 17.3% pCR). Additional information on bonemarkers will be ready for presentation at ECCO.
Conclusions: In our population treatment with ZA did not make a difference as regards clinical response nor pCR. Addition of ZA to neoadjuvant CT might be effective for enhancing clinical and pathological response in PMW with BC and predictive markers and should be further investigated.
No conflict of interest.

1859 ORAL

PI3KCA mutations and correlation with pCR in the NeoALTTO trial (BIG 01−06)

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Background: Understanding the mechanism of resistance to human epidermal growth factor receptor 2 (HER2)-targeted agents is a critical step toward identifying the best therapy for individual patients with HER2-positive breast cancer. Activation of the PI3K/AKT survival pathway is one of the molecular mechanisms that contribute to trastuzumab resistance.
Material and Methods: In the present, study we investigated the influence of PI3K pathway mutations (PIK3CA, KRAS, BRAF, AKT1) on sensitivity to trastuzumab (T), lapatinib (L), or both agents (L+T) in combination in early-stage HER2-positive breast cancer patients enrolled the neoALTTO trial. Genotyping was performed using Mass spectrometry in DNA extracted from 355 of 449 randomized patients with available frozen biopsies at baseline. The primary efficacy endpoint was pathological complete response (pCR) at surgery, defined as the absence of tumor in the breast.
Results: PIK3CA mutations were found in 23% of patients (n = 355, all arms), and 23% (29/124), 19% (21/112), and 25% (30/119) in L, T, and L+T respectively. Only 1 patient (0.3%) had KRAS mutation and no patients had BRAF mutation. PIK3CA mutation rate was similar in ER-positive and -negative groups (23% and 22% respectively). PIK3CA mutations were associated with lower pCR and this relationship was evident across the entire patient cohort, but was most pronounced in the L+T arm. In patients treated with L+T, pCR rate was 55.8% in those lacking PIK3CA mutations and 28.6% in those patients with mutations. The pCR rates for the Lapatanib arm was 14.8% for those with PIK3CA mutations and 20.4% for those without. For the Trastuzumab only arm, the pCR rates were 20.0% and 28.4%. A logistic regression model of pCR, which adjusts for treatment arm and ER status, found significant differences between those with and without the PIK3CA mutation (Odds ratio = 0.45, p = 0.015).
Conclusions: These data provide further evidence of the role of PIK3CA mutations in resistance to trastuzumab and lapatinib-based therapies. Thus, assessment of PIK3CA status might be an important tool in identifying patients unlikely to derive substantial benefit from these treatments.
Conflict of interest: *Advisory board: J Baselga and M. Piccart-Gebhart received honoraria/consultancy fees from Roche-Genentech. Other substantive relationships: C. Sotiriou is co-inventor on a provisional worldwide patent filed by the Université Libre de Bruxelles for a PIK3CA mutation associated gene signature*

1860 ORAL

Overall and subgroup findings of the aTTom trial: A randomised comparison of continuing adjuvant tamoxifen to 10 years compared to stopping after 5 years in 6953 women with ER positive or ER untested early breast cancer

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Background: Tamoxifen given for 5 years after surgery for ER-positive early breast cancer reduces recurrence and breast cancer mortality and is more effective than treatment for shorter durations. It has been uncertain what advantage there may be to extending tamoxifen treatment to 10 years.
Methods: 6953 women with ER+ (n = 2755), or ER untested (4198) invasive breast cancer from 176 UK centres, relapse free after 5 years of prior adjuvant tamoxifen, were randomised to stop tamoxifen or continue to year 10. 53% were node negative, 31% node positive and 16% unknown nodal status. Annual follow-up recorded compliance, recurrence, mortality, and hospital admissions.
Results: Allocation to continue tamoxifen reduced breast cancer recurrence (580/3468 vs 672/3485, p = 0.003). This reduction was time dependent: rate ratio (RR) 0.99 during years 5−6 after diagnosis [95% CI 0.86–1.15], 0.84 [0.73–0.95] during years 7−9, and 0.75 [0.66–0.86] later. Longer treatment reduced breast cancer mortality (392 vs 443 deaths after recurrence, p = 0.05), RR 1.03 [0.84–1.27] during years 5−9 and 0.77 [0.64–0.92] later; and overall mortality (849 vs 910 deaths, p = 0.1), RR 1.05 [0.90–1.22] during years 5−9 and 0.86 [0.75–0.97] later. Non-breast-cancer mortality was little affected (457 vs 467 deaths, RR 0.94 [0.82–1.07]). There were 102 vs 45 endometrial cancers RR = 2.20 (1.31–2.34, p < 0.0001) with 37 (1.1%) vs 20 (0.6%) deaths (absolute hazard 0.5%, p = 0.02). Combining results of aTTom and its international counterpart ATLAS (Lancet 2013) enhances statistical significance of the reductions in recurrence (p < 0.0001), breast cancer mortality (p = 0.002) and overall survival (p = 0.005) from longer tamoxifen. Rate ratios for recurrence from years 2 onwards were not significantly affected by age with RR <55 years 0.70 [0.53–0.92], RR >55 years 0.80 [0.68–0.94] or nodal status: node-negative RR 0.80 [0.64−1.0] node-positive 0.73 [0.58–0.91].
Conclusions: aTTom confirms the recently reported findings of the complementary ATLAS study that, continuing tamoxifen to year 10 rather than just to year 5 produces further reductions in recurrence and breast cancer deaths. The proportional reduction in recurrence was unaffected by age or nodal status. Benefits from continuing tamoxifen treatment beyond year 5 emerge only after 7 years from start of treatment for recurrence and 10 years for mortality.
No conflict of interest.

Poster Discussion Session and Poster Session (Mon, 30 Sep)
Breast Cancer

1861 POSTER DISCUSSION

Comparing the 70-gene signature to the Dutch Breast Cancer guidelines in the prospective RASTER study

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Background: The microarRAy-prognoSTics-in-breast-cancER (RASTER) study was the first study specifically designed to prospectively evaluate the performance of the 70-gene signature and compare the risk estimations of the 70-gene signature to clinico-pathological guidelines. The aim of this study is to compare the risk estimations of the 70-gene signature to the Dutch Institute of Healthcare (CBO) guidelines used at the time of the study (2004) and the CBO guidelines used today (2012).
Methods: A 70-gene signature result was available for 427 patients (cT1−3N0M0). Adjuvant systemic treatment decisions were based on the CBO 2004 guidelines, the 70-gene signature, and doctors' and patients' preferences. Five-year distant-recurrence-free-interval (DRFI) probabilities were compared between subgroups based on the 70-gene signature and the CBO 2004 guidelines and the CBO 2012 guidelines.
Results: Median follow-up was 61.6 months. Fifteen percent (33/219) of the 70-gene signature low-risk patients received adjuvant chemotherapy (ACT) versus 81% (169/208) of 70-gene signature high-risk patients. The 5-year DRFI probabilities for 70-gene signature low-risk and high-risk patients were 97.0% and 91.7%. The 5-year DRFI probabilities according to the CBO 2004 and 2012 guidelines were respectively 96.6% (n = 243) and 99.2% (n = 124) for the low risk patients and 91.5% (n = 184) and 92.4% (n = 303) for the high risk patients. For 70-gene signature low-risk − CBO 2012 high-risk patients who had not received ACT (n = 98), 5-year DRFI was 95.5%. According to the CBO 2012 guidelines 303 patients should receive ACT. If patients were treated according to the 70-gene signature result only 184 patients would have received ACT, a reduction of 39%.

Conclusions: In a prospective observational study, the 5-year DRFI probabilities confirmed the additional prognostic value of the 70-gene signature to clinico-pathologic factors. A reduction of 39% in the use of ACT can be achieved when the result of the 70-gene signature is applied. Omission of ACT despite poor clinico-pathological factors, as judged appropriate by doctors and patients, supported by a low-risk 70-gene signature result, did not compromise outcome.

		70-GS Low risk (n = 219)	70-GS High risk (n = 208)	Total (n = 427)
CBO 2004	Low risk	167 (76%)	76 (37%)	243
	High risk	52 (24%)	132 (63%)	184
CBO 2012	Low risk	88 (40%)	36 (17%)	124
	High risk	131 (60%)	172 (83%)	303

Conflict of interest: *Other substantive relationships: L.J. van 't Veer is listed inventor of 70-gene signature and stockholder, co-founder and employee Agendia NV.W.H. van Harten was until recently a non-stakeholding, non-remunerated member of the supervisory board of Agendia NV.*

1862 POSTER DISCUSSION

Receptor conversion between primary ductal carcinoma in situ (DCIS) and corresponding local relapse

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Background: Emerging data propose biomarker change between primary invasive breast cancer and corresponding metastasis; in addition impact on survival has been shown. We wanted to investigate change of hormonal- and human epidermal growth factor 2 (HER2) receptor status between primary ductal carcinoma in situ (DCIS) and corresponding new ipsilateral events.
Material and Methods: The source population includes 1,504 women from two separate cohorts, diagnosed with a primary DCIS between 1986 and 2004. Out of all 274 women developing a local relapse, 135 (49.3%) women developed an *in situ* relapse and 139 (50.7%) an invasive relapse up to 31st of December 2011. TMA-blocks were constructed from both primary DCIS and relapses. Estrogen receptor (ER) and progesterone receptor (PR) were stained for by immunohistochemistry (IHC) and HER2 by silver-enhanced in situ hybridization (SISH) as well as IHC.
Results: ER (n = 112), PR (n = 113) and HER2 (n = 114) status from both primary DCIS and corresponding relapse was assessed and showed altered receptor status in 15.1%, 29.2% and 10.5% respectively. The receptor conversion was both from negative to positive and from positive to negative and we could not find any general pattern for either loss or gain of receptors for the different biomarkers. Primary DCIS was HER2 positive in 40.3% whereas *in situ* and invasive relapses were HER2 positive in 42.9% and 34.5% respectively. The proportion of patients with altered intraindividual ER or HER2 status between primary tumor and relapse was highest in the group not receiving postoperative radiotherapy, 16.5% versus 11.1% and 13.0% versus 3.4%, respectively.
Conclusions: Receptor conversion for ER, PR and HER2 status occurred between primary DCIS and corresponding new ipsilateral events in 10−30%. When stratified for either *in situ* relapse or invasive relapse, no general pattern for the conversion was seen. This study could not confirm that HER2 status in primary DCIS was of any major importance for tumor progression towards invasive cancer, which has been proposed.
No conflict of interest.

1863 POSTER DISCUSSION

Genetic polymorphisms in the vascular endothelial growth factor gene and breast cancer metastases. An update of the Austrian "tumor of breast tissue: incidence, genetics, and environmental risk factors" study

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Background: Vascular endothelial growth factor (VEGF) is a key regulator of tumor-induced angiogenesis and essential for tumor growth and distant tumor spread. Aim of the present study was to evaluate the role of VEGF polymorphisms and haplotypes for metastatic progression in breast cancer patients.
Patients and Methods: We performed a prospective study including 801 breast cancer patients from the Austrian TIGER ("tumor of breast tissue: incidence, genetics, and environmental risk factors") study. Occurence of metastases was examined in regular follow-up investigations. Seven VEGF polymorphisms were selected and determined by 5′-nuclease assays (TaqMan). Haplotypes and linkage disequilibrium were determined using the Haploview program.
Results: Within a median follow-up time of 84 months, 165 (21%) patients developed distant metastases. In univariate analysis, the CCCCC haplotype formed by five polymorphisms upstream the coding region was significantly associated with distant metastases-free survival (hazard ratio (HR)=0.743; 95% CI 0.579–0.953; p = 0.019). After adjustment for age, tumor stage, grade, lymph node involvement, and hormone receptor status, the HR for the development of distant metastases was 0.757 for carriers of the CCCCC haplotype (95% CI 0.571–1.003; p = 0.052). In postmenopausal patients, a significant association of the CCCCC haplotype and the VEGF −634G>C polymorphism with distant metastases was observed. Multivariate analysis showed a HR of 0.586 (95% CI 0.393–0.873; p = 0.009) for carriers of the CCCCC haplotype and a HR of 0.651 (95% CI 0.447–0.948; p = 0.025) for carriers of the VEGF −634C>G polymorphism.
Conclusion: We conclude that VEGF gene polymorphisms and haplotypes may influence the development of distant metastases in postmenopausal breast cancer patients.
No conflict of interest.

1864 POSTER DISCUSSION

Sentinel node identification with indocyanine green: concordance and validation study by comparison with 99mTc-labelled radiotracer method (Study IEO S562/510 EudraCT Number 2010–021815−18)

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Background: Sentinel node biopsy (SNB) is the standard procedure for staging the axilla in breast cancer. A growing body of evidence supports the feasibility and efficacy of using the fluorescent dye indocyanine green (ICG) to identify the SN, however this method has not been formally and prospectively compared with the gold-standard radiotracer method in terms of SN detection rate. The aim of the present study was assess concordance between the ICG method and gold standard ^{99m}Tc-radiotracer method and hence determine whether ICG can be used alone to identify the SN.
Materials and Methods: Between June 2011 and January 2013, 134 women with clinically node-negative early breast cancer received subdermal/peritumoral injection of ^{99m}Tc -labeled tracer for lymphoscintigraphy, followed by intraoperative injection of ICG for fluorescence SN detection with an exciting light source (near-infrared) combined with a camera. In all patients, SNs were first identified by the fluorescence method (ICG-positive) and removed. A gamma ray-detecting probe was then used to determine whether ICG-positive SNs were hot (^{99m}Tc-positive) or cold (^{99m}Tc-negative). The gamma ray probe was then used to identify and remove any ^{99m}Tc-positive (ICG-negative) SNs remaining in the axilla. The study IEO S562/510 (EudraCT Number 2010–021815−18) was powered to perform an equivalence analysis − i.e. evaluate whether the ICG method was non-inferior and also non-superior to the ^{99m}Tc method in terms of its ability to identify SNs.

Results: The 134 patients provided 246 SNs, detected by one or both methods. One, 2 and 3 SNs, respectively, were detected, removed and examined in 70 (52.2%), 39 (29.1%) and 17 (12.7%) patients; 4−10 SNs were detected and examined in the remaining 8 patients. The two methods were concordant for 230/246 (93.5%) SNs and discordant for 16 (6.5%) SNs. The ICG method detected 99.6% of all SNs, with only 1 (0.4%) SN detected by the ^{99m}Tc and not the ICG method.
The analysis enabled us to conclude that the ICG method was not inferior and at least equivalent to the ^{99m}Tc method.
Conclusions: Fluorescent lymphangiography with ICG allows good transcutaneous visualization of lymphatic ducts and easy identification of axillary SNs at a frequency non-inferior to that of the gold standard ^{99m}Tc-radiotracer method, suggesting the ICG method for hospitals where radioactive tracer user is is not practicable.
No conflict of interest.

1865 POSTER DISCUSSION

Residual breast tissue after mastectomy: How often and where is it located?

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Background: Residual breast tissue after a mastectomy can lead to a local recurrence (LR) or a (second) primary breast cancer. Findings of normal breast tissue around a LR or the development of breast cancer after prophylactic mastectomy support this assumption. To date, little is known about the prevalence and localization of residual breast tissue. The aim of the present study was to investigate the prevalence and localization of residual breast tissue after a mastectomy.
Methods: A series of 206 women who underwent a mastectomy between January 2008 and August 2009 in 11 hospitals were enrolled in this study, after signed informed consent. From each mastectomy specimen a total of 36 biopsies were obtained from the superficial dissection plane at predetermined locations. The biopsies were analyzed for the presence of benign breast tissue in the inked superficial area. Differences in percentage of positive biopsies were analyzed using generalized Estimating Equations to account for interdependency of biopsies.
Results: 7,374 biopsies from 206 breast specimens of 206 patients were included in the analysis. In 76.2% of the specimens (N = 157) one or more positive biopsies were found. The positive biopsies were found diffusely across the superficial dissection surface of the specimen with a significant predilection for the lower outer quadrant and the middle circle of the superficial dissection plane.
Conclusions: After a mastectomy there is a substantial probability of residual breast tissue. This tissue is predominantly located in the middle circle of the superficial dissection plane and the lower outer quadrant.
No conflict of interest.

1866 POSTER DISCUSSION

[18F]-fluorodeoxyglucose positron emission tomography can contribute to discriminate patients with poor prognosis in hormone receptor-positive breast cancer

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Background: Hormone receptor-positive breast cancer patients show a favorable survival. However, among these patients, identifying the patients in high risk of recurrence is a crucial issue in oncologic field. We tested the hypothesis that [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) scans can help predict prognosis in hormone receptor-positive breast cancer patients.
Materials and Methods: Between April 2004 and December 2008, 307 patients with breast cancer who underwent FGD-PET were enrolled in this study. The patients of luminal B were identified with positive human epidermal growth factor receptor-2 (HER-2) or high Ki67 (⩾14%). A cut-off value of SUV_{max} was defined as 4 according to the previous analysis. Patients were classified according to immunohistochemical (IHC) method or SUV_{max} acquired from FDG-PET.
Results: At a median follow-up of 5.09 years, the patients of luminal B (n = 83) or high SUV_{max} (n = 108) showed a reduced disease-free survival (DFS) ($P = 0.019$ and $P = 0.005$, respectively; all log-rank test). On multivariate analysis, the patients in luminal B showed a poorer disease-free survival independent of tumor size, nodal status, and estrogen receptor status (hazard ratio (HR) 3.05, 95% confidence interval (CI) 1.14–8.16). Instead of luminal B, on the same multivariate analysis with SUV_{max}, high SUV_{max} was demonstrated as a poor prognostic factor (HR 3.61, 95% CI 1.19–11.00). Finally, the patients with luminal B and high SUV_{max} independently showed a worst disease-free survival with 5.88 of HR (95% CI 2.12–16.29). Harrel *c*-indexes were 0.617 with luminal B and 0.656 with SUV_{max}, and 0.699 with the value combined with luminal B and high SUV_{max}, respectively.
Within the group of luminal B, patients with low SUV_{max} showed a significant longer DFS than patients with high SUV_{max} (P = 0.029). In the group of luminal A, patients with low SUV_{max} resulted in better DFS than patients with high SUV_{max} without statistical significance (P = 0.266). Finally, the patients with luminal B and high SUV_{max} independently showed a worst disease-free survival with 5.88 of HR (95% CI 2.12–16.29) compared to the remaining patients. Harrel *c*-indexes were 0.699 with the value combined with luminal B and high SUV_{max}.
Conclusions: Among hormone receptor-positive breast cancer patients, FDG-PET can help discriminate the patients in high risk of tumor relapse.
No conflict of interest.

	Multi (P)	HR	Multi (P)	HR	Multi (P)	HR
Tumor size						
2 cm> vs. ⩽2 cm	0.834	1.17	0.859	0.900	0.654	0.774
Lymph node						
Positive vs. negative	0.091	2.384	0.250	1.825	0.147	2.118
PR						
Positive vs. negative	0.010	3.908	0.005	4.268	0.013	3.848
IHC						
Luminal B vs. A	**0.044**	**2.788**				
Harrel's *c*-index	**0.675**					
SUV_{max}						
4⩾ vs. <4			**0.024**	**3.645**		
Harrel's *c*-index			**0.713**			
SUV_{max} + IHC						
SUV_{max}⩾4 + luminal B vs. the remaining					**0.001**	**5.651**
Harrel's *c*-index					**0.731**	

1867 POSTER DISCUSSION

Minimal molecular alteration in PI3KCA, FGFR1 and CCND1 is associated with increased benefit from everolimus in hormone receptor-positive, HER2− advanced breast cancer: Insights from the BOLERO-2 trial

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Background: In BOLERO-2 (NCT00863655), everolimus (EVE) plus exemestane (EXE) more than doubled progression-free survival (PFS) vs EXE alone in postmenopausal women with hormone receptor-positive (HR^+), $HER2^-$ advanced breast cancer (BC), with consistent benefits in all clinically defined subgroups in this population. Potential molecular markers for predicting EVE benefit were explored by analyzing alterations of a broad panel of cancer-related genes in archival tumor specimens collected from a subset of BOLERO-2 patients.
Material and Methods: Exon sequence and gene copy number variations in 182 cancer-related genes were assessed by next-generation sequencing (NGS). Univariate and multivariate Cox models were used to evaluate correlations with PFS.
Results: Patients with NGS data (>250X coverage; n = 227; 157 in EVE+EXE arm; 70 in EXE-alone arm) had comparable baseline characteristics and PFS outcomes vs the overall trial population (hazard ratio for PFS=0.40 and 0.45, respectively). Treatment benefit with EVE was maintained in almost all subgroups defined by each gene with a mutation rate >10% (eg, PIK3CA, CCND1), or by combined alterations in multiple

genes of the same pathway (regardless of their mutation rates). However, patients with no or only 1 genetic alteration in any of several key signaling or cell cycle genes (PI3K, FGFR1, CCND1) derived a greater PFS benefit from EVE.
In the EVE+EXE arm, patients without PIK3CA mutation trended toward longer PFS than patients with exon 20 mutations, who in turn appeared to have longer PFS than those with exon 9 mutations, suggesting distinct adaptation or feedback mechanisms conferred by variations in PI3K helical and kinase domains upon mTOR inhibition.
Conclusions: This is the first global registration trial in which efficacy-predictive markers were explored by correlating broad genetic variations with clinical efficacy. It demonstrated the feasibility and power of applying NGS in such trials. The observations suggest the potential complex interplay of multiple oncogenic pathways and of different PI3K functional domains in determining EVE sensitivity in HR^+, $HER2^-$ advanced BC. These exploratory results and their implications in testing new hypotheses for targeted combination therapies will be further investigated.
Conflict of interest: *Other substantive relationships: Chen, Robinson, Huang, McDonald and Taran are all employees of Novartis M. Piccart is a board member for PharmaMar, is a consultant to sanofi-aventis, Amgen, BMS, GSK, Boehringer, Roche, and Bayer, and has received grant support from Pfizer, Amgen, Bayer, Boehringer, BMS, GSK, Roche, and sanofi-aventis, as well as received honoraria from Bayer, BMS, GSK, Boehringer, Roche, Amgen, sanofi-aventis, and AstraZeneca J. Baselga is a consultant to Novartis, Roche, Merck, sanofi-aventis, Verastem, Bayer, Chugai, Exelixis, Onyx, Constellation M. Gnant: has received institutional Research Support from sanofi-aventis, Novartis, Roche, Pfizer and Honoraria (Speaking, Advisory Boards, etc.) and Travel Support fromAmgen, Pfizer, Novartis, GlaxoSmithKline, Bayer, Sandoz, AstraZeneca, GenomicHealth, and Nanostring Technologies G. N. Hortobagyi is a member of the Scientific Advisory Board of Allergan, is a consultant to Allergan, Novartis, Genentech, and sanofi-aventis, has received grant support from Novartis, and has received travel expense reimbursement from Novartis, Genentech, and sanofi-aventis*

1868 POSTER DISCUSSION

Pattern of rash, diarrhea, and hepatic toxicities secondary to neoadjuvant lapatinib and their association with age and pathological complete response (pCR) in breast cancer (BC) patients: Analysis from the NeoALTTO trial

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Background: We investigated the pattern of lapatinib-specific adverse events (AEs); rash, diarrhea, and hepatic AEs in BC patients (pts) and their association with age and pCR.
Material and Methods: NeoALTTO (BIG 1−06/EGF106903) is a multicenter phase 3 neoadjuvant trial in which pts with HER2+ early BC were randomized to either: lapatinib (arm A); trastuzumab (arm B); or the combination (arm C) for 6 weeks followed by the addition of paclitaxel for 12 more weeks prior to surgery. In the current analysis, only pts randomized to arm A or C were included. Per protocol, lapatinib was discontinued if pts developed: > grade (Gr) 2 hepatic AEs (elevated liver enzymes and/or bilirubin), Gr4 rash or persistent Gr3−4 diarrhea. We investigated the time to developing and frequency of each AE by CTCAE Gr version 3 according to age ($\leqslant$50 vs. $\geqslant$50), and the association between each AE and pCR in a logistic regression model adjusted for age, hormone receptor status, tumor size, nodal status, planned breast surgery at diagnosis and treatment arm.
Results: 306 pts were included. The median time in weeks to developing rash, diarrhea, and hepatic AEs was 2 (IQR: 1.1−4.2), 2.1 (0.4−7.7), and 6.8 (4.1–10.3), respectively. Younger pts ($\leqslant$50 years) experienced significantly more rash compared to older pts (74.4% vs. 47.9%, $p < 0.0001$). 4% of pts experienced Gr3−4 rash, with low treatment discontinuation and dose reduction rates; 1.3% and 5.8%, respectively. No differences were found according to age regarding the frequency or severity of diarrhea and hepatic AEs. Diarrhea occurred in 78.8% of pts (n = 241), of whom 28% were Gr3−4 (22% of all pts). 28.1% of pts required dose reduction due to diarrhea and 5% discontinued therapy for this reason. Hepatic AEs occurred in 41.2% of pts (n = 126), of whom 36% were Gr3−4 (14.3% of all pts). 10% of pts discontinued therapy (n = 33) and required dose reduction (n = 31) due to hepatic AEs. In a logistic regression model, pts who developed early rash (i.e. before starting paclitaxel) had a significantly higher chance of achieving pCR (OR: 1.71, 95% CI 1.01–2.88, p = 0.044) compared to pts who did not develop an early rash (44.2% vs. 31.8%). No significant association was observed between pCR and diarrhea or hepatic AEs.
Conclusions: Rash is more common in young pts receiving lapatinib. In addition, early development of rash is associated with a higher chance of achieving pCR, independent of age, treatment arm and other clinicopathologic features.
Conflict of interest: *Advisory board: GSK, Roche. Corporate-sponsored research: GSK, Roche. Other substantive relationships: Speaker Bureau, honararia (GSK, Roche)*

1869 POSTER DISCUSSION

Pre- and postdiagnostic physical activity levels in relation to breast cancer outcome in postmenopausal breast cancer patients − results of the TEAM-lifestyle study

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Background: Physical activity (PA) has been related to improved physical function, quality of life and overall and cancer specific survival in breast cancer (BC) patients. PA might have an extra value in treatment of elderly BC patients, since high age is associated with comorbidity and poor physical function. Therefore, the purpose of this study was to investigate the recovery of PA levels after BC treatment in different age groups, and to investigate the effects of PA before and after diagnosis on overall survival, BC survival and recurrence in patients of different ages.
Material and Methods: The TEAM-Lifestyle study is a side-study of the TEAM trial and prospectively investigated lifestyle habits of postmenopausal, hormone-receptor positive BC patients (n = 521). PA was assessed at one year after diagnosis (T1) (including an assessment of prediagnostic PA (T0)) and at two years after diagnosis (T2). The influence of age on recovery of PA (defined as an increase of 3 MET-hours or more from T1 to T2) was analysed in a logistic regression model. Cox regression analysis was used to assess the effect of PA on overall survival. Recurrence-free survival and BC specific survival were calculated by Fine and Gray analyses, taking the risk of competing mortality into account. Here, we present our preliminary findings.
Results: The mean PA level strongly decreased after BC diagnosis and treatment in all patients. Elderly (>65 years) were less likely to recover to prediagnostic PA levels after diagnosis than younger patients (OR 0.61, 95% C.I. 0.41–0.89 compared to patients <65). In both analyses using pre- and postdiagnostic PA data, increased levels of PA (i.e. the three highest quartiles of PA) were associated with an improved overall survival (multivariable HR 0.52, 95% C.I. 0.32–0.84 and HR 0.53, 95% C.I. 0.30–0.96 for the three highest quartiles of pre- and postdiagnostic PA levels compared to the lowest quartile). PA was not significantly associated with BC survival and recurrence-free survival.
Conclusions: In conclusion, elderly BC patients were less likely than younger patients to regain their original levels of PA two years after breast cancer diagnosis. Overall survival was higher in patients who had increased levels of PA, pre- or postdiagnostically, while no statistically significant association was observed for BC recurrence and BC specific survival. More research is needed to investigate the feasibility and efficacy of PA programs in elderly BC patients.
No conflict of interest.

1870 POSTER DISCUSSION

Estimation of an overall treatment time factor for local relapse after adjuvant radiotherapy for early breast cancer by the UK START Trialists' Group

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Background: There is level I evidence that overall treatment time affects the local cancer control rate of squamous carcinomas of the head and neck, but there is as yet no evidence for a similar effect in breast cancer.
Methods: 5861 patients entered into the START (ST)-pilot (P), ST-A & -B trials testing hypofractionated radiotherapy after surgery for early breast cancer form the basis of an estimation of the effect of treatment time.

The ST-P and ST-A trials tested 3.0−3.3 Gy against 2.0 Gy fractions in randomised studies in a constant overall treatment time (5 weeks), allowing direct estimates of the fractionation sensitivity of breast cancer (α/β=3.5 Gy, 95% CI 1.2−5.7). Joint analysis of 10-year local cancer control rates in these trials with those of the ST-B trial testing 15 fractions of 2.67 Gy in 3 weeks against 25 fractions of 2.0 Gy over 5 weeks allows estimation of the possible change in treatment effect in a 3-week vs. a 5-week schedule. A Cox proportional hazards regression analysis of time to loco-regional relapse was stratified for trial to allow for possible differences in case mix among trials. The model included terms for total dose, total dose x dose per fraction (Dxd) and a dummy variable for treatment time (0 = 5 weeks, 1 = 3 weeks), these parameter estimates were used in the following formula to estimate the dose recovered per day (in 2 Gy equivalent fractions), assuming a 14-day time difference between the 2 schedules in ST-B:
$D_{prolif} = (\beta_{time}/14)/(\beta_{Dose} + 2\cdot\beta_{Dxd})$.
Confidence limits of the D_{prolif} estimate were derived by bootstrap resampling.
Results: For N = 5831 patients with data for all variables in the model generated a crude estimate for D_{prolif} (unadjusted) = 0.64 Gy/day. Adjusting for prognostic factors for local-regional relapse in 5613 patients with data for all variables included in the model generated D_{prolif} (adjusted) = 0.59 Gy/day. Non-parametric bootstrap estimates of D_{prolif} and (bias-corrected) 95% CI generated a D_{prolif} (adjusted) = 0.60 Gy/day (95% CI 0.10 to 1.18 Gy/day).
Conclusions: A joint, stratified analysis of the START trials supports the hypothesis that overall treatment time is an important determinant of local cancer control after adjuvant whole breast radiotherapy, with potential for a substantial component of the daily dose required to compensate for proliferation. Overall treatment time should be considered when attempting to devise more efficient and convenient dose-fractionation schedules.
No conflict of interest.

1871 POSTER DISCUSSION

Long-term follow up of axillary recurrences after negative sentinel lymph node biopsy: Effect on prognosis and survival

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Background: As axillary recurrence (AR) after a negative sentinel lymph node biopsy (SLNB) is rare, the prognosis of these patients is unknown. Since treatment paradigms for patients with breast cancer are shifting towards less axillary surgery, the number of ARs might increase. In this study we evaluated primary and salvage treatment as well as long term survival of patients diagnosed with an AR.
Patients and Methods: A retrospective analysis of the cancer registry of 16 breast cancer units in the Netherlands was used to identify patients who developed an AR after a negative sentinel lymph node biopsy (SLNB) performed between 2002–2004. Using local hospital records we recorded primary patient-, tumor- and treatment characteristics, as well as salvage treatment.

Table 1. Treatment after axillary recurrence

ALND performed	45/54 patients
Lymphnodes removed: median (range)	12 (2−27)
Number of positive nodes, median (range)	3 (1−24)
1−3 positive nodes	26
4−9 positive nodes	9
>9 positive nodes	10
Lymphnode ratio	
mean	0.46
standard deviation	0.34
Restaged	50/54 patients
Ipsilateral in breast recurrence	2
Supraclavicular lymphnode metastases	3
Distant metastasis	7
Adjuvant treatment	(52)
External beam radiotherapy	28
Endocrine therapy	24
Chemotherapy	13
Both endocrine- and chemotherapy	10

Results: We identified 54 patients with an AR, median 30 months (range 3−79) after SLNB. Nineteen patients (35%) were initially treated with breast conserving therapy, 17 of whom received external beam radiation therapy (EBRT). Thirty-three patients (61%) did not receive adjuvant systemic treatment. In 45 of the 54 (83%) patients a salvage axillary lymph node dissection (ALND) was performed showing a median of 3 positive nodes (range 1−24). Nine patients (17%) were not treated surgically: 3 were treated with EBRT and 6 with systemic therapy only. At time of detection of the AR, a total of 7 patients (13%) had proven distant metastases. After a median follow up of 47 months (range 3–118) the 5-year 'post-recurrence' distant metastasis free survival was 50% and overall survival was 58%.
Overall survival was significantly worse in patients with an estrogen receptor negative (ER-) primary tumor (p = 0.012), and for patients who initially received chemotherapy (p = 0.021). Survival was not significantly different for patients with different salvage treatment regimens, or with an early versus late recurrence.
Conclusion: AR following a negative SLNB is associated with a 58% 5-year OS. Prognostic factors are ER negative primary tumor and an indication for adjuvant chemotherapy, reflecting an aggressive phenotype. Adequate regional and systemic salvage therapy constitute a chance for long term survival after AR.
No conflict of interest.

1872 POSTER DISCUSSION

Locoregional radiation therapy for left-sided breast cancer: should volumetric modulated arc therapy and breath hold be combined to minimize heart dose?

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Purpose: After the presentation of clinical trial results, the interest in optimising locoregional control for breast cancer increased. Since the relative risk of major coronary events increases linearly with the mean dose to the heart by 7.4% per Gy, with no apparent threshold, the dose to the heart should be kept as low as possible during locoregional breast irradiation.
In this study, we evaluated the role of volumetric modulated arc therapy (VMAT) and voluntary moderately deep inspiration breath hold (vmDIBH) for left-sided breast cancer patients treated to breast/chest wall and internal mammary-medial supraclavicular lymph nodes (IM-MS).
Materials and Methods: For 10 patients, CT scans in free breathing (FB) and vmDIBH were acquired. Three-dimensional conformal RT (3D-CRT) and VMAT plans were calculated for a prescribed dose of 42.6 Gy in 16 fractions. Dose volume values for planning target volume (PTV), heart, lungs and contralateral (CL) breast were compared.
Results: A selection of mean values is presented in Table 1. The coverage of the PTV (volume of PTV with >95% of prescribed dose, $V_{95\%}$) is significantly improved with VMAT, especially for the IM-MS. The heart dose is significantly reduced with both VMAT and vmDIBH, with the lowest values for the combination. The dose to the ipsilateral (IL) lung is also reduced with VMAT, however at the expense of a significantly higher mean dose to the CL lung and breast.

Table 1.

	3D-CRT FB	3D-CRT vmDIBH	VMAT FB	VMAT vmDIBH
IM-MS $V_{95\%}$(%)	90.5	94.6	98.9	99.1
Heart D_{mean}(Gy)	8.8	6.0	5.6	4.4
Heart $V_{30\,Gy}$(%)	10.8	6.0	1.2	0.7
IL lung D_{Mean}(Gy)	19.8	18.1	14.7	14.5
CL Lung D_{Mean}(Gy)	0.3	0.4	3.3	2.4
CL breast D_{mean}(Gy)	0.5	0.6	2.6	2.1

Conclusions: VMAT results in improved dose conformity and PTV coverage, as well as a reduction in heart and lung dose, compared to 3D-CRT. These effects are higher for vmDIBH than for FB. We do not advise standard use of VMAT for patients <40 y, because of possible secondary breast cancer induction, but VMAT might be considered for complicated patient geometries. For patients >40 y, we advise a combination of VMAT and vmDIBH for locoregional irradiation of all left-sided left cancer patients.
No conflict of interest.

Poster Session (Mon, 30 Sep)
Breast Cancer − Advanced Disease

1873 POSTER

Adipose-derived stromal cells isolated from adiponectin deficient mice promote the development of metaplastic mammary tumors

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Background: Adiponectin is a 30kDa glycoprotein secreted exclusively from adipocytes. Unlike most of the adipokines, adiponectin has potent insulin-sensitizing, anti-inflammatory, and anti-tumorigenic activities. Breast cancer development in mice lacking adiponectin exhibits aggressive biological characteristics, including unfavorable prognosis, triple-negative breast tumors and lung metastasis. However, the underlying mechanism remains largely uncharacterized. Adipose-derived stromal cells (ASCs), a population of cells resident in adipose, can regulate breast cancer progression by promoting breast cancer cell proliferation, invasion and migration. The present study aims to investigate the role of ASCs derived from adiponectin deficient mice in breast cancer development.
Materials and Methods: ASCs isolated from wild type [PyVT(+/−)/ADN(+/+)] and adiponectin deficient [PyVT(+/−)/ADN(−/−)] FVB/N-Tg(MMTV-PyVT)634Mul/J mice were implanted into NOD/SCID mice together with human breast cancer MDA-MB-231 cells. Tumor growth and metastasis were evaluated. Gene expression was studied using quantitative real time PCR. Western blot and immunofluoresence was applied for evaluating p63 expression patterns. Chromotin immunoprecipitation (ChIP) was performed to assess the effect of transcriptional factor binding on p63 promoter. Protein interactions were analyzed by co-immunoprecipitation and mass spectrometry.
Results: Tumors derived from MDA-MB-231 cells with co-implanted ASCs derived from PyVT(+/−)/ADN(−/-) mice showed metaplastic breast cancer phenotype, including increased expression of metaplastic markers (p63 and CK14) and muscle-like cellular transdifferentiation. Both protein and mRNA levels of dominate negative p63 (DN-p63) were significantly elevated in tumor tissues derived from MDA-MB-231 cells co-implanted with ASCs of PyVT(+/−)/ADN(−/-) mice, when compared to those co-implanted with ASCs of PyVT(+/−)/ADN(+/+) mice. Mechanistically, it was found that a transcriptional factor YY1 modulated the expression of p63. Adiponectin deficiency promoted the association of YY1 with the promoter of DN-p63. The zinc finger domain of YY1 played a key role in silencing DN-p63 expression.
Conclusion: ASCs of adiponectin deficient mice promotes metaplastic breast cancer development in mice.
No conflict of interest.

1874 POSTER

Glucocorticoid influences on breast cancer metastasis: bad, benign or beneficial?

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Background: Chemotherapy-induced nausea and emesis is commonly treated by administration of glucocorticoids. Despite being effective anti-emetics, glucocorticoids are also thought to directly modulate tumour cell behaviour. Breast tumour metastasis involves integrated and sequential processes, influenced by tumour cells and surrounding microenvironment, both of which are targeted by glucocorticoids. We have previously identified a class effect of glucocorticoids in inhibiting serum-induced migration in the human metastatic breast tumour cell line, MDA-MB-231, in a 2-dimensional scrape wound healing assay and a 3-dimensional modified Boyden chamber assay. This study has focused on extending the findings in a mouse model of breast tumour metastasis.
Methods: mCherry-expressing 4T1.2 murine breast tumour cells (500,000) were injected into the 4th mammary fat pad of Balb-c mice. Dexamethasone (dex) was administered subcutaneously at 0.1 mg/kg/day, commencing 2 days after a tumour was first palpable. Primary tumour and organs were harvested after a further 23 days. DNA was extracted from lung, spine and femur using phenol-chloroform and levels of mCherry were measured using qPCR along with vimentin as a reference. mCherry content normalised to vimentin was assessed as a measure of metastasis.
Results: Dexamethasone treatment reduced final body weight (Vehicle: 19.0±0.3g, Dex: 18.0±0.3g, $P<0.05$, $n = 24-27$) but there was no effect on primary tumour weight. There was a significant increase in mCherry content (metastasis) in the lungs of dex-treated mice (Vehicle: 1.2±0.3, Dex: 2.4±0.6, $P = 0.01$ Mann-Whitney non parametric test, $n = 24-27$).
Conclusions: Dexamethasone had no effect on primary tumour growth but increased metastasis to the lung. This effect was opposite to expectations based on previous *in vitro* studies. Our findings reveal that dexamethasone promotes tumour spread. Confirmation of these findings in xenograft models of human breast tumours in mice would raise questions about the use of glucocorticoids in treating breast cancer-associated emesis.
No conflict of interest.

1875 POSTER

An in vivo screen to identify novel modulators of cytotoxic chemotherapy response

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Background: Clinically, development of chemotherapy resistance is an inevitable event in the treatment of patients with advanced breast cancer. Currently, little information is available to guide selection of first line therapy, with anthracyclines and taxanes giving similar benefit to patients. The purpose of this study is first to identify novel targets in chemotherapy resistant advanced breast cancer. Second it aims to identify novel biomarkers of sensitivity or resistance, specifically to anthracycline based chemotherapy.
Methods: In recent years, pooled RNAi screening, combined with next generation sequencing, has allowed high-throughput identification of genes involved in a range of cellular processes. The adaptation of these screens to the *in vivo* setting, while technically challenging, has been shown to allow identification of novel determinants that would have been missed using in vitro approaches. To interrogate resistance mechanisms in advanced breast cancer, an *in vivo* RNAi screen was designed, to discover novel genes involved in the response to anthracycline based chemotherapy. This screen utilized the Cancer 1000 shRNA library targeting 1000 genes of known cancer association.
Results: From this screen, 168 candidate genes were identified as involved in either sensitization or resistance to anthracycline based chemotherapy. These candidates include a number of genes known to be involved in chemotherapy response, including the known target of anthracyclines, *Top2a*. A combination of statistical, pathway, expression and literature analysis has been used to shortlist 7 candidate genes for initial validation studies.
Conclusions: Pooled RNAi screening has allowed identification of novel candidate genes involved in sensitization or resistance to anthracycline based chemotherapy. Further studies are focusing on the validation of these candidates. In addition, it is being investigated as to whether these genes mediate an anthracycline specific response, or a multidrug resistance or sensitivity phenotype. Determination of the mechanism of action will be critical to assess the suitability of these candidates as therapeutic targets and their use as predictors of patient response.
No conflict of interest.

1876 POSTER

Individual risk profiling for breast cancer recurrence: Towards tailored follow-up schemes

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Background: Breast cancer follow-up is not tailored to the risk of locoregional recurrences in individual patients or as a function of time. The objective of this study was to identify prognostic factors, and to estimate individual and time dependent locoregional recurrence risk rates, in order to tailor follow-up for the individual patient in terms of intensity and duration.
Material and Methods: Prognostic factors for locoregional recurrence were identified by a scoping literature review, field expert consultation, and stepwise multivariate regression analysis based on 5-years of population data from the Netherlands Cancer Registry from women diagnosed with breast cancer in the Netherlands in 2005 or 2006 ($n = 17762$). Inter-patient variability was elucidated by examples of five-year risk profiles of average, medium, and high risk patients, whereby six-month interval risks were derived from regression estimates.
Results: Eight prognostic factors were identified: age, tumour size, multifocality, gradation, adjuvant chemo-, adjuvant radiation-, hormonal therapy and triple negative receptor-status. The mutual weights of the contribution to the local regional recurrence risks were determined. Risk

profiles of the low-, average-, and high risk example patients showed non-uniform distribution of recurrence risks (2.9%, 7.6%, and 9.2% respectively over a five year period).
Conclusions: Individual risk profiles differ substantially in subgroups of patients defined by prognostic factors for recurrence and over time as defined in six-month time intervals. To tailor follow-up schedules, decrease anxiety in patients and to optimise allocation of scarce resources, risk factors, frequency and duration of follow-up should be taken into account.
No conflict of interest.

1877 POSTER

Long-term results of reirradiation and hyperthermia in recurrent breast cancer

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Introduction: Reirradiation combined with hyperthermia is an effective treatment for recurrent breast cancer. Here we report long-term results of patients treated since 1992.
Materials and Methods: 198 patients with subclinical disease and 250 with irresectable disease were treated, including 36 patients with tissue transfers. All patients were treated with 8 fractions of 4 Gy twice weekly, and 8 (until 1996) or 4 one-hour hyperthermia treatments applied after radiotherapy. Approximately half of the patients received radiotherapy in another institute.
Results: In subclinical disease the 3- and 5-year local control (LC) was 83% and 78%. In patients with irresectable disease complete response was 70%, and 3- and 5-year LC was 40% and 39%. Five- and 10-year overall survival was 60% and 36% for subclinical disease, and 18% and 10% for irresectable disease. Both LC and toxicity in patients with tissue transfers were similar to those in the other patients. Superficially measured temperatures >43ºC were associated with more hyperthermia toxicity.
Patients irradiated elsewhere had a better LC than patients irradiated in the Erasmus MC. For patients with gross disease, the radiating institute was the only singificant factro influencing LC in multivariate analysis. At the same time, patients with subclinical disease irradiated elsewhere had significantly less late grade 3−4 toxicity (7% at 5 years) than patients irradiated in Erasmus MC (15%).
Conclusions: These results again show that reirradiation with hyperthermia is worthwhile for patients with recurrent breast cancer. Patients with transfers can be treated safely. The better results in patients irradiated elsewhere was unexpected. Hyperthermia toxicity may be decreased when superficially measured temperatures are kept below 43ºC.
No conflict of interest.

1878 POSTER

Bevacizumab preconditioning followed by etoposide and cisplatin (BEEP) is a highly effective treatment for brain metastases of breast cancer progressing from radiotherapy − result of a multi-center phase II study

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Background: Management of brain metastasis of breast cancer progressing from whole brain radiotherapy (WBRT) remains a severe challenge. We hypothesized that starting bevacizumab (BE) 1 day before chemotherapy could further enhance the activity of etoposide (E) and cisplatin (P), two of the cytotoxic agents that have moderate activity in brain metastases of breast cancer, by increasing drug delivery into tumor tissue via BE-induced vascular normalization. This trial is registered with ClinicalTrials.gov, number NCT01281696.
Material and Methods: Breast cancer patients (pts) with brain metastases and brain lesions progression after WBRT were enrolled. Treatment was given in 21 day cycles: pts received BE 15 mg/kg on day 1, E 70 mg/m^2/day from day 2 to day 4, and P 70 mg/m^2 on day 2 (BEEP regimen), for a maximum of 6 cycles. The primary endpoint was a centrally assessed objective central nerve system (CNS) response, defined as a $\geqslant$50% reduction in the volumetric sum of all measurable CNS lesions in the absence of increasing steroid use, development of new CNS lesion, or progressive neurologic symptoms. An objective CNS response rate of 30% is assumed and 15% as a minimum interest, using a Simon's optimum two-stage design with a significance level α of 0.15 and a power of 80%, a total of 31 assessable pts are required. Serial dynamic contrast enhancement MRI (DCE MRI) 1 hr and 24 hrs after BE infusion were performed in selected suitable pts.
Results: Thirty five pts were enrolled from Jan 2011 to Jan 2013. All pts were included for safety and efficacy analysis (reported by intent to treat analysis). Median age was 54.3 (range 33−75); 6 pts were ER+HER2−, 23 pts were HER2+, and 6 pts were ER−HER2−. The median treatment cycles were 5 (range 1−6). Twenty seven of 35 pts (77.2%; 95% CI 59.9–89.6) achieved CNS response including 12 pts (34.3%) with $\geqslant$80% and 15 pts (42.9%) with 50−80% CNS volumetric reduction, respectively. Six pts (17.1%) had 20−50% CNS volumetric reduction. Six pts had non-CNS disease progression while CNS tumors remained under control. With median follow-up of 11.0 months, the median CNS progression free survival was 6.7 months (95% CI 5.1−8.3), and overall survival was 9.4 months (95% CI 7.3–11.5). Grade 3 /4 toxicities ($\geqslant$1%) included neutropenia, leukopenia, infection, anemia, and thrombocytopenia in 32.1%, 16.4%, 9.5%, 8.2%, and 6.9% per cycles, respectively. One pt died of infection and 1 pt died of tracheo-esophageal fistula. The latter pt had extensive mediastinal lymph node metastases, but her CNS tumors completely resolved after 3 cycles of BEEP. Seventeen pts (48.6%) needed dose reduction of E to 60 mg/m^2 and P to 60 mg/m^2, and 3 pts discontinued from treatment due to toxicity. Eight pts received serial DCE MRI study. In general, tumor vascular normalization could be observed at 1 hr, but become much more obvious 24 hrs after BE infusion.
Conclusions: BE given one day before E and P (BEEP regimen) induces better vascular normalization and significantly improve the efficacy of chemotherapy against brain metastases of breast cancer progressing from previous WBRT.
No conflict of interest.

1879 POSTER

Integrated genomic analysis identify candidates genes in luminal B breast cancer

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Background: Breast cancer is a complex and heterogeneous disease. Characterization of genomic alterations such as amplification of oncogenes and loss of tumor suppressor genes (TSG) combined with expression data could identify candidate genes. We focused on luminal B breast cancer molecular subtype whose clinical course is particularly pejorative and for which no targeted therapy exists.
Material and Methods: High-Troughput molecular analysis such comparative genomic hybridization on microarrays (aCGH) was used to characterize the regions targeted by chromosomal alterations in breast cancers. In addition, an integrated analysis of genomic and expression profiling from DNA microarrays has contributed to the identification of candidate genes.
Results: We demonstrate that the candidate gene *L3MBTL4* is targeted by multiple genomic alterations, suggesting its involvement as a potential TSG in luminal B breast cancer molecular subtype. Furthermore, our comparative analyses of integrated profiles of breast cancers identified specific luminal B molecular subtype candidate genes.
Conclusion: High-Troughput molecular analysis of breast cancer has already revealed some part of their potential. Such integrated approaches could contribute to better understand the various levels of the molecular changes in the mammary oncogenesis and identify new markers.
No conflict of interest.

1880 POSTER

Management of bone metastases secondary to breast cancer: a comprehensive survey of practice patterns in five European countries

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Background: Bone metastases occur in over 70% of patients with advanced breast cancer. They are frequently associated with debilitating skeletal-related events (SREs; pathologic fracture, need for radiation or surgery to bone, spinal cord compression), which can cause severe pain, immobility and reduced quality of life. Bone-targeted agents (BTAs) delay

and prevent SREs. We evaluated the management of bone metastases in patients with breast cancer.
Material and Methods: Prospective, observational patient record study involving physicians from France, Germany, Italy, Spain and United Kingdom. Data for the patients with breast cancer are reported here. In total, 881 physicians took part, completing brief questionnaires on 3096 patients with breast cancer and bone metastases seen during the observation period, and collecting detailed information on a further 1915 patients. Patient cases were weighted according to the probability of prospective inclusion in the study (i.e. patient consultation frequency and length of observation period).
Results: Only 61% of patients with bone metastases were receiving bisphosphonates (the only BTAs available at the time of this study) and 11% were expected never to receive them. One-fifth of patients had discontinued treatment with bisphosphonates; the most common reason was 'end of treatment as planned'. Of patients who discontinued treatment, 25% stopped due to adverse events of which, 36% experienced renal toxicity. Renal issues were also the main reason physicians expected patients never to receive bisphosphonates, although short life expectancy and poor risk/benefit profile for the patient were also concerns. Treatment patterns were generally consistent across countries, although in Germany patients were more likely to be diagnosed with solitary, rather than multiple, metastasis.
Conclusions: Many patients who could benefit from BTAs are not receiving treatment. Most guidelines do not specify that treatment should have a pre-planned duration; therefore, better education of physicians regarding the risk/benefit profile of BTAs may prevent patients stopping treatment unnecessarily. A considerable number of patients did not receive bisphosphonates due to their renal toxicity, suggesting there is a need alternative treatment options.
Conflict of interest: *Ownership: PS, IH, SS − own Amgen stock. Corporate-sponsored research: AF − Amgen. Other substantive relationships: PS, IH, SS − own Amgen stock*

1881 POSTER

Quality-of-life in HER2-positive metastatic breast cancer for patients initiating an oral anticancer drug: results from a French prospective observational study

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Background: The impact of disease on quality-of-life (QoL) is a seldom studied domain. This study aimed at evaluating the evolution of patient's QoL with HER2-positive (+ve) metastatic breast cancer (mBC) between oral treatment initiation and the 6 month of follow-up.
Material and Methods: A prospective observational multicenter study was conducted among 284 HER2+ve mBC patients included by 68 oncologists initiating oral anticancer drug. Data were collected on clinical characteristics, treatment patterns, adherence and QoL. Patients were invited to complete a questionnaire at treatment initiation (T0) and after each 3-month period. QoL was assessed using generic (Short-Form Health Survey, SF-12) and specific (EORTC QLQ-BR23) scales. The general health status was evaluated through an additional question. For comparison purpose, analyses were conducted on the 64 patients who returned their self-questionnaire at T0 and after 6 months (T6).

	T0 (n = 64)	T6 (n = 64)	p-value [1]
EORTC QLQ-BR23, mean (SD)			
Body image	53.3 (29.4)	58.9 (27.7)	0.276
Sexual functioning	25.0 (21.6)	24.9 (22.4)	0.980
Sexual enjoyment *(only if sexual functioning)*	39.7 (27.9) *	40.5 (21.8) **	0.905
Future perspective	35.4 (35.4)	36.4 (29.4)	0.862
Systemic therapy side effects	39.6 (19.8)	32.0 (16.5)	0.023
Breast symptoms	21.5 (26.1)	18.6 (21.0)	0.498
Arm symptoms	24.0 (24.2)	23.2 (22.5)	0.849
Upset by hair loss	45.6 (32.0)	44.4 (19.0)	0.857
SF-12 score, mean (SD)			
Physical component of QoL	37.7 (8.9)	40.2 (7.8)	0.102
Mental and social component of QoL	39.0 (10.4)	40.9 (8.5)	0.272

[1] Student test. *Analyses conducted on 26 patients, **analyses conducted on 32 patients.

Results: Apart from a significant impact of systemic therapy side effects on QoL between T0 and T6, there is no significant difference in the dimensions explored by the QLQ-BR23 scale. The results from the SF-12 scale showed no difference on either dimensions. The additional question showed a significant increase in the proportion of patients stating to be in a 'very good/good health status' (48% of patients at T0 versus 70% at T6 ($p = 0.036$)).
Conclusions: Overall, no significant trend was showed in the QoL evolution possibly due to the low number of patients analyzed as usually seen in such studies. Concurrently results showed stable QoL data on the large majority of criteria. Patients felt an improvement in their general health status over time. Even though this study is not comparative, the convenience of oral anticancer drugs may partly explain stable QoL outcomes across time.
Conflict of interest: *Advisory board: GSK. Corporate-sponsored research: Boehringer-Ingelheim Pfizer Roche Sanofi-Aventis. Other substantive relationships: Cephalon GSK Roche*

1882 POSTER

Count us, know us, join us global survey: information needs among women living with metastatic breast cancer

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Background: Advanced breast cancer (stage III and stage IV/metastatic) is the most serious form of breast cancer. Defined by the cancer's spread to distant parts of the body such as the bone or liver, metastatic disease is rarely static, has increasing health implications, requires lifelong treatment, and is ultimately fatal. Support needs for this patient group are unique, yet rarely met. Hoping to identify new approaches to meeting the needs of this community, a global survey was commissioned by Novartis Oncology in partnership with the global advocacy community.
Methods: Harris Interactive conducted an online survey between October 2012 and March 2013. It was completed by 1,273 metastatic breast cancer patients from 10 countries (US, Canada, Mexico, Brazil, Argentina, UK, Germany, Russia, India, and Lebanon), as well as Taiwan and Hong Kong. Total sample data are not weighted and representative only of the individuals surveyed. A global post-weight was applied to ensure all countries received an equal weight in the global and regional data.
Results: Overall, a majority of patients (77%) actively seek out information, but nearly half (45%) say information is hard to find, and more than half (55%) say available information does not address their needs. 72% of patients, especially those in Mexico and Brazil (91% each; n = 102 and n = 100, respectively), feel that resources to help friends and family cope and better understand the disease would be helpful. US women (n = 349) are much more likely to rely on websites (84%), written materials (66%), support groups (60%), scientific journals (33%), and in-person/telephone workshops or conferences (35%), whereas 74% of Russian women (n = 100) rely heavily on non-governmental organizations (NGOs) for information. More than half of the women surveyed indicated Internet-based resources would be helpful, including websites (68%) and social networking tools (52%). Of note, 77% of UK women (n = 66) agree there is enough information available, but also feel overwhelmed by it (64%). Additional results highlight regional differences in gathering and utilizing information.
Conclusions: The means of collecting metastatic breast cancer information varies by region, and there is great global commonality in the type of information sought as well as the need for relevant, easily accessible data. Finding culturally-friendly ways to supply information worldwide is urgently needed.
No conflict of interest.

1883 POSTER

Strong compliance with electronic patient-reported (ePRO) reporting in multinational breast cancer trials

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Background: Patient Reported Outcomes (PRO) and electronic PRO (ePRO) are increasingly becoming an important aspect of cancer clinical trials and patient care, especially with regard to measuring drug efficacy, patient quality-of-life and drug safety. Subject compliance with completion of PRO/ePRO assessments is an important component for obtaining accurate and high-quality data when conducting clinical trials. It has been hypothesized that patient health status, age, length of time in a trial and country of origin, may affect compliance.
Material and Methods: To address this hypothesis, an operational analysis was conducted to assess oncology subject completion compliance of PRO reports using an electronic tablet to determine its suitability and performance in use. Toward this objective, the compliance of breast cancer patients in completing three electronic questionnaires that were

administered at clinic visits was evaluated. Subjects were asked to complete the EORTC QLQ-C30, EORTC QLQ-BM22, and the EQ-5D. Questionnaires were completed electronically on the tablet. Percent completion was calculated as the number of questionnaires completed divided by the number of questionnaires expected, based on attended clinic visits compiled for this review and the administration schedule for the questionnaires.
Results: This review draws on the experience of over 450 subjects from 16 countries, and describes the individual and overall compliance with the expected questionnaire completion, completion as a function of age, the variance between subsequent visits, and compliance by country. From age 20 to 89 years of age, there was no impact on compliance with overall compliance for all questionnaires between 95% and 100%.
Conclusions: The collection of ePRO using a clinic-based tablet yielded a highly complete data set in breast cancer subjects demonstrating that this is an effective and feasible approach for recording symptoms and quality-of-life assessments.
No conflict of interest.

1884 POSTER

Progression of breast cancer following ipsilateral recurrence: Importance of stage, age and interval time between the two diagnoses

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Background: Studies comparing prognosis of breast cancer (BCa) between women with and without a local recurrence (LR) present conflicting results. We aimed to improve understanding of the biology of LR and its impact on prognosis using a large cohort from Guy's and St Thomas' NHS Foundation Trust.
Methods: Risk factors associated with BCa-specific death were investigated in 5,055 women diagnosed between 1975 and 2007 using Cox proportional hazards regression. BCa-specific death following LR was assessed with Poisson regression.
Results: 552 women (10%) developed LR during a median follow-up time of 4.19 years. Factors associated with BCa-specific death (stage, grade and nodal status) were also associated with risk of LR. For instance, the HR for BCa-specific death among women undergoing mastectomy with $\geqslant$10 positive nodes was2.29 (95% CI: 1.38–3.79) compared to those with no positive nodes. Women with shorter disease-free interval had a worse prognosis. The risk of BCa-specific death following LR occurring <6 years of diagnosis dramatically increased during the first three years, but this levelled off with time.

Table 1. Hazard Ratios (HRs) and 95% confidence Intervals (CI) for risk of BCa-specific death following LR, stratified by surgery type and adjusted for age, tumour grade, nodal stage and treatment of initial BCa.

Time between primary diagnosis and LR	Mastectomy		Breast conservation	
	HR	95% CI	HR	95% CI
<1	5.68	3.42–9.44	9.52	5.35–16.95
1−3	3.04	1.95–4.73	3.79	2.43–5.91
4−6	2.22	1.20–4.13	2.81	1.63–4.83
>6	1.00	(ref)	1.00	(ref)

Conclusion: The sharp increase in risk of BCa-death after LR suggests that some LRs may be components of active disease, particularly for women who have a short interval time between primary diagnosis and LR. These findings have implications for diagnostic work up and treatment of women with LR.
No conflict of interest.

1885 POSTER

Association of genetic polymorphisms in the tumor suppressor ERP29 and in the DNA transcription factor IKBKAP with breast cancer risk

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Background: The *ERP29*, a tumor suppressor gene, and *IKBKAP*, a gene that act in transcriptional process, seems to be related with the onset of tumors. The analysis of the influence of *ERP29* c.*293A>G and *IKBKAP* p.Cys1072Ser polymorphisms in breast cancer (BC) risk has never been performed before and was the aim of the present study.
Materials and Methods: *ERP29* c.*293A>G and *IKBKAP* p.Cys1072Ser genotypes of 742 BC patients (median age: 53 years, 638 Caucasians, 104 non-Caucasians) and 742 healthy women (median age: 40 years, 638 Caucasians, 104 non-Caucasians) were obtained in genomic DNA by polymerase chain reaction in real time using primers and TaqMan® probes. The differences between groups were analyzed by the χ2 test. Power of analysis (PA) was used to determine the effect of sample size on the results obtained in the study.
Results: Patient's and control's samples were in HW equilibrium at *ERP29* c.*293A>G (χ2= 0.14, P = 0.71; χ2= 3.75, P = 0.05) and *IKBKAP* p.Cys1072Ser (χ2= 2.16, P = 0.14; χ2= 2.44, P = 0.12) loci. The frequency of *ERP29* c.*293AG+GG genotype was higher in patients than in controls (36.6% *versus* 30.7%, P = 0.03; PA= 74.0%). Carriers of G variant allele were under a 1.33-fold (95% CI: 1.03–1.72) increased risk for BC than those with AA wild genotype. *ERP29* c.*293AG+GG (62.5% *versus* 32.4%, P<0.0001, PA>99.0%) and *IKBKAP* p. 1072SerSer (50.0% *versus* 34.4%, P = 0.002, PA= 86.2%) genotypes were more frequent in non-Caucasian patients than in Caucasian ones. Besides, *ERP29* c.*293AG+GG genotype was also higher in non-Caucasian patients when compared to controls (62.5% *versus* 30.7%, P = 0.01, PA> 99.0%). Carriers of G variant allele were under a 2.31-fold (95% CI: 1.22–4.39) increased risk for BC development. The frequency of *ERP29* c.*293AG+GG genotype in underweight and normal patients was higher than that found in pre-obese and obese ones (43.9% *versus* 33.0%, P = 0.005, PA= 81.9%), and also than in controls (43.9% *versus* 30.7%, P = 0.003, PA= 96.0%). Underweight and normal carriers of G allele of the above-mentioned gene were under a 1.64-fold (95% CI: 1.19–2.27) increased risk for BC. Moreover, *IKBKAP* p. 1072SerSer genotype was more common among women who breastfed compared to those who did not (6.5% *versus* 2.3%, P = 0.03, PA= 65.4%).
Conclusion: Our data suggest, for the first time, that *ERP29* c.*293A>G and *IKBKAP* p.Cys1072Ser polymorphisms alter the risk of BC and its clinical features. We believe that women with variant alleles of the above-mentioned genes should receive additional medical attention for disease prevention and early diagnosis.
No conflict of interest.

1886 POSTER

How accurately can we pre-operatively stage the axilla for breast cancer?

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Introduction: Pre-operative staging of the axilla in breast cancer patients is essential for deciding initial surgical treatment and often avoids the need for a second operation. The aim of this study was to evaluate pre-operative axillary ultrasound imaging +/− ultrasound guided FNAC/biopsy in assessing axillary node status.
Method: We performed a retrospective analysis of 392 patients diagnosed with breast cancer. Data collected included preoperative and postoperative axillary node status, and requirement for further treatment. The proportion of patients that pre-operative staging correctly identified was ascertained.
Results: Axillary disease was present in 147 (39%) patients. Preoperative axillary ultrasound and FNAC/biopsy correctly identified 51 (49%) of these patients. Sensitivity and specificity of pre-operative axillary ultrasound was 48% and 86%, respectively. Sensitivity and specificity of preoperative axillary ultrasound and FNAC/biopsy was 84% and 73%, respectively. On post-operative histology 46 (31%) patients required a further axillary procedure due to negative pre-operative staging.
Conclusion: Axillary ultrasound +/− ultrasound guided FNAC/biopsy determined the correct initial axillary procedure in 278 (73%) of our patients. The percentage of false negative results of ultrasound and ultrasound guided FNAC/biopsy was high at 10% and therefore, remains an inadequate definitive predictor of axillary node involvement.
No conflict of interest.

1887 POSTER

Prognostic factors for survival after recurrent metastasized breast cancer by hormone receptor status

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Background: Metastases after curatively treated breast cancer are considered incurable. Survival among patients with metastases is poor, but varies considerably between patients. Hormone receptor (HR) status is an important prognostic factor for patients with recurrent metastatic breast cancer (MBC). HR status is correlated to other prognostic factors such as age, tumour grade, metastasis-free interval (MFI) and site of distant metastasis. The aim of this nationwide population-based study was to determine the independent prognostic effect of these factors for survival after MBC according to HR status.
Methods: Dutch women diagnosed with breast cancer in the period 2003–2006 treated with curative intent who developed metastatic breast cancer within 5 years of follow-up were selected from the nationwide population-based cancer registry (N = 1,961). Independent prognostic factors for survival were determined by univariable and multivariable cox survival analyses, stratified by HR status.
Results: HR positive patients (65% of total) were younger and had longer metastasis-free intervals (MFI), compared to patients with a HR negative tumour (P<0.001). Their tumours were also more likely to be smaller, low grade, HER2 negative and to be associated with MBC in bones. Median overall survival for HR positive patients was 18 months vs 8 months for HR negative patients. Univariable and multivariable analyses revealed that a longer MFI resulted in better survival for HR negative patients (HR = 0.62; P<0.001), while no significant association was seen for HR positive patients (HR = 0.87; P = 0.052). HR positive patients with a higher grade primary tumour had a worse survival (HR = 1.41; P<0.001), no significant association was seen for HR negative patients (HR = 1.23; P = 0.082). For both HR negative and HR positive patients older age at MBC diagnosis and multiple sites were independent prognostic factors for poorer survival.
Conclusion: The influence of MFI and tumour grade on overall survival of patients with metastatic breast cancer is associated with HR status. The unfavourable prognostic impact of the number of metastatic sites and older age was independent of the HR status. This prognostic information according to HR status may assist physicians in clinical decision making and can support clinical decision making in personalized medicine.
No conflict of interest.

1888 POSTER

Patterns of disease management for European postmenopausal women with hormone-receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2−) advanced breast cancer

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Background: International guidelines (ESMO, NCCN) for HR^+ advanced breast cancer (ABC) recommend multiple lines of hormonal therapy (HT) if response is observed. Chemotherapy (CT) is recommended for patients with extensive visceral involvement or rapidly progressive disease. This study evaluates actual physician-reported treatments from adjuvant therapy to completion of at least 3 lines of therapy in the ABC setting.
Materials and Methods: Retrospective chart review in Belgium, France, Germany, The Netherlands, and Sweden of 355 postmenopausal women (PMW) diagnosed with HR^+, $HER2^-$ ABC in the past 4 years. Patients had to progress on $\geqslant$1 line of HT and complete $\geqslant$1 line of CT in ABC. Treatment choice was evaluated for each line of therapy. Factors considered for treatment decisions included performance and disease status and change in disease status.
Results: Of 355 patients, 111 (31%) received 1st-line CT whereas 218 (61%) and 26 (7%) switched from HT to CT in 2nd and 3rd line, respectively. More patients receiving 1st-line HT had bone metastases (73% HT vs 27% CT) and strong ER^+ status (92% HT vs 68% CT). Patients treated with 1st-line CT had more brain (0% HT vs 12% CT) or extensive liver (0% HT vs 13% CT) metastases. High (>20%) Ki-67 status was not a strong predictor of CT use. Subgroup analysis of 188 patients with *de novo* metastatic or recurring disease who received 1st-line HT and did not have rapidly recurring disease (ABC diagnosis during/within 1 year of completing adjuvant therapy) found that the majority (89%) of these patients switched to CT in 2nd line. However, among these 167 patients, 27% had no significant changes in metastases between 1st and 2nd line and a mean duration of 1st-line therapy of 9.5 months. Among the 73% (n = 122) of patients who had a significant change in metastases, 20% (n = 24) had no brain or extensive visceral disease and a mean duration of 1st-line therapy of 8.7 months.
Conclusions: Physician-reported use of HT and CT in European PMW with HR^+, $HER2^-$ ABC suggests that the majority of patients receive CT earlier than recommended by treatment guidelines. Our study provides evidence suggesting that the guideline-recommended use of multiple lines of HT may be less than optimal for ABC patients who responded to HT and lacked extensive visceral disease.
Conflict of interest: *Advisory board: FA Advisory Board and Speaker Bureau for Novartis Advisory Board for AstraZeneca. Other substantive relationships: NM Consultant, Novartis Pharmaceuticals Corporation JZ Novartis employee RD Consultant, Novartis Pharmaceuticals Corporation GB and SS Novartis employee with stock/stock options GJ Advisor, consultant, Novartis Pharmaceuticals Corporation*

1889 POSTER

The number needed to treat for everolimus plus exemestane or fulvestrant relative to exemestane alone from BOLERO-2, EFECT, and SoFEA trials

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Background: The phase 3 study Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2; N = 724) at 18 months' median follow-up demonstrated that everolimus (EVE) + exemestane (EXE) more than doubled progression-free survival (PFS) versus placebo (PBO) + EXE in patients with hormone-receptor-positive (HR^+), $HER2^-$ advanced breast cancer (ABC) recurring/progressing on/after nonsteroidal aromatase inhibitor (NSAI) therapy. Number needed to treat (NNT; the reciprocal of absolute risk reduction) is the number of patients who need to be treated with a new therapy to avoid 1 additional event compared with standard therapy. For randomized controlled trials, NNT is a clinically useful measure of treatment effect. The Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT; N = 693) and Study of Faslodex, Exemestane, and Arimidex (SoFEA; N = 723) trials compared fulvestrant (FUL, 500 mg day 1; 250 mg day 15, then monthly) versus EXE (the control arm of BOLERO-2) in a patient population similar to BOLERO-2. Thus, these treatment alternatives were assessed via comparison of the NNTs for both EVE+EXE and FUL versus EXE alone.
Materials and Methods: The NNT for EVE+EXE versus EXE in BOLERO-2 was calculated using survival probabilities for PFS at 12 months for both investigator and central assessment. The NNTs for FUL versus EXE were calculated for time to progression (TTP; EFECT) and for PFS (SoFEA), based on survival probabilities estimated from Kaplan–Meier plots (Johnston S, et al. EBCC 2012 and Chia S, et al. *J Clin Oncol*. 2008;26:1664−70, respectively) using ByteScout software.
Results: At 12 months in BOLERO-2, NNT to prevent progression for EVE+EXE versus EXE was 4.5 (95% confidence interval [CI], 3.5 to 6.2) per investigator assessment and 3.4 (95% CI, 2.6 to 5.1) per central assessment. In comparison, the 12-month NNTs with respect to TTP or PFS for FUL versus EXE from 2 trials in patients with HR^+ ABC after prior NSAI were 36.8 in EFECT and 35.1 in SoFEA. Additionally, 6- and 18-month NNTs from the 3 trials will be presented.
Conclusions: These results support the clinically meaningful improvement in PFS with EVE+EXE versus PBO+EXE in patients with HR^+, $HER2^-$ ABC and recurrence/progression on/after NSAI. The NNT range to prevent progression with EVE+EXE versus EXE alone was 3.4 to 4.5 patients. In contrast, the estimated NNT to prevent progression with FUL versus EXE was 35.1 to 36.8.
Conflict of interest: *Other substantive relationships: J Zhang and H Gao are employees of Novartis*

1890 POSTER

Breast scintigraphy with 99mTc-MIBI in clinical practice

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Purpose: To evaluate different applications of breast scintigraphy (SMG) in routine clinical practice.
Material and Methods: SMG was performed in 232 women with suspect for breast cancer (BrCr). SMG was performed in planar and tomography modes 15 min. after i/v injection of 740–860 MBq 99mTc-sestamibi. Images with focal and scattered patchy uptake were considered as abnormal. All lesions were verified by biopsy and/or by operation.
Results: Sensitivity (Sen), Specificity (Sp) and Accuracy (Ac) of SMG in the whole group was as following: 94.8%, 72.5%, 90.9%. In 36 women with *lesions below 1 cm* SMG revealed 12 of 14 cases of BC and refused malignancy in 16 of 21 women's with benign breast lesions. Sen, Sp and Ac of SMG in this group were 86%, 76% and 80%.
SMG showed moderate Sen, Sp and Ac in diagnosis of axillary metastases (60%, 86%, 76%) but help to detect involvement of internal mammary and/or sub-supraclavicular lymph nodes in 8% and 6.3% cases.
SMG demonstrated high efficacy in diagnosis of multicenter/multifocal BrCr which was revealed in 14.8% cases: 7.4% − multicenter and 7.4% − multifocal. For comparison conventional imagings (US and mammography) were able to detect multicentre/multifocal disease only in 3.7% cases.
Conclusion: SMG is effective tool for diagnosis and staging of BrCr with additional advantages of high accuracy in detection of multicenter/multifocal disease and metastatic involvement of internal mammary and/or sub-supraclavicular lymph nodes.
No conflict of interest.

1891 POSTER

Does the prior chemotherapy treatment sequence affect the overall survival (OS) benefit associated with eribulin?

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Background: Based on questions from health authorities, prior chemotherapy or sequencing may affect the OS benefit of eribulin. We explored the effects of three prior chemotherapy treatment sequences on the OS benefit of eribulin in locally advanced or metastatic breast cancer patients.
Materials and Methods: Post-hoc analyses were conducted using a phase III multicenter, randomized, clinical trial for the treatment of eribulin versus treatment of physician's choice (NCT00388726). OS was analyzed when the event rate was 54% and 76%, separately. The effects of three chemotherapy treatment sequences prior to eribulin were explored: prior capecitabine (PCAPE), prior vinorelbine (PVIN), and prior capecitabine plus prior vinorelbine irrespective of sequence (PCAPE+PVIN). Kaplan–Meier (KM) plots and the log-rank test were used to assess the difference in OS between patients who received a particular prior chemotherapy sequence versus those who did not. Hazard ratios (HRs) with 95% confidence intervals (CIs) were generated using a Cox model. Interactions between PCAPE or PVIN and treatment were also tested using a Cox model stratified by region and Her2/neu status.
Results: These post-hoc analyses used the 508 eribulin patients for the intent-to-treat (ITT) population. At a 54% event rate, eribulin patients who received prior treatment with PCAPE, PVIN or both did not have a larger OS benefit than eribulin patients who did not*:* PCAPE [HR: 1.09, (0.830, 1.430)]; PVIN [HR: 1.20, (0.946, 1.524)]; and PCAPE+PVIN [HR: 1.24, (0.970, 1.574)]. Statistical analyses at a 76% event rate showed consistent results as the analyses at 54% of event rate: PCAPE [1.26, (1.000, 1.593), p = 0.0489], PVIN [1.16, (0.947, 1.420)], or PCAPE+PVIN [1.23, (1.000, 1.512), p = 0.0495].
Conclusions: Overall these results show that sequencing of prior treatment (i.e., PCAPE, PVIN, and PCAPE+PVIN) does not demonstrate additional OS benefit with eribulin. Therefore the only therapies that should be required prior to the use of eribulin are those required per study inclusion criteria, an anthracycline and a taxane in either the neo/adjuvant and/or metastatic setting.
No conflict of interest.

1892 POSTER

Helical tomotherapy for inoperable breast cancer: a new promising tool

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Background: Locally advanced breast cancer (BC) not eligible for upfront radical surgery remains a challenging situation for oncologists, both in a non-metastatic as well as in some metastatic settings (responsive or stable systemic disease). This is a small series of patients treated with preoperative Helical Tomotherapy® (HT) followed by radical surgery.
Material and Methods: Five patients with locally advanced not operable BC received neoadjuvant chemotherapy (NCT) followed by preoperative HT. Four women received concomitant chemotherapy (CCT) using a combination of fluorouracil (5-FU) and vinorelbine (VBN). Irradiated volumes included: whole breast (WB) in all patients, axillary lymph nodes (ALN) in 2 patients, internal mammary lymph nodes (IMLN) in 2 patients, supraclavicular (SCV) and infraclavicular fossa (ICV) in 3 patients. In one patient a simultaneous integrated boost (SIB) dose to GTV (gross tumor volume) was used. Radiation doses are described in detail in table. Toxicity was reported using the CTCAE v.4 scale. Patients were evaluated for surgery at the end of treatment.
Results: Five women with stages IIIA to IV BC (3 right sided and 2 left sided) have been treated. All patients received upfront NCT before HT, median number of delivered cycles was 8 (range: 6−8). HT was associated in 5 patients with CCT. The following regimen was used: 5-FU 500 mg/m^2 days 1−5 and VBN 25 mg/m^2 days 1 and 6, every 21 days. Early toxicity is available in the table. Following treatment, all patients were considered operable and underwent radical mastectomy (RM) and axillary lymph node dissection (ALND). Surgery was performed at a median interval of 43 days (range: 31 to 52) from last day of radiotherapy. Median follow-up from surgery date was 10.6 months (range: 0.8–26.2). Pathological response is summarized in the table.
Conclusions: HT offers several advantages in locally advanced BC: can potentially convert inoperable disease to operable disease, shows good pathological response rates with moderate acute toxicity. These results need confirmation in the setting of a prospective clinical trial.
No conflict of interest.

Table (abstract 1892).

No	TNM stage	Initial largest tumor diameter (mm)	Planned WB doses (Gy)	Helical tomotherapy			CCT	Early toxicity CTCAE grade		Pathological specimen	
				Volume	TD (Gy)	D/fx (Gy)		Skin	Digestive	T size	pN+/total no of ALN
1	T4bN2aM0	105	47.5	WB ALN	41.8 41.8	1.9 1.9	Yes	2	0	50	7+/11
2	T4cN2aM1	88	50	WB ALN	48 48	2 2	Yes	3	1	80	4+/5
3	T4cN2aM0	160	50	WB GTV	50 55	2 2.2	No	2	1	55	13−/13
4	T3N0M0	75	50	WB IMLN SCV ICV	50 45 45	2 1.8 1.8	Yes	2	0	22	15−/15
5	T4bN2aM0	85	50	WB IMLN SCV ICV	46 46 46	2 2 2	Yes	2	1	4.5	2+/8

WB: whole breast; TD: total radiotherapy dose; D/fx: dose per fraction; CCT: concomitant chemotherapy; T: tumor; pN+: pathological positive nodes; LN: lymph nodes; ALN: axillary lymph nodes; IMLN: internal mammary lymph nodes; SCV: supraclavicular fossa; ICV: infraclavicular fossa;

1893 POSTER

Low dose radiotherapy and concomitant neoadjuvant chemotherapy for breast cancer: Final results of a phase II study

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Background: Hyper-radiosensitivity of cancer cell lines at low dose radiotherapy (LDRT) (<0.5 Gy) and chemo-potentiator effect of LDRT have been demonstrated in several *in vitro* and *in vivo* studies. The aim of this phase II study was to evaluate the safety and the efficacy of a neoadjuvant regimen combining LDRT and chemotherapy in breast cancer.
Material and Methods: Eligible patients had histological diagnosis of breast cancer obtained by core-needle biopsy, previously untreated, ECOG <2, no evidence of distant metastases. The accrual was determined by the single proportion powered analysis (α=0.05, power = 0.8); 21 was the number required. Patients received LDRT (40 cGy bid, on day 1 and 2, for 6 cycles, for a total dose of 960 cGy, on PTV: gross tumour volume + 0.5−1 cm margins; by tangential technique) and concurrent neoadjuvant chemotherapy with non-pegilated liposomial anthracycline and docetaxel. After clinical and radiologic rexamination, patients underwent surgery and axillary node dissection. Pathological response was evaluated by the Mandard score and expressed as tumor regression grade (TRG). The evaluation of TRG was confirmed by an external audit.
Results: Twenty-one patients with stage IIA–IIIA invasive ductal and lobular carcinoma were enrolled in the study. Median age was 52 years (range, 34−76). Six patients had grade 1 haematological toxicity. No grade 3−4 haematological and acute skin toxicity was observed. After neoadjuvant chemotherapy and LDRT 18 patients underwent quadrantectomy, and 3 patients underwent mastectomy with breast reconstruction. Overall TRG1 (absence of residual cancer) was achieved in in 3 patients (14.3%), and grade 2 (residual isolated cells scattered through the fibrosis) in 4 patients (19%); TRG3−5 was observed in 14 patients (66.6%). The pathological major response rate (tumor regression grade 1 + 2) was 38%.
Conclusions: Neoadjuvant LDRT and concurrent non-pegilated anthracyclines and docetaxel has a similar toxicity profile to chemotherapy alone. The response rate on primary tumor of this new treatment approach is encouraging, since it was higher than what was reported for chemotherapy alone. Additional investigations about long term results are warranted.
No conflict of interest.

1894 POSTER

Sustainability of a short stay programme after breast cancer surgery in four early-adopting hospitals

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Background: New treatments and health care care programmes are constantly being developed and introduced to improve quality and efficiency of care. It is highly desirable to maintain achieved quality improvements after an implementation project has ended. However, research shows that it is difficult to sustain change as people tend to relapse into old routines as soon as the change agents have finished their mission. Breast cancer care is a field that is constantly changing. Between 2005 and 2007 a short stay programme in breast cancer surgery was successfully implemented in 4 hospitals. The primary implementation study showed an increase from 45% to 83%. uptake of short stay without a negative effect on the number of readmissions and complications. Overall compliance of the key recommendations increased from 59% in the pre-implementation phase to 76% in the post-implementation phase. The aim of this study was to assess the extent of sustainability of this short stay programme in breast cancer surgery in real world.
Material and Methods: A retrospective audit of 40 consecutive patients undergoing breast cancer surgery was performed 5 years after the original implementation study was ended. Sustainability was assessed by measuring if patients were still treated according the short stay criteria, being day admission or 24 hours admission. Compliance to the key recommendations of the short stay programme was also determined per patient.
Results: The total proportion of patients treated in short stay sustained at an average level of 82% in the retrospective audit phase. The overall proportion of patients treated in day admission however decreased from 33% to 28%, in favor of 24 h admission which increased from 67% to 72%. Compliance to the key recommendations sustained at 78% in the retrospective audit phase. 7 out of 9 key elements fully sustained or improved in the retrospective audit phase compared with the implementation group.
Conclusion: This study shows that the Short Stay Programme after breast cancer surgery was fully sustained in 4 early-adopting hospitals five years after successful implementation. However, the percentage of patients treated in day admission decreased in favor of 24 hour admission. More research is needed to find possible explanations of the decrease in day admissions after breast cancer surgery.
No conflict of interest.

1895 POSTER

RAD001 (everolimus) in combination with letrozole in the treatment of hormone receptor positive HER2-negative postmenopausal women (PMW) with advanced breast cancer (ABC) after failure of endocrine therapy − a phase II study

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Background: Approximately 75% of ABC in PMW are ER+/HER2-. Currently there is an unmet medical need for new treatment modalities after failure of endocrine therapy. Activation of the mTOR pathway is a key adaptive change driving endocrine resistance. Pre-clinical and early clinical data suggest a synergism between RAD001 (Everolimus, a Novartis mTOR inhibitor) and Letrozole resulting in restoration of sensitivity to endocrine therapy.
Our objectives were to assess Overall Response Rate (ORR), Disease Control Rate (DCR), Progression Free Survival (PFS), Overall Survival (OS) and Safety Profile of the combination after failure of one or more endocrine therapies.
Methods: A multi-center (7), Israeli phase II open label study evaluating treatment of RAD001 (oral 10 mg/d) combined with Letrozole (oral 2.5 mg/d) in PMW with ABC after progression on Tamoxifen and/or Anastrozole and/or Letrozole and/or Fulvestant and/or Exemestane.
73 patients were enrolled. Median age was 55 (28−80) years. All had ABC with one to three metastatic sites.
Patients were previously exposed to a median of 2 (1−5) lines of hormonal therapy, 54% to Letrozole.
Results: Analysis was performed on ITT population With a median follow up of 12.23 months (2−22), ORR was 19%(15/73), DCR 58% (43/73) and progressive disease in 25% (18/73) of patients. PFS was 7.9 months (1−22) while 25% (18/73) are still on treatment. OS is too early to evaluate with 78% of patients still alive.
Commonly observed all grade toxicities include: stomatitis (50%), weakness (50%), weight loss (30%), anorexia (27%), anemia (28%), hyperlipidemia (23%), diarrhea (19%), myalgia/arthralgia (16%), and pneumonitis (10%).
Conclusions: Our preliminary results are consistent with BOLERO-2 findings showing significant prolongation of PFS with the addition of RAD001 to an Aromatase Inhibitor in PMW HR+/HER-2 negative ABC patients who have progressed following previous endocrine therapy with an acceptable toxicity profile. Longer follow-up and further evaluation is warranted.
No conflict of interest.

1896 POSTER

Oral Vinorelbine as a single-agent as first-line chemotherapy for metastatic breast cancer patients with bone metastases: first safety results of an international phase II study (NorBreast-228 trial)

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Background: Oral chemotherapy (CT) is an attractive treatment option for hormone receptor positive, metastatic breast cancer (MBC) patients (pts)

pretreated by a hormone therapy. In our phase II study, we evaluated the role of single-agent Oral Vinorelbine (OV) as first-line CT in pts presenting bone metastases without visceral involvement. In this abstract, first safety results of this trial are presented.
Material and Methods: Main eligibility criteria included: age ⩾18 years, documented bone involvement previously untreated by CT, hormone receptor positive disease previously treated by at least one hormone therapy, HER2-negative disease, Karnofsky PS ⩾70 and absence of visceral metastases. All pts received a bisphosphonate during the study. Study treatment (until progression): OV 80 mg/m^2 weekly (following a first cycle at 60 mg/m^2 and dose escalation to 80 in the absence of grade 3 or 4 toxicity). One cycle was defined as four weeks of treatment.
Results: Main pts characteristics in the full population were (n = 70): median age: 60.6 years (34% ⩾65 years); median Karnofsky PS 90%. Prior hormone therapy 100% (53% in advanced setting); prior (neo)adjuvant CT 63%; prior anthracyclines/taxanes 59/24%; prior palliative radiotherapy 41%. Bone involvement 100%; other metastatic sites: lymph nodes 14%, soft tissue 3%. Median duration of treatment 5.5 months (range 0.9–18.3), median number of cycles: 6 (range: 1−18); 61% of pts received at least 6 cycles, 37% of pts received more than 6 cycles and 29% received at least 9 cycles; median relative dose intensity: 83.5%; dose escalation was performed in 79% of pts. Grade 3/4 adverse events per pt: neutropenia 37%, anemia 4%, diarrhoea 3%, nausea 3%, asthenia 1%, liver toxicity 1%, neutropenic infection 1%, non-neutropenic infection 1%. Grade 2 alopecia was reported in 6% of pts. No cases of febrile neutropenia or toxic death had been observed.
Conclusions: In this particular population of metastatic pts, with hormone receptor positive disease and bone involvement, OV showed an optimal safety profile. This data shows that OV is a well tolerated first-line CT option in this setting, allowing prolonged active treatment in non-progressing pts.
Conflict of interest: *Other substantive relationships: PIERRE FABRE*

1897 POSTER

Overall survival of metastatic breast cancer patients: the Italian ten-year experience

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Background: Several studies suggest that newer therapies can improve survival in metastatic breast cancer (MBC), but a different impact on overall survival (OS) is observed according to histology, extension of disease and prognostic factors. This survey was performed for evaluate Italian experience in cancer treatment in the last ten years.
Methods: We retrospectively collected data from several Italian Medical Oncology Units (OUs); we registered all consecutive patients (pts) with breast cancer who have developed metastasis between 2000 and 2008; demographic data, pathological characteristics and treatments administered were collected; OS was defined as the time from the diagnosis of MBC to death from any cause; the statistical significance was reached with a p-value <5%.
Results: 17 OUs participated and 1998 pts were analyzed; median age 61.7 years (range: 22.7–94.7 years); MBC at diagnosis: 13.1% pts; site of disease recurrence: bone 25.5%, visceral 23.5%, bone and visceral 21.1%, soft tissue 14.0%, soft tissue and visceral 8.0%, bone and soft tissue 7.9%; molecolar classification: luminal A 66.3%, luminal B 14.4%, triple negative 11.7%, HER2+ like 7.6%. Pts received a median of 2 lines of chemotherapy (range 0−10) and 1 line of endocrine therapy (range 0−7); 22.1% received biological drugs. 16.4% of metastatic pts were enrolled in clinical trials. After a median follow up of 6.9 years (range: <0.1–12.9 years) 1657 (82.9%) pts died and the median OS was 2.7 years (95% CI: 2.6−2.9 years); we didn't observe any statistical significant trend in OS for pts divided into 3 groups according to recurrence date (2000–2002, 2003–2005, 2006–2008); a longer median OS was observed in luminal B (3.6 years; 95% CI: 3.3−4.1 years) versus luminal A (2.8 years; 95% CI: 2.5−3.0) and HER2+ like (2.6 years; 95% CI; 2.1−3.1 years) and triple negative disease (1.3 (1.0−1.7 years).
Conclusions: Our survey describe a large number of MBC pts treated in 17 Italian Oncology Units. OS analysis did not show statistically significant differences according to recurrence date, but for different prognostic factors. OS data are superimposable to literature ones, showing a good transfer from clinical trials to clinical practice.
No conflict of interest.

1898 POSTER

A phase I combination study of eribulin mesylate with trastuzumab for advanced or recurrent human epidermal growth factor receptor 2-positive (HER2+) breast cancer

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Background: Eribulin mesylate is a novel inhibitor of microtubule dynamics that has demonstrated a survival benefit in patients (pts) with advanced or recurrent breast cancer (BC) previously treated with anthrayclines and taxanes. Trastuzumab is indicated for pts with HER2-positive BC, but the combination of eribulin mesylate with trastuzumab has not been established yet. A phase I study of eribulin mesylate in combination with trastuzumab was conducted to evaluate the dose limiting toxicity (DLT), tolerability/safety, pharmacokinetics and preliminary antitumor activity in Japanese patients.
Methods: Pts with advanced or recurrent HER2-positive BC were enrolled. Eribulin mesylate (1.4 mg/m^2 [equivalent to 1.23 mg/m^2 eribulin expressed as free base]) was administered on Days 1 and 8 every 3-week/cycle and trastuzumab was administered as 4 mg/kg loading dose, 2 mg/kg/weekly (Part 1) and 8 mg/kg loading dose, 6 mg/kg/tri-weekly (Part 2). DLT was evaluated during the first cycle. Left ventricular ejection fraction (LVEF) assessment was conducted on before the treatment, Day 15 of Cycle 1, Day1 of each 4 cycles and if clinically indicated.
Results: A total of 12 pts were enrolled in Part 1 (n = 6) and 2 (n = 6). The median age was 60 years (range 39−72) and the median number of prior chemotherapy regimen was 4.5 (range 1−14). As of 26 Feb 2013, no DLT was observed and the common adverse events were similar in Part 1 and 2, including neutropenia [100% (Gr 3/4: 92%)], leukopenia [100% (Gr 3/4: 75%)], anemia [67% (Gr 3/4: 0%)] and alopecia (67%). The safety and PK profile was similar to the prior clinical study of eribulin mesylate monotherapy. LVEF decreased (Gr 2) was observed in 2 pts (17%) at Day 15 of Cycle 1, but both recovered after 1 week without treatment for it. Current response results according to RECIST v1.1 from 11 evaluable pts were: 1 pt (9%) with PR, 9 pts (82%) with SD (⩾5 weeks) and 1 pt (9%) with PD. Disease Control Rate (CR+ PR+SD ⩾11 weeks) was 64%.
Conclusions: The combination of eribulin mesylate with trastuzumab was considered well tolerated and the neutropenia observed was manageable in Japanese pts with advanced or recurrent HER2-positive BC. No pharmacokinetic drug–drug interaction between eribulin and trastuzumab was observed. Since a transient LVEF decrease was observed in 2 pts, the assessment of cardiac function should be performed routinely in the combination with trastuzumab. The evaluation of long-term safety and efficacy is ongoing.
Conflict of interest: *Other substantive relationships: T.Nakanishi, H.Obaishi, M.Namiki, T.Narita, M.Masuda: Eisai Co.,Ltd: Employee*

1899 POSTER

First year daily clinical experience with eribulin in Spain; EUFORIA-1 study (Eribulin Use For the treatment of advanced breast cancer: Observational, Retrospective Analysis)

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Background: Spanish MoH authorized Eribulin use for advanced breast cancer (ABC) patients as per license in 04/2011. Pending reimbursement price, public hospitals have accessed the drug through a national compassionate use program. After 1 year, patient selection criteria and eribulin efficacy and safety results in a representative sample were analyzed to determine whether real world use matched the data from the pivotal phase III study.

Methods: An observational, retrospective study was proposed to the top 20 hospitals by eribulin use, with at least 3 candidate patients who had/could have received ⩾3 cycles of treatment by 03/2012. Patient and disease characteristics, as well as efficacy and safety parameters were obtained. Patients' data were collected until 01/2013. Living patients able to respond at the time of the study signed an informed consent. Study was approved by ethics committees.
Results: Out of 112 screened patients, 104 were enrolled in 19 hospitals. Median age was 56.6 years; 66% were post-menopausal. Visceral disease occurred in 2/3 of patients. ECOG status was ⩽1 in 75.4% of patients. Sixty-four % tumors were ER+; 15.4% overexpressed Her-2 and 29.8% were TNBC. Forty-nine % of patients received 1−5 treatment lines for ABC before eribulin. The mean duration of eribulin treatment was 3 months (4.7 cycles). Disease control rate was 48.8% (1.1% CR, 22.1% PR, 25.6% SD). By end 01/2013, 30.8% patients were still alive, with median OS and PFS of 263 days (95% CI: 210–299) and 97 days (95% CI: 81–129), respectively. 78.8% of patients reported ⩾1 adverse event, being asthenia, neutropenia, anemia, alopecia, nauseas, and mucositis the most frequent ones (⩾10%). Grade ⩾3 adverse events occurred in ⩽5% of patients.
Conclusions: The favorable efficacy and safety profile of eribulin observed in this observational study is consistent with the pivotal phase III study (EMBRACE) and confirms its position for the treatment of ABC. Pre-reimbursement drug request procedures and lack of experience have increased initial eribulin usage in later lines of treatment but use per the licensed indication in 3L is expected to yield additional clinical benefit. A confirmatory observational study (EUFORIA-2) is planned.
Conflict of interest: *Advisory board: Ruiz-Borrego M, González-Martín A. Other substantive relationships: Ruiz-Borrego M, García Saenz JA*

1900 POSTER

Adherence and patients' attitude towards oral anticancer drugs: a prospective series of 226 patients focusing onto targeted therapies

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Background: Patients' adherence has been identified as a challenge in oncology and hematology practice. Hormone therapy data in breast cancer suggest insufficient adherence and poor persistence. Limited data is available for targeted therapies such as tyrosine kinase (TK) and mTOR inhibitors whereas poor adherence to TK treatment was linked to treatment failure in GIST and CML.
Methods: We report the result of a prospective survey in 226 patients (pts), with solid tumors and hematologic malignancies receiving oral anticancer therapy including chemotherapy or hormone therapy (CT), and targeted therapies (TT). Treatment duration and setting (adjuvant vs metastatic), cancer type, age, co-medication were analyzed. Patients were given a 15-item questionnaire and asked to anonymously answer questions regarding their attitude towards oral anticancer drugs. To analyze adherence, patients were asked whether they voluntarily or not missed any drug dosing during the last month.
Results: 226 patients (median age 65.5 y.o) participated, 115 with TT and 111 with CT, with a median time of drug intake of 10.5 months. Both TT and CT patients stated to be well informed about treatment modalities in (92%), mostly by their oncologist or hematologist (87%). Written information was more frequently given in TT pts (67.0 vs 27.0%, $p < 0.0001$). TT pts declared to be more often fully adherent to therapy (84.3 vs 66.7%, $p = 0.01$) despite experiencing more side-effects ($p < 0.0001$) and taking more concomitant oral medication ($p = 0.029$). The mean treatment duration was 28.0 vs 20.3 months in TT vs CT pts (NS), but in both groups non-adherence was observed at any time since initial prescription.
Conclusions: Despite advances in patients' information leading to better treatment adherence in TT pts, efforts are still warranted such as the onset of dedicated staff for early and prolonged monitoring of outpatient anticancer oral therapy.
No conflict of interest.

1901 POSTER

Mixed-treatment comparison of second line therapy for postmenopausal women with hormone-sensitive advanced breast cancer: clinical efficacy, persistence on treatment, and tolerability

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Background: Hormone-sensitive breast cancer (BC) is usually associated with an under expression of human epidermal growth factor receptor 2. For postmenopausal women, international guidelines suggest treatment with non-steroidal aromatase inhibitors as first line. Due to the lack of a preferred regimen for second line treatment (necessary in 20−70% of cases), it is justifiable to perform a mixed treatment comparison (MTC) in order to assess the relative effect of all available options for this population of women.
Methods: Randomized controlled clinical trials (RCT) enrolling post-menopausal women with hormone-sensitive advanced BC were systematically reviewed from the literature. All hormonal and chemotherapeutic agents used as second line treatment were considered. Outcomes reviewed were progression-free survival (PFS), time-to-progression (TTP), overall survival (OS) and discontinuation due to any reason (treatment persistence) and due to adverse events (tolerability). A Bayesian generalized linear model framework for MTC was adopted to pool the evidence from the selected RCT and estimate the relative treatment effects and the probability of each considered treatment being the best.
Results: Of the 235 references identified, 25 RCT met the inclusion criteria and 19 entered the quantitative analysis (coherent evidence network). Treatment options analysed were: aminoglutethimide; anastrozole; everolimus; exemestane (EXE); formestane; fulvestrant; letrozole (LET); megestrol acetate; premarin; vorozole. Everolimus + exemestane (EVE+EXE) was estimated to have the highest probability of being the best treatment in delaying progression and death and maximizing treatment persistence. Compared to EXE single agent EVE+EXE was found to be the only treatment option significantly reducing the risk of progression (HR = 0.45; 95% CI [0.38–0.54]). EVE+EXE and LET 2.5 mg were estimated to show a significantly lower chance of discontinuation due to any reason than EXE (OR=0.46; 95% CI [0.33–0.64] for EVE+EXE, OR=0.49; 95% CI [0.26–0.90] for LET 2.5 mg). With respect to OS and discontinuation due to adverse events, none of the considered treatment options was found to demonstrate a significant reduction in risk, when compared to EXE.
Conclusion: Results suggest superiority in terms of efficacy and treatment persistence of EVE+EXE over other hormonal therapeutic options, for the treatment of postmenopausal women with hormone-sensitive advanced BC after failing a first line of treatment.
Conflict of interest: *Corporate-sponsored research: Unrestricted grant of Novartis Oncology.*

1902 POSTER

Thymidylate synthase expression as a novel predictive factor in metastatic breast cancer patients

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Background: S-1, an oral fluoropyrimidine formulation that combines tegafur, 5-chloro-2,4-dihydroxypryidine, and potassium oxonate in a molar ratio of 1:0.4:1, has been widely used against solid cancers including gastric, colorectal, pancreatic, lung and breast cancer in Japan. In a phase II study, the response rate (RR) was 41.7% and the median survival was 872 days among taxane-pretreated patients with metastatic breast cancer (MBC). However, the predictive factor of S-1 in patients with MBC has not been determined yet. The purpose of this study is to investigate the correlation between 5-FU-related enzyme and clinical efficacy of S-1 in patients with MBC.
Material and Methods: Forty-eight patients with MBC were treated with S-1 twice daily at a dose of 80 mg/m^2 for 4 weeks, followed by a 2-week rest interval at Keio University Hospital from January 2005 to January 2010, excluding the patients who were concurrentry treated with trastuzumab. Laser-captured microdissection was performed from the formalin-fixed, paraffin-embedded tumor sections at surgery and the expression of 5-FU-related enzyme including thymidylate synthase (TS), thymidine phosphorylase (TP) and dihydropyrimidine dehydrogenase (DPD) was evaluated by RT-PCR.

Results: The median age was 49 years (range 30−73) and the median time from diagnosis to metastasis was 49.4 months (range 3.3–286.5). Estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor type 2 (HER2) was positive in 63, 38, and 21% of the entire patients, respectively. The median number of pretreated chemotherapy regimens was 2 (range 0−6). The median number of metastatic site was 2 (range 1−4). The sites of metastatic disease were the viceral in 25 patients, bone in 9 patients and soft tissue in 17 patients. The overall response rate (RR) was 22.9% (11/48) and clinical benefit rate was 45.8% (22/48). The median time to tumor progression (TTP) was 14.3 months (range 6.2–22.4). ER, PgR and HER2 status was not significantly correlated with RR (P = 0.724, 0.288, 1.000, respectively). TS expression was significantly associated with clinical efficacy of S-1 (Table 1). Moreover, it is notable that triple negative breast cancer (TNBC) revealed lower TS expression than luminal type (TNBC vs luminal type = 1.03 (0.32–4.70) vs 2.45 (0.42–10.1), P = 0.020). According to the correlation between metastatic sites and RR, better RR was noted for soft tissue metastases (soft tissue vs visceral = 25% (5/20) vs 84% (5/6), OR 15.0 (95% CI 1.40–161.05).
Conclusion: This study demonstrated that TS can be a significant predicitve factor of S-1 in patients with MBC.
No conflict of interest.

Table 1. Correlation between 5-FU related enzyme and clinical response of S-1.

	RR (CR+PR)	P-value
TP		0.333
Low (<8.5)	5/12 (41.7%)	
High (⩾8.5)	3/12 (25.0%)	
DPD		0.286
Low (<0.6)	5/9 (55.6%)	
High (⩾0.6)	2/7 (28.6%)	
TS		0.041
Low (<2.0)	8/13 (61.5%)	
High (⩾2.0)	2/12 (16.7%)	

1903 POSTER

Chemotherapy treatment for older women with breast cancer in ELIPPSE 65 French cohort

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Background: Since a few years, recommendations have been issued for the treatment of old people with cancer: treatment decision must be based on physiological age instead of chronological age. In the context, our objectives were to determine factors associated with access to chemotherapy in a French cohort of elderly women with breast cancer.
Material and Methods: ELIPPSE 65 is an ongoing cohort of women aged 65 to 80 years, included in 2006–2010 in the month following breast cancer diagnosis. Women were interviewed face-to-face and a mini geriatric assessment was made including ADL and IADL scales, Charlson index, mini Cog and nutritional assessment. Medical information was collected from the physicians. Chemotherapy analysis were performed among all eligible women for treatment according to the French recommendations (n = 234). Logistic regression procedure have taken into account explanatory variables such as age, socio-demographic and medical characteristics, year of diagnostic, functional status, cognitive function and presence of comorbidities. Age at diagnosis was categorized into three classes as follows: 65−70, 70−75 and 75−80. The final model was adjusted for geriatric assessment variables.
Results: Among the 234 patients, 30% were aged between 75 and 80, 68% were living in couple and 91% had children. Concerning geriatric assessment, 68% were considered as 'independent' regarding their functional status, 20% had at least one severe comorbidity and 20% were cognitively impaired. Fifty-seven percent of patients eligible for chemotherapy according to medical criteria received chemotherapy. Factors associated with access to chemotherapy are: tumor stage II/III versus I [AOR (95% CI) = 7.7 (3.6–16.3)], hormone-independent breast cancer [AOR (95% CI) = 9.1 (3.1–26.8)], most recent year of diagnosis [AOR (95% CI) = 4.1 (1.0–16.8)] but also age, with women aged 75−80 having less access to chemotherapy [AOR (95% CI) = 0.3 (0.1−0.6)] than younger ones. None of geriatric assessment variables were associated to access to chemotherapy.
Conclusions: Despite a better consideration of elderly patients by medical staff and the improvement of geriatric medicine in developed countries, chronological age remains a barrier to chemotherapy for oldest women with breast cancer in France. The lack of clinical trials among old cancer patients may explain the reluctance of physicians to offer these heavy therapies to their oldest patients.
No conflict of interest.

1904 POSTER

Out-of-pocket burden and trastuzumab persistence among US managed care patients with presumed HER2+ metastatic breast cancer

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Background: Out-of-pocket expenditure (OOP) is deemed as a potential barrier to treatment compliance, particularly for costly-targeted oncology therapies. This study explores the relationship between OOP and trastuzumab persistence in metastatic breast cancer (mBC) patients enrolled in US managed care plans.
Materials and Methods: This retrospective cohort study of the IMS LifeLink™ Health Plan Claims Database included women aged 18+ years; with a first (index) trastuzumab between July 2006 and December 2010; continuous enrollment 180 days pre- to 30–360 days post- index; a primary malignant breast cancer (ICD-9-CM 174.x, 233.0) and a secondary malignant neoplasm (ICD-9-CM 196.x–198.x) pre-index; no trastuzumab pre-index; and no other primary cancer pre- or post-index. Persistence was defined as days from trastuzumab index to discontinuation (90 days of treatment gap) or end of enrollment. OOP post-index was defined as 'allowed amount' minus 'paid amount' summed across claims. Mixed-effects Cox proportional hazard models estimated the relative hazard of trastuzumab discontinuation as a time-varying function of OOP before each 30 days post-index; time-constant covariates included demographic and clinical characteristics, pre-index healthcare spending and Charlson Comorbidity Index score.
Results: 1109 patients (mean age=50.9 years) met all study criteria. OOP was positively skewed for trastuzumab (mean=$2404, median=$68, interquartile range [IQR]=[$0, $1430]) and all medical services (mean=$7828, median=$3049, IQR=[$1407, $5821]). Patients persisted on trastuzumab for a median of 359 days. For patients where trastuzumab OOP was >$2000, there was a predicted higher discontinuation risk vs. trastuzumab OOP ⩽$500 ($2001-$4000: hazard ratio [HR]=1.62 [95% CI 1.12–2.34]; furthermore, for patients where trastuzumab OOP was >$4000: HR = 1.88 [95% CI 1.20–2.94]). OOP for all medical services >$7000 predicted higher discontinuation risk vs. all services OOP ⩽$1000 ($7001-$9000: HR = 2.72 [95% CI 1.60–4.62]; $9001+: HR = 2.32 [95% CI 1.45–3.70]). Covariates in the trastuzumab Cox model that predicted higher discontinuation risk included hospital outpatient treatment setting vs. physician office (HR = 1.57[95% CI 1.06–2.31]) and Medicare Risk vs. commercial payer type (HR = 2.65[95% CI 1.06–6.59]).
Conclusions: 75% of US managed care mBC patients had OOP ⩽$5821 for all medical services and ⩽$1430 for trastuzumab in year one of therapy. OOP exceeding $7000 for overall or $2000 for trastuzumab predicted lower trastuzumab compliance. Monitoring OOP in HER2+ mBC patients may identify those with increased risk for treatment discontinuation.
Conflict of interest: *Other substantive relationships: M. Brammer, D. Lalla, E. Santos: Employees of Genentech Inc. Y.J. Chen, V. Schabert, P. Iversen, L. Cen: Employees of IMS Health, which provides consulting services for Genentech Inc.*

1905 POSTER

Final results of an international three-arm randomised phase II study evaluating oral vinorelbine plus capecitabine versus paclitaxel plus gemcitabine versus docetaxel plus gemcitabine as first-line chemotherapy in patients with metastatic breast cancer (NorCap-CA223 trial)

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Background: Combination chemotherapy (CT) is among the standard treatment options in metastatic breast cancer (MBC), especially in patients (pts) with visceral metastases or need of rapid symptom or disease control. Full oral combination CT of Oral Vinorelbine (OV) + Capecitabine (C) is a convenient and effective alternative to taxane-based intravenous regimens. Aim of this study was to evaluate the efficacy of a full oral and two full intravenous combinations in MBC.
Material and Methods: Pts with HER2-negative taxane-naive MBC, with an age $\geqslant$18 years were eligible. Pts were randomised to receive, as first-line CT, 3 weekly-cycles of either: ARM A: full oral combination of OV, given as a 80 mg/m^2 dose (following a first cycle at 60 mg/m^2, dose escalation to 80 in the absence of grade 3 or 4 toxicity at cycle 1) D1 & D8 and C 1000 (750 if $\geqslant$65 years) mg/m^2/bid D1 to D14; ARM B: paclitaxel 175 mg/m^2 D1 plus gemcitabine (G) 1250 mg/m^2 D1 & D8; ARM C: docetaxel 75 mg/m^2 D1 plus G 1000 mg/m^2 D1 & D8. Primary endpoint was disease control rate (DCR), defined as complete response + partial response + stable disease $\geqslant$3 months. Pts were stratified according to prior anthracycline CT and age < or $\geqslant$65 years.
Results: 149 pts had been treated (ARM A 49; ARM B 50; ARM C 50). Baseline pt characteristics (Arms A/B/C): median age 58/56/57 years; hormone receptor positive 61/50/66%; prior hormone therapy 59/64/66%; prior (neo)adjuvant CT 49/46/58%; prior anthracycline 39/42/42%; visceral metastases 80/82/74%; $\geqslant$3 metastatic sites 53/44/58%; measurable disease at baseline 94/90/98%. Median number of cycles (range): 6(1−37)/6(1−12)/7(1−25); dose escalation of OV was performed in 78% of pts. Safety: G3/4 adverse events per pt: neutropenia 50/46/86%, anemia 2/4/8%, infections 2/2/10%, diarrhoea 6/4/2%, vomiting 10/2/2%, fatigue 10/12/22%, alopecia (G2) 8/72/76%, febrile neutropenia (pts) 4/0/3, toxic deaths (pts) 2/1/0. Efficacy: DCR in the intent-to-treat population was [95% CI] 73.5 [59−85] /78 [64−88] /80 [66−90] %; progression-free survival: 7.6 /9.0/11.4 months; time to treatment failure: 4.6/4.8/5.2 months; overall survival: 30.2/29.6/31 months.
Conclusion: The DCR as well the OS results reported in this trial confirm that the full oral combination of OV + C is an active combination which can be proposed as an alternative to taxane-based regimens as first-line CT in MBC, allowing to delay the constraints of an intravenous CT. As expected, each regimen presented a specific and particular tolerance profile, with, in particular, a low incidence of alopecia after full oral CT.
Conflict of interest: *Other substantive relationships: PIERRE FABRE*

1906 POSTER

No difference in prognosis and response to systemic treatment between patients with invasive lobular and invasive ductal hormone receptor positive metastatic breast cancer

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Background: Invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) are the two most frequent histological subtypes of breast cancer and are known to be distinct tumor-biological entities. Response to neo-adjuvant chemotherapy is known to be poorer for ILC than for IDC. More recently, data on the use of chemotherapy in the adjuvant setting showed that patients with ILC did not seem to benefit from the addition of chemotherapy to hormonal therapy. However, data on possible differences between ILC and IDC in the effectiveness of chemotherapy in patients with metastatic breast cancer is lacking.
Patients and Methods: We analyzed 815 consecutive breast cancer patients diagnosed with metastatic breast cancer in eight hospitals between 2007 and 2009. All hormone receptor positive patients with either IDC or with (mixed) ILC were included. Data on patient and tumor characteristics, as well as outcomes and treatments were collected. Survival curves were estimated using the Kaplan–Meier method. Progression-free survival (PFS) on palliative chemotherapy was compared between the two histological subgroups with log-rank test.
Results: A total of 568 hormone receptor positive patients were included; 437 patients with IDC and 131 patients with (mixed) ILC. The median survival after diagnosis of metastatic breast cancer was 25 months (95% confidence interval (CI) 22−32 months) for patients with IDC and 29 months (95% CI 23−37 months) for patients with ILC (log-rank $P = 0.53$).
The hazard ratio for mortality was 0.94 (95% CI 0.72–1.21) for patients with IDC treated with palliative chemotherapy compared to those not treated with palliative chemotherapy, and for patients with ILC this hazard ratio was 1.47 (95% CI 0.92–2.36). There was also no difference in PFS between patients with IDC or ILC for first-line chemotherapy, with 1-year PFS of 52.5% for the patients with IDC and 1-year PFS of 54.0% for patients with ILC (log-rank $P = 0.68$).
Conclusions: In patients with hormone receptor positive metastatic breast cancer no significant differences in survival after diagnosis of metastatic breast cancer were found between ILC and IDC. Furthermore, unlike the findings in the (neo-)adjuvant setting, we did not observe any difference regarding chemotherapy effectiveness between the two histological subtypes.
No conflict of interest.

1907 POSTER

Hypertension as a predictive marker for bevacizumab in metastatic breast cancer: updated results from a retrospective matched-pair analysis

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Background: Several phase-III studies showed improvement in PFS by bevacizumab when added to chemotherapy in advanced breast cancer. However, the extent of improvement varied and no trial showed benefit in OS. To reduce the number needed to treat, predictive markers are urgently required. Therefore, besides effectiveness and safety, we investigated hypertension as potential predictive biomarker for bevacizumab. Here we report the updated results*.
Patients and Methods: All patients with metastatic breast cancer treated with bevacizumab in combination with chemotherapy at our institution between 2005 and 2011 were retrospectively analyzed. A control group was matched according to the following criteria: receptor status, treatment-line, type of chemotherapy, presence of visceral disease, and age.
Results: All 212 patients were evaluable for toxicity, 198 for response; 430 controls allowed a complete matching for 85 patients. The addition of bevacizumab to chemotherapy significantly prolonged PFS and OS. CBR was significantly better in the bevacizumab group, while ORR did not differ significantly. Patients developing hypertension during treatment had a more favorable outcome regarding PFS and OS.

			Hazard ratio (HR) and Relative risk (RR)	P
Matched-pair population	Control (n = 85)	Bevacizumab (n = 85)		
PFS [mo]	7.6	9.3	HR 0.70 (95% CI 0.51–0.97)	0.031
OS [mo]	22.6	28.9	HR 0.67 (95% CI 0.45–0.99)	0.043
ORR CR+PR)	30 (35%)	41 (48%)	RR 1.25 (95% CI 0.85–1.86)	0.210
CBR (ORR+SD)	50 (59%)	64 (75%)	RR 1.28 (95% CI 1.02–1.59)	0.002
Bevacizumab population	No hypertension (n = 91)	Hypertension (n = 56)		
PFS [mo]	6.6	13.7	HR 0.34 (95% CI 0.23–0.49)	<0.001
2-yr-OS	30%	78%	HR 0.20 (95% CI 0.12–0.35)	<0.001
ORR CR+PR)	34 (37%)	29 (52%)	RR 1.39 (95% CI 0.92–2.03)	0.086
CBR (ORR+SD)	56 (62%)	53 (95%)	RR 1.54 (95% CI 1.28–1.67)	<0.001

Conclusion: Bevacizumab in addition to chemotherapy prolonged PFS and OS even in a non-selected, partly intensively pretreated breast cancer population. Hypertension could provide a simple biologic biomarker for bevacizumab efficacy.

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Conflict of interest: *Advisory board: Greil R., Mlineritsch B., Bartsch R for Roche(R). Corporate-sponsored research: Gampenrieder S.P., Rinnerthaler G., Greil R., Bartsch R. from Roche(R). Other substantive relationships: Gampenrieder S.P., Romeder F., Muß C., Pircher M., Ressler S., Rinnerthaler G., Bartsch R., Mlineritsch B., Greil R. from Roche(R)*

1908 POSTER

Clinical outcomes according to molecular-guided therapy strategies in phase I for breast cancer patients

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Background: Over the last decade, the focus of anticancer drug development has shifted from empirical cytotoxic chemotherapy to mechanism-defined molecularly targeted agents. Our study aims to identify a possible association of oriented strategy and patient outcome in patients treated for a metastatic breast cancer in a phase I trial.
Material and Method: We analysed patients with metastatic breast cancer recruited in phase I trial from February 2004 to February 2008 at Gustave-Roussy Institute. Population was divided in two groups: non-oriented therapy or oriented therapy. Baseline was defined as first day of treatment. Overall survival (OS) and progression-free survival (PFS) were estimated using Kaplan–Meier method. Progression was determined by both clinical and radiological assessments. Oriented therapy was defined as any therapy targeting a specific molecular alteration found in the patient's tumor (angiogenesis inhibitors, cellular cycle inhibitors, FGF inhibitors, cell metabolism inhibitors, EGFR/PI3K/Akt/mTOR inhibitors). The effect of oriented therapy on OS and PFS adjusted for prognostic factors (performance status, albumin level, age, body mass index, inhibitor type and previous or concomitant chemotherapies) were assessed using multivariable Cox proportional hazards model. Analyses accounting for HER2 and estrogen-receptors status are currently ongoing.
Results: Among the 78 patients recruited in phase I trials, 64 fulfilled the analysis inclusion criteria. Of them, 52 patients had complete data, including 15 (29%) patients receiving oriented therapy. Median OS and PFS were respectively 11.2 (95% CI=6.9; 33.4) and 3.7 (95% CI=1.6; 7.4) months in the oriented therapy group versus 6.8 (95% CI=5.0; 11.0) and 2.4 (95% CI=1.7; 2.9) months in the non-oriented therapy group. Factors associated with longer OS included oriented therapy HR = 0.40 (95% CI=0.18–0.87, p = 0.02) and high albumin levels HR = 0.24 (95% CI=0.11–0.50, p < 0.001). Factors associated with longer PFS were oriented therapy HR = 0.47 (95% CI=0.23–0.94, p = 0.03) and age <50 years (HR = 0.41; 95% CI=0.19–0.91) versus age 50−60 years-old (HR = 1.04; 95% CI=0.51–2.10; p = 0.05).
Conclusion: Oriented therapy was independently associated with longer OS and PFS in breast cancer patients treated in a phase I trial. However, we cannot rule out the impact of unmeasured indication bias.
No conflict of interest.

1909 POSTER

Molecular profiling of advanced breast cancer patients and benefit obtained from matched targeted therapy in early phase clinical trials

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Background: Breast cancer (BC) clinical research has evolved into a personalized field with biomarker enrichment strategies and development of oncogene-driven molecular targeted agents (MTA). Our objective was to compare the outcome of BC patients (pts) treated with a MTA with their previous and subsequent unmatched therapies.
Methods: Inclusion criteria: advanced BC pts with molecular alteration in tumor tissue (A) PI3K pathway dysregulation: *PIK3CA*/*AKT* mutation(m) and/or PTEN downregulation (PTENd) (HScore⩽50); (B) *FGFR1* amplification(a), treated ⩾2nd line and matched with MTA-driven phase 1 or 2 clinical trial, received at least >2/3 of the maximum tolerated doses, ECOG 0 or 1.
Results: From 2009 to 2012, 269 BC pts were screened for MTA-driven phase 1/2 trials (60%, primary site; 40%, metastatic site). 43 BC pts received matched therapies, 41.9% *PIK3CA*m (18/43), 30.2% PTENd (13/43), 11.6% *PIK3CA*m and PTENd (5/43), 4.7% *AKT*m (2/43), 7% *FGFR1*a (3/43), 2.3% *PIK3CA*m and *KRAS*m (1/43), 2.3% PTENd and *KRAS*m (4/43). 60.5% matched pts had molecular analysis from a metastatic site. Overall, 43 BC matched pts received 50 MTAs within 15 different trials including pan or alpha PI3K, AKT, mTORC1/2, dual PI3K/mTORC1/2 and FGFR1 inhibitors as single agents or combined with endocrine, chemotherapy or trastuzumab-based therapy. Median age 51.7; ECOG 0 39.5%, ECOG 1 60.5%; ER+/HER2−72%, HER2+ 21%, ER-/HER2−7%; median prior therapies 6. 7 BC pts participated in 2 or 3 trials. Median time-to-treatment failure (mTTF) on MTA was 2.3 months (95% CI 1.9−3.7) *vs.* 5.5 months (95% CI 3.41–7.11) for their previous systemic antitumor therapy (p < 0.001). There were no statistical differences for mTTF on MTA *vs.* subsequent therapy line (N = 34 pts, 4.32 *vs.*7.02 months; 95% CI 0.39–1.07, p = 0.087). Partial responses were seen in 16% (8/50) matches (Table 1). Stable disease >16 weeks was observed in 11/23 matches (47.8%).
Conclusions: In advanced BC, matching molecular profile with the available first-generation MTA phase 1/2 trials does not seem to prolong mTTF as compared to the previous or subsequent unmatched therapy; however, it might confer a clinical benefit for some pts in terms of objective responses and disease stabilization.
No conflict of interest.

Table 1. Partial responses with matched targeted therapy (8/50)

Pt no.	Molecular alteration	Molecular targeted agent	Combination therapy
4	FGFR1 amplification	FGFR1 and VEGFR-1−3 inhibitor	No
5	PIK3CA mutation	pan-PI3K inhibitor	No
9	PIK3CA mutation	PI3K/mTOR dual inhibitor	No
16	PIK3CA mutation	pan-PI3K inhibitor	No
21	FGFR1 amplification	FGFR1 and VEGFR-1−3 inhibitor	No
37	PTEN downregulation	PI3K/mTOR dual inhibitor	paclitaxel
42	PIK3CA mutation	PI3K/mTOR dual inhibitor	trastuzumab
45	PTEN downregulation	PI3K/mTOR dual inhibitor	paclitaxel + trastuzumab

1910 POSTER

Role of HER2 FISH ratios in predicting pathological complete response (pCR) to neoadjuvant systemic chemotherapy with trastuzumab in patients with inflammatory breast cancer (IBC) and non-inflammatory locally advanced breast cancer

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Background: Neoadjuvant systemic chemotherapy with trastuzumab (NST-T), a standard treatment option for patients with HER2-overexpressing (HER2+) primary breast cancer, produces a significantly higher pathological complete response (pCR) rate and has led to better outcomes than NST without trastuzumab. However, whether the HER2 fluorescence in situ hybridization (FISH) ratio is a predictor of pCR rate in patients with primary inflammatory breast cancer (IBC) or non-inflammatory locally advanced breast cancer (Stage III non-IBC) is unknown. We hypothesized that a high HER2 FISH ratio is a predictor of pCR, extended time to recurrence (TTR), and overall survival (OS) in IBC and non-IBC patients taking NST-T.
Material and Methods: In this retrospective review, we included 169 patients with stage III HER2+ IBC and 388 patients with stage III HER2+ non-IBC who were treated with NST and definitive surgery from 1999 through 2012. Trastuzumab was concurrently administered in 121 (71.6%) IBC and 286 (73.7%) non-IBC patients. HER2 was defined as positive if the immunohistochemistry score was 3+ or the FISH ratio was positive (>2.0). FISH ratios were available for 132 (78.1%) IBC and 331 (85.3%) non-IBC patients.
Results: Univariate analysis revealed that age less than 50 years, negative estrogen receptor (ER)/progesterone receptor (PR) status, no lymphatic invasion, non-IBC, and NST-T were significantly associated with high pCR. The median HER2 FISH ratio of the pCR group was significantly higher than of the non-pCR group ($p = 0.0039$). The logistic regression model for pCR demonstrated that a HER2 ratio of ⩾7.0 ($p = 0.0153$), negative ER or PR status ($p = 0.0394$ and $p = 0.0232$, respectively), and no lymphatic invasion ($p<0.0001$) were independent predictors of pCR. In both IBC and non-IBC, NST-T was strongly related with pCR, though this association was not significant ($p = 0.0523$); in non-IBC patients, NST-T

Table (abstract 1911).

	Progression event					
	NM		IPEL		Other	
	E (n = 271)	C (n = 285)	E (n = 147)	C (n = 129)	E (n = 136)	C (n = 134)
Median OS, months (95% CI)	15.5 (14.2, 17.5)	12.9 (11.3, 14.5)	17.4 (14.4, 19.7)	17.4 (15.3, 20.9)	16.7 (14.8, 24.2)	15.5 (11.7, 18.3)
HR (95% CI)	0.81 (0.68, 0.97)		1.13 (0.87, 1.46)		0.78 (0.59, 1.03)	
Nominal p-value	0.02		0.35		0.08	
Time to NM, months (95% CI)	5.8 (5.2, 6.5)	5.2 (4.3, 5.9)				
HR (95% CI)	0.90 (0.77, 1.05)					
Nominal p-value	0.17					

was significantly associated with pCR (p=0.0024). Survival evaluation with univariate analysis revealed that positive ER/PR status, no lymphatic invasion, NST-T, and non-IBC had significant prognostic value for TTR, and the same variables, other than positive PR status, had significant prognostic value for OS. The Cox model showed that a HER2 FISH ratio of $\geqslant$7.0 was a borderline-independent prognostic indicator of TTR and OS (p = 0.0559 and p = 0.0520, respectively). Only lymphatic invasion was a strong independent prognostic factor (p<0.0001 and p = 0.0044, respectively).

Conclusion: A HER2 FISH ratio of $\geqslant$7.0 is an independent predictor of pCR in IBC and non-IBC patients taking trastuzumab-containing neoadjuvant chemotherapy. Prospective evaluation of HER2 FISH ratio of $\geqslant$7.0 is needed. This may be an important stratification factor for randomized clinical trials.

No conflict of interest.

1911 POSTER

New metastases versus increase in size of pre-existing lesions and its correlation with overall survival in patients with MBC treated with eribulin or capecitabine in study 301, a phase III randomised trial

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Background: Improved progression-free survival (PFS) in metastatic breast cancer (MBC) often does not translate into overall survival (OS) benefit. A recent Phase III trial (NCT00337103) in MBC comparing eribulin (E) with capecitabine (C) showed a trend for improved OS (HR 0.88 [95% CI 0.77, 1.00]; p = 0.056) but not PFS (HR 1.08 [95% CI 0.93, 1.25]; p = 0.30) with E. In response to a European Health Authorities request to investigate this apparent discordance, a post-hoc analysis assessed the relationship between OS and the different events defining disease progression: the appearance of a 'new' lesion or metastasis (NM); the increase in size of pre-existing lesions (IPEL); or other (death, clinical progression or censored).

Materials and Methods: Patients (pts) with locally advanced or MBC who had received $\leqslant$3 prior chemotherapy regimens, including an anthracycline and a taxane, were randomised to receive E (n = 554) or C (n = 548). Co-primary endpoints were OS and PFS. In this post-hoc analysis, the relationship between progression events and OS was investigated by Cox regression with a time-dependent covariate; time from randomisation to NM was also analysed.

Results: Progression due to NM or IPEL occurred in 271 and 285, and 147 and 129 of E and C pts respectively. OS by type of progression event is shown in the table. Median OS was similar between arms in pts with IPEL; it was higher in pts with NM treated with E compared with C. Pts who progressed due to a NM were at higher risk of death (HR 2.12 [95% CI 1.84, 2.43]; Wald nominal p < 0.0001).

Conclusions: These results suggest that the conventional PFS definition may not be adequate and that clinically meaningful differences may exist among different MBC 'subsets'. Namely, pts with NM may have a worse prognosis than those with an IPEL. Further, the difference in OS observed in Study 301 may have been driven by pts whose disease progressed due to NM rather than IPEL, and the discordance between PFS and OS may be due to this heterogeneity. These hypotheses are being tested with existing EMBRACE study data and warrant prospective study.

Conflict of interest: *Advisory board: Eisai Inc.: Joyce O'Shaughnessy, Christopher Twelves, Ahmad Awada. Corporate-sponsored research: Eisai Inc.: Christopher Twelves, Louise Yelle, Peter A. Kaufman. Other substantive relationships: Advisory relationship for Roche, Novartis and Celgene and received honoraria for Roche, Novartis, Celgene and Eisai Inc.: Javier Cortes. Speakers Bureau: Eisai Inc.: Christopher Twelves, Joyce O'Shaughnessy. Former employee, Eisai Ltd: Jantien Wanders. Employee, Eisai Inc.: Martin Olivo, Yi He.*

1912 POSTER

BOLERO-2: Efficacy, safety, and quality of life in patients with advanced breast cancer receiving first-line everolimus plus exemestane

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Background: In the BOLERO-2 study (NCT00863655), the combination of everolimus and exemestane (EVE+EXE) more than doubled progression-free survival (PFS) versus placebo (PBO) and EXE (median PFS 7.8 vs 3.2 mo; hazard ratio = 0.45; P <. 0001). Consistent efficacy results were observed in all predefined subgroups, including patients with visceral metastases and patients whose disease recurred after adjuvant endocrine therapy (alone or with chemotherapy). This analysis of BOLERO-2 examines efficacy, safety, and quality of life (QOL) in the subgroup of patients who received EVE+EXE after adjuvant therapy (ie, as first-line therapy in the advanced setting).

Materials and Methods: BOLERO-2 enrolled patients with hormone-receptor-positive (HR^+) advanced breast cancer who had a recurrence or progressed after prior nonsteroidal aromatase inhibitors, and compared EVE (10 mg/d) + EXE (25 mg/d) versus PBO+EXE. The primary endpoint was PFS by local investigator review. QOL was assessed using the EORTC QLQ C-30 questionnaire, with definitive deterioration defined as a 5% decrease in global health status versus baseline, with no subsequent increase on-study.

Results: Of 724 patients in BOLERO-2, 137 (19%) received first-line EVE+EXE (n = 100) or PBO+EXE (n = 37) in the advanced setting. The EVE+EXE group had significantly longer PFS compared with the PBO+EXE group (by local assessment: 11.50 vs 4.07 mo, respectively; hazard ratio = 0.39; 95% confidence interval, 0.25–0.62; by central assessment: 15.24 vs 4.21 mo, respectively; hazard ratio = 0.32; 95% confidence interval, 0.18–0.57). The safety profile was consistent with the known profiles of each agent. Median time to definitive deterioration in global health status was numerically longer in the EVE+EXE arm compared with the PBO+EXE arm (11.07 vs 7.23 mo, respectively; P =. 1715).

Conclusions: EVE+EXE significantly prolonged PFS while maintaining QOL in patients with HR^+ advanced breast cancer who received this treatment as first-line therapy (ie, disease recurred after adjuvant therapy). The robust results observed in this population (PFS by local assessment 7.4 mo longer with EVE+EXE) support using the combination of EVE+EXE earlier in the advanced setting. An ongoing phase 2 trial, BOLERO-4, is prospectively evaluating the efficacy of EVE plus letrozole as a first-line therapy in patients with HR^+ advanced breast cancer (target N = 200).

Conflict of interest: *Advisory board: G. N. Hortobagyi Member of the Scientific Advisory Board of Allergan. Corporate-sponsored research: H.*

S. Rugo has received grant support from Pfizer, Novartis, and Merck. Other substantive relationships: M. Campone is a consultant to and has received honoraria from Novartis H. S. Rugo has received travel support from NovartisJ. Baselga Consultant to Novartis, Roche, Merck, sanofi-aventis, Verastem, Bayer, Chugai, Exelixis, Onyx, and Constellation T. Brechenmacher is an employee of Novartis T. Sahmoud and T. Taran are employees of Novartis with stock/stock options G. N. Hortobagyi is a consultant to Allergan, Novartis, Genentech, and sanofi-aventis has received grant support from Novartis and has received travel expense reimbursement from Novartis, Genentech, and sanofi-aventis

1913 POSTER

First line therapy of metastatic or locally advanced HER2-positive breast cancer: Update of the HERNATA study

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Background: The HERNATA study was a randomised phase III study comparing docetaxel plus trastuzumab (DT) with vinorelbine plus trastuzumab (VT) as a first line therapy og metastatic og locally advanced HER2-positive breast cancer (Anderson et al 2010).
No differences in terms of efficacy between DT and VT was demonstrated but toxicity was much more pronounced with DT. Because of this better benefit-risk balance, standard of care has changed at many institutions. A 2 year update of the study is presented.
Materials and Methods: Patients with HER2 positive locally advanced og metastatic breast cancer naive to chemotherapy and trastuzumab, were randomly assigned to docetaxel 100 mg/m^2 day 1 or vinorelbine 30−35 mg/m^2 days 1+8 both combined with trastuzumab 8 mg/kg loading dose and 6 mg/kg maintenance dose day 1 q 3 weeks. Tumor assessments were conducted every 9 weeks. Analyses were according to intention-to-treat. Primary endpoint was time to progression (TTP).
Results: 143 patients were randomly allocated to docetaxel and 141 to vinorelbine. With median follow-up of 68 months, 217 have progressed and 184 died. The median TTP for vinorelbine and docetaxel respectively was 14.9 (95% CI:11.9–18.2) vs. 13.5 (95% CI10.7–16.6) months (hazard ratio (HR) 0.99, 95% CI: 0.76–1.30, p = 0.96), median overall survival was 41.1 (95% CI: 35.3–50.8) vs. 38.1 (95% CI: 33.0–58.4) months (HR 1.05, 95% CI: 0.79–1.40, p = 0.74). 2-year survival rate was 73% in VT arm and 70% in DT arm, whereas 5-year survival rates were 35% and 40% respectively.
Median time to treatment failure for study chemotherapy was 8.3 (VT arm) vs 6.2 (DT arm) months (HR 0.51, 95% CI: 0.39–0.65, p < 0.0001). The investigator assessed overall response rate among 241 patients with measurable disease were 72% for VT and 69% for DT. More patients in the docetaxel arm discontinued therapy due to toxicity (p < 0.0001). More patients had grade III−IV toxicity with docetaxel than with vinorelbine.
Conclusion: The outcome was similar for first line treatment with vinorelbine and docetaxel both combined with trastuzumab but vinorelbine could be asministered for longer time and had a more favourable toxicity profile. It should therefore be considered as a potentially better first line alternative and ad an regimen for future combination with HER2 directed therapy ex. pertuzumab.
Conflict of interest: *Other substantive relationships: M Andersson have received honoraria and travel grant from Roche, Sanofi Aventis and Pierre Fabre. ST Langkjer have recieved travel grants from Pierre Fabre and Roche*

1914 POSTER

Clinical significance of p95HER2 Overexpression, PTEN loss and PI3K expression in p185HER2-positive metastatic breast cancer patients treated with trastuzumab-based therapies

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Background: Overexpression or amplification of p185HER2 is an established poor prognostic factor in breast cancer portending an aggressive course and potential for early metastasis. On the other hand, monoclonal antibody trastuzumab is widely used in the clinic to target this overexpressed oncogene. Unfortunately, approximately 30−40% of all patients overexpressing HER2 respond to trastuzumab warranting further research regarding the structure and additional modulation of the receptor. In this study, we aimed to investigate the response to trastuzumab in terms of the potential roles of several oncogenic pathways (phosphatase and tensin homolog (PTEN), and phosphatidylinositol 3-kinase(PI3K) and a truncated receptor protein, p95HER2), retrospectively.
Material and Methods: Paraffin embedded primary tumor tissues of hundred HER2 positive metastatic breast cancer patients who received trastuzumab with combination cytotoxic chemotherapy were analyzed with immunohistochemical method for p95HER2, p85 and PTEN. Relationship between variables were tested via chi-square, Fischer's exact test and Mann Whitney U tests, wherever appropriate. Progression free survival (PFS) and overall survival (OS) periods were calculated with Kaplan–Meier method and survival curves of subgroups were compared with log-rank test.
Results: Levels of immunohistochemical expression of p95 and PI3K were 33% and 42%, respectively. In 43% of patients loss of PTEN was observed. p95 expressing tumors had statistically lower response rates for trastuzumab than tumors not-expressing p95 ($p = 0.001$).
On the contrary, PTEN expressing tumors had statistically higher response rates for trastuzumab than tumors not-expressing PTEN ($p = 0.012$). PI3K expression had no significant effect on trastuzumab response. Median PFS for p95 expressing and not-expressing tumors were 8 months (95% CI, 2.5–13.4 months) and 22 months (95% CI, 9.9−34 months), respectively ($p = 0.0001$). Median PFS for PTEN expressing and not-expressing tumors were 15.3 months (95% CI, 12.6−34 months) and 12.1 months (95% CI, 7.9–16.2 months), respectively ($p = 0.04$). Median OS for p95 expressing and not-expressing tumors were 24 months (95% CI, 8.3–40.4 months) and 29.1 months (95% CI, 8.6–43.2 months), respectively ($p = 0.045$). Median OS for PTEN expressing and not-expressing tumors were 25.1 months (95% CI, 7.5–40.1 months) and 26.8 months (95% CI, 8.1−42 months), respectively, which was not statistically significant ($p = 0.5$). Level of PI3K expression had no effect on PFS and OS in our patient population.
Conclusion: Presence of p95 predicted a poorer response to trastuzumab treatment, shorter PFS and OS in our HER2 positive metastatic breast cancer cohort. Additionally, loss of PTEN predicted a poorer response to trastuzumab treatment and shorter PFS but not OS. We could not find an effect of PI3K expression on the above mentioned parameters.
No conflict of interest.

1915 POSTER

Etirinotecan pegol prolongs survival in an experimental model of brain metastasis of human triple negative breast cancer

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Background: Incidence of brain metastases of breast cancer (BMBC) in HER2$^+$ and triple negative breast cancer (TNBC) is ~35%. Despite newer targeted therapies, survival for women with BMBC has not dramatically improved. Etirinotecan pegol (EP) is a unique, long acting topoisomerase 1 inhibitor that provides continuous exposure to SN38 with reduced peak concentrations. EP resulted in a RECIST response rate of 39% (7/18) in patients with metastatic TNBC. Here we present encouraging survival and pharmacokinetic (PK) results for EP in an experimental mouse model of TNBC brain metastasis using irinotecan (IRN) as a control.
Methods: For survival, brain seeking MDA-MB-231Br breast cancer cells were injected intracardially and allowed to circulate. After 21-days, mice were randomized (10/ group) and treated IV with vehicle, 50 mg/kg IRN, or 50 mg/kg NKTR-102 IV q7d until death due to brain metastases. For measurement of SN38 in plasma and brain tumors, MDA-MB-231Br cells were injected intracranially and allowed to reach 20−30 mg. Then, 5 mice per sampling time received 50 mg/kg IRN or EP IV and plasma and tumors were harvested between 0–168 hr. SN38 concentrations were determined by LC-MS/MS and PK was assessed with noncompartmental methods.
Results: Plasma and brain tumor SN38 AUCs after IRN and EP are shown (Table). SN38 tumor to plasma ratio was 0.8 after IRN, while a tumor to plasma ratio of 6 after EP indicated preferential SN38 accumulation in brain tumor tissue. In the survival study, vehicle treated animals died on days 16−23 post start of treatment and all IRN animals died on day 21, leading to a median survival of 21 days in both groups. In contrast, 50% of EP treated animals were still alive 61 days after treatment initiation, with a censored median survival of 51 days.

Table: SN38 AUC (ughr/mL) after 50 mg/kg IV of IRN or EP

Trtm	Plasma	Brain tumor	Brain tumor to plasma ratio
IRN	0.13	0.11	0.8
EP	2.1	12	6
EP to IRN Ratio	16	109	–

Conclusions: Tumor SN38 exposure after EP is 6-fold greater than that in plasma and 109-fold greater than after IRN, suggesting that EP penetrates the compromised blood tumor barrier. The higher tumor SN38 exposure after EP appears responsible for the greatly prolonged survival observed in this model of TNBC brain metastasis. Plasma SN38 trough concentrations observed in this model are achieved clinically with 145 mg/m^2 EP used in the Phase 3 BEACON study in patients with metastatic BC, emphasizing the potential translational relevance of these results.
Conflict of interest: *Other substantive relationships: Employee of Nektar Therapeutics (U Hoch and ME Eldon)*

1916 POSTER

Molecularly well-characterized human breast cancer cell lines offer an alternate model system to understand in vivo subtype-specific biology of human breast tumors

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Background: Breast cancer (BC) is a disease with intra- and inter-tumor heterogeneity and models representing the complete variety of clinical BC phenotypes are not available. In this study, we explored the tumor growth potential and metastatic behavior of twenty-four human BC cell lines in nude mice and determined whether these cell lines can recapitulate subtype-related biological behavior when implanted under the mammary fat pad of mice.
Material and Methods: Cell lines were transduced using lentiviral particles with a luciferase reporter gene. Subsequently, per cell line 3 independent monoclonal clones with similar luciferase activity and molecular features comparable to the parental lines were selected and implanted orthotopically under the mammary fat pad of nude mice. Xenograft tumor growth was monitored by measuring tumor size twice a week for a period of 12 months. At the end of the experiment, using the IVIS Imaging System, tumor size and presence of distant organ metastases were assessed by measuring the tumor bioluminescence. Subtype-specific differences in tumor growth and mice survival were compared using a Kruskal-Wallis test and Cox regression analysis.
Results: Subtype-specific differences in tumor growth, ability to metastasize to distant sites and tumor-related survival of mice were observed. 87.5% of the cell lines gave rise to xenografts of which 57% showed metastasis to distant sites (mostly lymph node and lungs but rarely bone and brain). A clear difference was observed in growth of xenografts from cell lines of different molecular subtypes ($P = 0.016$; Kruskal-Wallis test). Mice bearing the basal-like and the normal-like xenografts showed poor tumor-related survival (HR: 5.93; $P = 0.007$ and HR: 5.55; $P = 0.009$, respectively) compared with those bearing the ERBB2-positive xenografts, which had the longest survival. Luminal xenografts showed an intermediate behavior. Subtype-specific metastasis to distant sites between xenografts was not however observed. In summary, comparable to clinical behavior in humans, we observed that the basal-like and the normal-like cell lines grew more aggressive in mice than the cell lines of other molecular subtypes. However, in contrast to clinical findings, we observed no relationships between intrinsic subtype and preferences for site of relapse.
Conclusion: In conclusion, we have established xenograft models from 21 phenotypically and molecularly diverse human BC cell lines, which can be exploited as useful tools to perform functional studies and screening of interfering drugs.
No conflict of interest.

1917 POSTER

Analysis of mir-339-5p expression and function in breast cancer

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Background: MicroRNA (miRNA) expression has been found to be altered in many diseases including breast cancer. miRNAs are small non-coding RNA molecules that control gene expression post-transcriptionally. The focus of this study was to quantify expression of miR-339-5p in both tissue and circulation of patients with breast cancer and determine any relationship with clinicopathological characteristics. The effect of miR-339-5p on breast cancer cell proliferation in vitro was also determined.
Materials and Methods: Following informed patient consent and ethical approval, breast tissues (n = 163) were harvested from patients undergoing surgery, including malignant (n = 103), normal (n = 30) and fibroadenoma (n = 35). To determine the level of circulating miR-339-5p, whole bloods were collected from patients with breast cancer (n = 40) and healthy controls (n = 40). miRNA was extracted, reverse transcribed, and the level of miR-339-5p in all samples quantified using RQ-PCR. Results were correlated with patient clinicopathological details. Expression of miR-339-5p was also detected in breast cancer cell lines, and the effect of a miR-339-5p mimic on cell proliferation investigated.
Results: miR-339-5p was detectable in 159/168 breast tissue samples analysed. A significant decrease in miR-339-5p expression in breast cancer was observed (n = 101, Mean(SEM) 2.0(0.06) Log_{10} Relative Quantity (RQ)) compared to both healthy control tissue (n = 24, 2.5(0.1) Log_{10} RQ, $p < 0.01$), and benign tissue (n = 34, 2.45(0.1) Log_{10} RQ, $p < 0.01$). miR-339-5p was also detectable in the circulation of individuals included in the study, although no significant difference was observed between breast cancer patients (n = 40, 1.49(0.05) Log_{10} RQ) and healthy controls (n = 40, 1.59(0.06) Log_{10} RQ, $p = 0.41$). Further investigation revealed no significant association with patient clinicopathological details. Functional assays revealed reduced proliferation following transfection of breast cancer cells with miR-339-5p (T47D; −17% and SK-BR-3; −27%).
Conclusion: Although not a suitable circulating biomarker of the disease, this study highlights miR-339-5p as a tumour suppressor in breast cancer, potentially mediated through knockdown of cellular proliferation. Further investigation is required to determine the target mRNA involved in this response.
No conflict of interest.

1918 POSTER

Co-expression of HER3 in HER2-positive metastatic breast cancer patients is an independent predictor of impaired prognosis

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Background: Improved understanding of the pathobiology of the metastatic cascade as well as the identification of new prognostic markers may lead the path to the development of novel targeted agents in breast cancer patients (BC pts). Recently, HER3-expression was postulated as independent risk factor for metastatic spread and especially brain metastatic disease.
We aimed to analyze the impact of HER3 expression in terms of occurrence of brain metastases and overall survival in an equally between breast cancer subtypes distributed population.
Methods: Pts of different BC subtypes (luminal, HER2-amplified, triple-negative) with metastatic disease were identified from a breast cancer data base. Tissue of the primary tumor was retrieved from the local pathology institute. Immunohistochemical staining of estrogen-receptor, progesterone-receptor, and HER2 and HER3 was performed, according to standard protocol. In HER2 equivocal cases, subsequent FISH analysis was performed. HER3 FISH was performed for all HER3 positive specimens.
Results: Specimens of 110 pts (36/110 luminal, 35/110 HER2-amplified, 40/110 triple-negative) were available for this analysis. 23/110 (21%) specimens showed strong, complete, membranous staining for HER3 of at least 10% of all tumor cells. HER2/HER3 co-expression was observed in 12/110 (11%) specimens. HER3 showed a statistically significant association with HER2-expression ($p = 0.02$; Chi square test). No correlation was observed for HER3-expression and overall survival (OS), incidence of brain metastases, or time to diagnosis of brain metastases in the entire patient cohort ($p > 0.05$; log rank). In the HER2-amplified subgroup, however, HER3-expression was significantly associated with shorter OS (median 30 vs. 63 months; $p = 0.02$; log rank test) and remained significant when entered into a multivariate model ($p = 0.02$; Cox regression).
Conclusions: HER2/HER3 co-expression is significantly associated with impaired OS in pts with HER2-positive metastatic breast cancer but not with occurrence of brain metastases. Co-inhibition of HER2 and HER3 or inhibition of HER2/HER3 hetero-dimerization could improve prognosis of this patient population.
No conflict of interest.

1919 POSTER

Occurrence of metastasis and in vitro aggressiveness of triple negative breast cancer is related to the glycolytic phenotype, microenvironment metabolism and MCT4 lactic acid transporter

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Background: Comparing with hormone positive and Her-2 overexpressing breast cancers, triple negative (TNEG) breast cancers are characterized by a more systematic and far stronger 18-FDG uptake that suggests a glycolytic addiction in this tumour subset (PMID: 18098228 and 22011459).
Material and Methods: Correlation between proteins involved in glycolytic metabolism and intracellular pH regulation (c-myc, GLUT-1, LDH-A, MCT1, MCT4, Basigin, CA9) and metastasis has been analyzed in 158 patients with TNEG disease using tissue-micro arrays. Proteins that were indicative of poor prognosis were inhibited or knocked-out *in vitro* to determine potential new targets in TNEG breast cancers.
Results: With a median follow-up of 6 years (0.25–14.4) the metastasis rate was 27.4% at 6-years. Tumours were highly proliferative (70% with Ki-67 staining >20%) and had a glycolytic phenotype with a strong expression of GLUT-1 (78%), LDH-A (78%), MCT1 (60.4%), MCT4 (85.7%), Basigin (78%), CA9 (53.7%) and C-myc (84.2%). The Log-rank test identified as bad prognostic factors for metastasis-free survival (MFS), large pT ($p < 0.001$), positive pN ($p = 0.001$), positive MCT4 ($p = 0.01$) and LDH-A ($p = 0.04$). MCT4 staining and LDH-A staining were even stronger prognostic factors when excluding tumors with stromal staining ($p = 0.001$ and $p = 0.005$ respectively for MFS). Ki-67, age and grade were not correlated with MFS. pT stage, pN and tumoral MCT4 staining were considered as independent prognostic factors in multivariate analysis (Cox regression, HR of respectively 2.4, 2.2 and 2.2, $p < 0.05$). These results were similar for overall and cancer specific survival. *In vitro,* knock-out of MCT4 in a TNEG cell line (HS578t) reduced clonogenic survival by 50%. Use of the strong inhibitor of the mitochondria respiratory chain, phenformin, resulted in a marked reduction of clonogenic survival (by 99%) regardless of MCT4 expression status in normoxia. However, in hypoxia phenformin application prevented clonogenic survival only when combined with MCT4 knock-out.
Conclusions: This study demonstrates the role of glycolytic metabolism in the tumour microenvironment and in the occurrence of metastases of TNEG breast cancer. Our *in vitro* data suggests that targeting this metabolic cancer hallmark in combination with phenformin could provide a potential novel anticancer treatment for TNEGs.
No conflict of interest.

1920 POSTER

Reverse-phase protein array for prediction of patients unlikely to develop bone metastasis from breast cancer

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Background: The aim of this study was to identify bone-metastasis-related markers in patients with primary breast cancer using reverse-phase protein array (RPPA) analysis. RPPAs enable quantification of total and phosphorylated proteins, providing information about their functional status.
Marial and Methods: Tumor samples were obtained from 169 patients with primary invasive breast carcinoma who underwent surgery on an investigational protocol to assess protein expression by RPPA between June 1992 and March 2007. Seventy six patients (45.0%) had hormone receptor-positive tumors and 33 patients (19.5%) had HER2-negative tumors. Clinical characteristics and protein expression (determined by RPPA) were compared between patients who developed breast cancer bone metastasis (BCBM) and no BCBM. Variables identified as significantly correlated with BCBM in univariate logistic regression analyses were then used to build a multivariate model. The models' predictive abilities were assessed using leave-one-out cross-validation.
Results: Twenty one of the 169 patients developed BCBM (a median follow-up time, 47 months; range, 2.5–237 months). Lymph node status ($p = 0.023$) and RPPA expression levels of 22 proteins were significantly correlated with BCBM in univariate logistic regression analyses. After filtering variables through a stepwise algorithm, a final model consisting of 8 proteins and lymph node status After filtering the variables through a stepwise algorithm, the final model consisting of 8 proteins (CDK2, CDKN1A, Rb1, Src, phosphorylated-RSK, HER2, BCL11A, and MYH11) and lymph node status had a sensitivity (positive predictive value) of 30% and specificity (negative predictive value) of 90.5% in cross-validation. Most proteins in the final model are associated with cell cycle or signal transduction.
Conclusions: Our model can potentially identify patients who are unlikely to develop BCBM. Prospective validation of this model can show whether clinical trials excluding these patients have the potential to clarify the benefit of bisphosphonates in the adjuvant setting.
No conflict of interest.

Poster Session (Mon, 30 Sep)
Breast Cancer – Early Disease

1921 POSTER

Regulation of MMP-13 (collagenase-3) in human breast cancer cells by the transcription factor Pit-1

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An important aspect of cancer cells is its ability to invade other tissues and create metastases. This process involves proteolytic enzymes such as matrix metalloproteinases (MMPs), which have the ability to degrade the extracellular matrix proteins and basement membrane. The Pit-1 transcription factor was originally described in the pituitary gland, but it is also expressed in the mammary gland. Pit-1 overexpression or knockdown in human breast cancer cell lines induces profound phenotypic changes in the expression of proteins involved in cell proliferation, apoptosis, and invasion. Interestingly, patients with breast cancer and elevated expression of Pit-1 showed a significant association with metastasis in lung. In this study we evaluate the possible relationship between Pit-1 and MMPs, specifically with MMP-13 which has been related to breast cancer cell metastasis.
The MCF-7 and MDA-MB-231 human breast adenocarcinoma cell lines were transfected with Pit-1 overexpression vector (pRSV-hPit-1) and 48 hours later MMP-13 mRNA and protein expression were evaluated by real-time PCR and Western blot. MMP-13 enzymatic activity after Pit-1 overexpression was carried out by zymography and ELISA assays. To determine MMP-13 transcriptional regulation by Pit-1, we carried out chromatin immunoprecipitation (ChIP) and luciferase reporter assays. We also evaluate the role of Pit-1 overexpression and MMP-13 knock-down using the severe combined immunodeficient (SCID) mouse tumor xenograft model. Finally, by immunohistochemistry, we correlated Pit-1 and MMP-13 protein expression in human breast tumors samples.
Our data show that Pit-1 overexpression increases MMP-13 mRNA and protein expression and induces significant MMP-13 activation in culture medium. ChIP and luciferase assays demonstrate direct binding and transcriptional regulation of the MMP-13 gene by Pit-1. Knock-down of MMP-13 in Pit-1 overexpressing MCF-7 cells injected in the mammary fad pat of SCID mice significantly decrease the presence of lung metastasis. In patients with breast cancer, high expression of Pit-1 was significantly correlated with MMP-13 positivity.
In summary, our results indicate that Pit-1 transcription factor regulates MMP-13 expression at transcriptional level by binding to the MMP-13 promoter region. This regulation could be related with Pit-1 induction of breast cancer cell metastasis to the lung.
No conflict of interest.

1922 POSTER

IRAK4 modulates growth and migration in breast cancer cells

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Background: Breast cancer (BrCa) is the most prevalent form of cancer among women worldwide. While early detection improves health prospects,

overall medical prognosis continues to be poor. Current studies suggest the innate immune toll-like receptor (TLR) pathway impacts BrCa tumor progression, yet its exact role remains unclear. We have analyzed sixteen single nucleotide polymorphisms (SNPs) from ten TLR-associated genes and found that African American women who possessed the homozygous minor interleukin-1 receptor-associated kinase 4 (IRAK4) rs4251545 allele demonstrated a greater than 4-fold increase in BrCa risk. IRAK4 is a central regulator of the TLR pathway which mediates cell invasion and cytokine and chemokine production. Therefore, this study aimed to assess the molecular involvement of IRAK4 in BrCa development and progression. We hypothesized that functional breast epithelial IRAK4 promotes BrCa growth and migration.
Materials and Methods: To test this hypothesis, triple-positive MCF7 and triple-negative MDA-MB-231 (wild-type IRAK4) and MDA-MB-468 (IRAK4 rs4251545 minor variant expressing) human BrCa cell lines were compared. Cells were treated for 24 hours with or without IRAK1/4 inhibitor. IRAK-1 and −4 protein levels were monitored by western blot. Cell migration and cell growth were examined by wound healing and crystal violet assays, respectively. As a test of metastatic potential, we also used western blot to monitor expression of matrix metalloproteinases 9 (MMP-9) and 13 (MMP-13), both secreted proteinases that participate in the degradation of extracellular matrix prior to metastasis.
Results: All BrCa cell lines expressed comparable levels of IRAK4, whereas IRAK1 expression was reduced in MDA-MBA-231 cells compared to MCF-7 and MDA-MB-468 cells. Treatment with IRAK1/4 inhibitor delayed wound healing and inhibited growth in all BrCa cells lines. While MMP-9 was exclusively expressed in MDA-MB-231 cells, its levels were unaffected by IRAK1/4 inhibitor. In contrast, MMP-13 protein levels were up-regulated in IRAK1/4 inhibitor treated MDA-MB-231 cells. By comparison, the less aggressive MCF7 and MDA-MB-468 cells expressed high MMP-13 levels yet were unresponsive to IRAK1/4 inhibitor.
Conclusion: Together these results indicate that IRAK4 may regulate BrCa growth and migration. Furthermore, the up-regulation of cellular MMP-13 upon IRAK4 inhibition suggests a feedback signal which promotes metastasis. Thus, these findings suggest that IRAK4 and the TLR pathway as promising drug targets to modulate BrCa tumor progression.
No conflict of interest.

1923 POSTER

mRNA expression of p14 ARF and hTERT in human breast cancer: evidence suggestive of an antagonistic relationship

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Background: p14 has a role in cell cycle regulation, cell senescence. It is characterised as a 15 kDa nucleolar protein, believed to exert the majority of its function through the regulation of p53, which is has a key role in DNA repair, cell cycle regulation and metabolism.
Previous evidence is highly suggestive of a highly significant role for human telomerase reverse transcriptase (hTERT) in human breast cancer.
In this study, we have endeavoured to elucidate the relationships between the mRNA expressions of p14 and the clinicopathological parameters of human breast cancer.
Materials and Methods: Specimens of breast cancer (BC) tissues (N = 127) and normal tissues (N = 23) underwent RNA extraction and reverse transcription. Transcript levels were determined using real-time quantitative PCR. Expression levels were analysed against clinicopathological data accrued over a median follow-up period of 10 years.
Results: Higher p14 mRNA transcript levels were associated with non-cancerous background tissue specimens (median copy numbers: 103 vs. 4, p = 0.0095), with better overall and disease-free survival. The p14 mRNA expression was higher in TNM2 stage tumours compared with TNM1 lesions (TNM2 vs. TNM1, 27.2 vs. 3.5, $p = 0.049$). However, p14 mRNA expression subsequently declined with further tumour progression (TNM1/TNM2 vs. TNM3/4, 26 vs. 2, p = 0.009).
Furthermore, a highly significant correlation between p14 and human telomerase reverse transcriptase (hTERT) levels was seen (r = 0.406, p = 0.00005).
Conclusions: p14 expression seems to increase initially in early breast cancer and decrease with further tumour progression. The correlation p14 with hTERT suggests that p14 may be induced to counteract cell immortalisation due to hTERT surge.
No conflict of interest.

1924 POSTER

Identification of two novel mutations in exon 20 of brca1 gene among Eastern Indian breast cancer patients

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Background: Breast cancer is the most common neoplastic disease in women. In India, breast cancer is the second most common malignant condition among women. Seventy percent of breast cancer is sporadic and 5−10% of the disease is caused by inherited genetic mutations which put women at the threshold of high risk for developing breast cancer. The main purpose of this hospital based study is to identify mutations in exon 20 of BRCA1 gene among breast cancer patients of eastern India having a strong family history.
Materials and Methods: The period of this study is from January 2010 to March 2013. The total number of the patients studied during this period is 106. Point mutation 5382insC in exon 20 of BRCA1 gene was detected by using Amplification Refractory Mutation System based Polymerase Chain Reaction. DNA sequencing was also performed to detect unknown mutations in the above mentioned exon. Attempts are also taken to correlate ER, PR, HER2/neu hormonal status with BRCA1 gene mutation.
Result: Out of 106 patients (age range: 23−54 years) family history was taken from 65 patients. Peripheral blood samples were collected from all these patients and from eight family members. ARMS-PCR was performed for all samples whereas direct sequencing was done for 30 samples. In the present study we reported two novel mutations 1) A5356C and 2) G5329A in exon 20 of BRCA1 gene from two breast cancer patients of 34 years and 39 years old respectively. Substitution of nucleotide A5356C at codon 1746 (CAC>CCC) and G5329A at codon 1737 (AGA>AAA) result the replacement of Histidine by Proline and Arginine by Lysine respectively (NCBI Reference U14680.1). In our hospital based study, we have found a frequency of 0.075 for the mutation 5382insC in exon20 at BRCA1 gene.
Conclusion: To the best of our knowledge A5356C and G5329A, are two novel mutations as they have not yet been reported earlier in any population. Identification of these novel mutations
No conflict of interest.

1925 POSTER

Beta 3-integrin promotes the reversion of luminal breast cancer cells to a normal like phenotype

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Loss of cell polarization and luminal filling of mammary glands are key structural alterations in breast cancer disease. Recent findings support the notion that disruption of cell-polarity mechanisms plays a causal role in tumor initiation thus, implicating a role of cell and tissue polarity mechanisms as potential non-canonical tumor suppressors. We present here for the first time the role of beta 3 -integrin (Intβ3) in promoting the commitment of luminal breast cancer progenitor like cells to differentiate to polarized acini like structure. Our results demonstrate that overexpression of Intβ3, in MCF-7 cells (MCF-7-Intβ3) promoted their reversion to acini like organoids resembling a normal breast tissue, when cultured in the physiological relevant 3 dimensional basement membrane extract (3D BME system). The phenotypic reversion was demonstrated by the generation of acinus like organoids with apicobasal polarity displayed by the apical expression of GM130 and mucin-1 (MUC1), and basal expression of laminin 5. These organoids gradually progressed into spherical lumen containing structures resembling normal breast tissue. Conversely, control MCF-7 cells stably expressing empty vector (MCF-7-vec) did not undergo phenotypic reversion. Intriguingly, this reversion was driven by cancer progenitor like cells derived from non-adherent mammospheres, (either expressing $CD44^{-/low}$ $CD24^{high}$ or $EpCAM^{high}CD49f^{low}$ phenotype) that expressed Intβ3. Whereas, Intβ3^{-} cancer progenitor like cells could not differentiate to acini like structure in the 3D BME system. Therefore, these results suggest that commitment of the cancer luminal progenitor like cells to differentiate is dependent on Intβ3 expression. Finally, we have preliminary results demonstrating that the reversion of MCF-7-Intβ3 cells to a normal like phenotype induced a dormant state depicted by induction of p21 expression and reduction in Ki67 positive cells compared to MCF-7-vec cells.
Hence, these finding exhibits a novel mechanism to reprogram cancer luminal progenitor like cells to differentiate to a normal like acini by inducing the expression of Intβ3. Therefore, promoting such differentiation of luminal

breast cancer cells in conjunction to their microenvironment, can potentially promote the normalization of their malignant phenotype.
No conflict of interest.

1926 POSTER

Thirteen miRNAs involved in the response of cancer cells to doxorubicin

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Background: Mature microRNAs (miRNAs) are a class of naturally occurring, small non-coding RNA molecules, about 21−25 nucleotides. Growing evidence shows that miRNAs exhibit a variety of regulatory functions related to cell growth, development, and differentiation, and are associated with a wide variety of human diseases. Several miRNAs have been linked to cancer; since expression analysis studies have revealed perturbed miRNA expression in tumors compared to normal tissues. As a consequence, human miRNAs are likely to be highly useful as biomarkers, especially for future cancer diagnostics, and are emerging as targets for disease intervention.
Since doxorubicin (DOX) has been used for a long time in breast cancer treatment, and resistance mechanisms are not clear understood, the aim of this work was to find a miRNA expression profile that could explain the regulation in different breast cancer cell lines under DOX treatment.
Methods: Three breast cancer cell lines (MDA-MB-231, MDA-MB-468 and MCF-7) were cultured in normal conditions and also treated with DOX. Total RNA containing small non-coding RNA was isolated and its expression profile was performed by using GeneChip miRNA 2.0 array. Real time PCR validation was carried out to confirm the results.
Results: Principal Component Analysis (PCA) of the small non-coding RNA profiles showed different expression patterns between normal conditions and DOX treatment in each cell line separately. Taken together in a Heat Map, miRNA expression profiles of MDA-MB-231 and MDA-MB-468 cell lines were closer in both normal and DOX treatment conditions, while miRNA expression profile of MCF-7 cell line showed strong differences. Total of 13 common miRNAs between the three cell lines were found to be significantly affected by DOX treatment. PCR validation confirmed the results obtained.
Conclusions: We conclude that 13 common miRNAs are responsables of changes compared to treatment with DOX in breast cancer cell lines MDA-MB-231, MDA-MB-468 and MCF-7. This miRNAs are mainly related with cellular processes such as cell differentiation, vascularisation, apoptosis and cell proliferation and also involved in other cellular processes, such as cell migration.
No conflict of interest.

1927 POSTER

Alteration in expression of MDR genes in breast carcinoma patients following preoperative chemotherapy is related with clinical response

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Drug resistance of tumour cells to chemotherapeutic agents is considered to be one of the most important causes of tumour therapy failure but our understanding of the underlying molecular mechanisms is in complete. The neoadjuvant chemotherapy (NACT) revealed to be suitable model for direct assessment of response to treatment in depends on multidrug resistance (MDR) gene expression before and after NACT. We examined the association between the alteration in MDR gene expression measured both before and after chemotherapy in the short-term response to neoadjuvant chemotherapy in the cohort of IIA IIIC stage breast cancer (BC) patient (n = 84). All patients were primarily treated with two-four preoperative cycles of FAC (Cyclophosphamide, Adriamycin, Fluoracil), CAX (cyclophosphamide, aryamycin, Xeloda), or Taxane regimes. The transcriptional profile of key MDR genes (ABCB1, ABCG1, ABCG2, ABCC1, ABCC2, ABCC3, ABCC5, MVP and GSTP1,)was evaluated in both pre-therapeutically obtained tumour tissue and in specimens removed by final surgery, using a qPCR assay. No significant difference in the average level of MDR-genes expression in paired breast tumours before and after NACT was found when analysed both responsive and nonresponsive patients along. There was no correlation between MDR gene expression in pre-NACT tumour specimens and immediate NACT response. In the group with tumour response, we found a statistically significant down-regulation of the expression of ABCB1, ABCG1, ABCG2, ABCG2, ABCC1, ABCC2, ABCC5, MVP and GSTP1 (67−93% of cases) genes following NACT in BC patient treated with FAC and CAX. In contrast we found up-regulation of these gene expressions after NACT in mostly nonresponsive patients (55−96% of cases). Response to taxotere has been related to reducing mRNA level of ABCB1, ABCG1, ABCG2, ABCC2 and MVP genes in the tumour sample derived following chemotherapy.
No conflict of interest.

1928 POSTER

Clinical and morphological characteristics of triple-negative breast cancer in patients with different BMI

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Background: The aim of this retrospective analysis was to investigate the morphological features of triple-negative breast cancer (TNBC) patients with different body mass index (BMI).
Material and Methods: The study included 110 patients with TNBC aged 25 to 76 (54.6±1) years old, who sought medical care in oncology clinic National Medical University named after A.A. Bogomolets in 2005–2006. Morphological characteristics of TNBC were evaluated in relation to BMI.
Results: According to WHO criteria women with TNBC were divided into the 3 groups: group 1−27 patients (24%) were normal/underweight (BMI <25 kg/m^2), group 2−47 patients (43%) were overweight (BMI from 25 to 29.9 kg/m^2), and group 3−36 patients (33%) were obese (BMI $\geqslant$30 kg/m^2). Postmenopausal TNBC is diagnosed in significantly more patients with obesity, and in premenopausal in patients who are overweight. Lobular TNBC was significantly more frequent in patients with obesity (25%) and ductal − in patients in group 1 and 2 in 74% and 77% of cases. Low histological grade (G3, G4) occur in overweight and obese patients (32% and 42%, respectively). Lymph node metastases were often (for 13%) in patients with obesity.
Conclusions: Our study shows an association between high BMI and poor prognostic morphological characteristics in patients with TNBC.
No conflict of interest.

1929 POSTER

Dietary supplementation with molecular iodine may revert epithelial–mesenchymal transition in human breast cancer

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Breast cancer is the neoplasia with the highest incidence and mortality rate for women worldwide. Although current therapies have succeeded in increasing survival after diagnosis, relapses occur at a significant rate. Many models have been established in an effort to better understand tumour initiation and growth in order to develop more efficient therapies. The Cancer Stem Cell (CSC) model states that a subpopulation of tumour cells with distinct, stem-like properties drive the tumour initiation, growth, and metastasis. These stem-like characteristics include self-renewal, drug resistance, and migration capacity and may be acquired by mutation of a normal stem cell, or after processes such as the epithelial mesenchymal transition (EMT). In methylnitrosourea (MNU)-induced mammary cancer models, we have demonstrated that dietary supplementation with molecular iodine (I_2) has dose-dependent effects on differentiation and apoptosis. Furthermore, in a human study, women with breast cancer who were supplemented with I_2 during chemotherapy showed no tumour relapse, as compared to 30% relapse observed in placebo-treated patients, suggesting that I_2 may affect CSC populations. To examine this hypothesis we carried out a human study (Hospital General de Queretaro, protocol # 185−09−03) that included 22 women diagnosed with early stage breast cancer (IIa and IIb). Patients were supplemented with I_2 (5 mg daily) or placebo (vegetable dye) for 2−5 weeks before surgery. We identified the CSC populations present in breast tumours by detecting changes in the expression of e-cadherin and vimentin (proteins related to EMT) with immunohistochemistry and confocal microscopy. Preliminary results show that the I_2 supplementation is accompanied by normal e-cadherin and vimentin expression in most tumours, whereas tumours from placebo-treated women show aberrant e-cadherin and vimentin expression. Thus far, our results suggest that I_2 could delay or even revert the EMT process. Additionally, current studies are being carried out to determine such possible effects of I_2 in combination with chemotherapy in advanced breast cancer patients.

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No conflict of interest.

1930 POSTER

Pre-diagnostic smoking behavior and poorer prognosis in breast cancer patients from Germany − potential differential effects by NAT2 acetylation status, BMI, and tumor subtypes

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Background: Inconsistent results of smoking on breast cancer-specific mortality might be explained by subgroups of patients with different susceptibility to harmful effects of smoking.
Methods: We investigated the effect of pre-diagnostic smoking behavior on breast cancer outcomes (all-cause (OS), breast cancer-specific (BCSS), non-breast cancer cancer-specific survival (non-BCSS), and risk of recurrence) using a German prospective cohort of 3,340 breast cancer patients. The study participants were aged 50−74 years at breast cancer diagnosis and recruited between 2001 and 2005. We assessed effect modification by N-acetyltransferase (encoded by the *NAT2* gene) status, body mass index (BMI), alcohol consumption, and tumor subtypes. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated by multivariable Cox proportional hazards models.
Results: After a median follow-up time of 5.7 years, 449 patients were deceased. Smoking at time of breast cancer diagnosis vs. never/former smoking was significantly associated with poorer OS (HR 1.39, 95% CI 1.10–1.76), which was mainly due to non-BCSS (HR 1.96, 95% CI 1.28–2.99), and non-significantly associated with BCSS (HR 1.23, 95% CI 0.93–1.64) and risk of recurrence (HR 1.29, 95% CI 0.95–1.75). Associations were consistently stronger in NAT2 slow than in fast acetylators for all survival endpoints (e.g. BCSS: HR 1.77, 95% CI 1.13–2.79 vs. HR 1.09, 95% CI 0.60–1.98; $P_{heterogeneity}$ >0.05). There was evidence for effect modification by BMI for non-BCSS (BMI <25 kg/m^2: HR 2.52, 95% CI 1.52–4.15 vs. BMI $\geqslant$25 kg/m^2: HR 0.94, 95% CI 0.38–2.36; $P_{heterogeneity}$=0.04). Smoking at time of diagnosis was also associated with significantly poorer outcomes for triple negative tumors and luminal A tumors (e.g. OS: HR 2.24, 95% CI 1.17–4.30, and HR 2.13, 95% CI 1.43–3.18, respectively) and non-significantly associated for luminal B and Her2 positive tumors.
Conclusion: The harmful effects of smoking may be particularly relevant for certain subgroups of breast cancer patients. If verified in independent study populations, our findings on effect modification by NAT2 status on breast cancer prognosis might have relevant public health implications as the majority of Caucasians (50−60 %) are NAT2 slow acetylators. Smoking should be avoided because of poorer overall outcomes after breast cancer diagnosis.
No conflict of interest.

1931 POSTER

UPR Activation via glucose deprivation and depletion of GRP78 protein (using siRNA) do not alter radiosensitivity in the human breast cancer cell line MCF7

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Background: Adverse metabolic conditions in the tumour microenvironment such as glucose and oxygen deprivation activate cellular stress pathways including the Unfolded Protein Response (UPR), a pathway that confers resistance to some chemotherapeutic agents. Radiotherapy resistance has been associated with adverse metabolic conditions in the tumour microenvironment, but whether this is due to UPR activation or other cellular pathways, has never been studied. This study used both a hypoglycaemic cell culture model and also direct UPR knock down to determine whether glucose deprivation altered radiosensitivity via the UPR.
Material and Methods: The MCF7 (p53 wildtype) breast cancer cell line was used. UPR activation was confirmed by western blotting and qPCR. Hypoglycaemic culture was used at 0.2 mM, a glucose concentration that activated the UPR following 24 hours of culture, and irradiated alongside a normoglycaemic control (25 mM). Survival was determined using clonogenic assay and data is presented as fractions of the untreated control. Transfection of GRP78 siRNA was used to knock down the UPR, and knockdown cells were irradiated alongside the control (transfected with scrambled sequence).
Results: There was no difference in survival between cells cultured in low glucose and their normoglycaemic control at 2.5 Gy (0.27 vs 0.29 p=1) and 5 Gy (0.035 vs 0.058 p = 0.7) (n = 3). Furthermore, there was no significant difference in survival between GRP78 knockdown and control cells at 2.5G y (0.17 vs 0.22 p = 0.7) and 5 Gy (0.01 vs 0.023 p = 0.1).
Conclusions: UPR activation secondary to glucose deprivation does not alter response to irradiation therapy in the MCF7 cell line. The UPR knockdown does not appear to be a potential target for sensitizing to radiotherapy.
No conflict of interest.

1932 POSTER

Prediction of lymph node metastasis with CXCR4 presentation in the breast cancer patient

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Background: The expression of CXC chemokine receptor type 4 (CXCR4) is considered to correlated with the degree of axillary lymph node involvement, particularly in hormone receptor negative breast cancer. And it is also reported that CXCR4 play an important role in mediating migration, invasion and adhesion of breast cancer cells, which correlate with cancer cell metastases. The objective of this study is to evaluate the correlation of CXCR4 expression between primary tumors and lymph nodes in primary breast cancers and to know whether the presence of lymph node metastases can be predicted by CXCR4 expression of the primary tumors.
Patients and Methods: Sections of paraffin-embedded tissue samples were obtained from 30 patients who received breast cancer surgery with sentinel lymph node sampling and/or axillary dissection. All clinicopathological data were obtained from the patients' medical records. The expression of CXCR4 was evaluated in the nucleus and cytoplasm. The intensity of staining was graded in negative, positive staining <50%, and positive, >/=50%. The evaluation was performed on the nucleus and cytoplasm in each.
Results: Half of the tumors were shown to be cytoplasmic CXCR4 positive, while 1.3% of the tumors were nuclear CXCR4 positive. Among the 20 cytoplasmic CXCR4 positive patients, 13 patients with lymph node metastases were recognized (P = 0.02), although preoperative clinical diagnosis of them was N0. No significant correlation was recognized between the nuclear stating status and lymph node metastasis.
Conclusions: We found that the elevated level of cytoplasmic CXCR4 was correlated with nodal metastases of breast cancers, meaning cytoplasmic CXCR4 expression predict lymph node metastasis in clinically node-negative patients with breast cancer. Our present study revealed that the cytoplasmic CXCR4 positivity of the primary tumor, even though it might be core needle biopsy specimens, was related to lymph node metastasis of breast cancer and, therefore, could be a useful predictive biomarker of lymph node metastasis of breast cancer. We think that CXCR4 immunohistochemistry might give the additional information to considering sentinel node biopsy. This theory will be discussed with a case control study.
No conflict of interest.

1933 POSTER

Stage, biology and age

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Background: Breast cancer subtypes are prognostic and predictive for patients. In this study, prognostic value of TNM stage, intrinsic subtype, and age were compared.
Patients and Methods: We analyzed results from 7,626 breast cancer patients registered on the Asan medical center database between 1999 and 2009. We compared survival according to the TNM stage, intrinsic subtype using ER, PR, Her2− immunohistochemical staining, and age.
Results: Luminal A subtype showed the best survival rates while triple negative subtype showed the worst survival rate amongst intrinsic subtypes. Survival analysis showed that Stage I triple negative breast cancer showed better survival compared to Stage III Luminal A subtype breast cancer (89.0% vs 76.6% P<0.001). Survival differences between intrinsic subtypes were more significant in lymph node positive breast cancer compared to lymph node negative breast cancer. Age did not affect survival between stages and intrinsic subtypes except for the young age subgroup ($\leqslant$35), for whom there was no survival difference amongst intrinsic subtypes.
Conclusion: Staging of breast cancer showed a more direct correlation to survival than known prognosis for intrinsic subtypes, as advanced, good prognostic intrinsic subtype breast cancer had worse survival than early, worse prognostic intrinsic subtype breast cancer. However for the young age group ($\leqslant$35), the survival of all intrinsic subtypes were similar.
No conflict of interest.

1934 POSTER

Cancer testis antigens and topoisomerase 2-alpha expression in triple negative breast carcinomas

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Background: Patients with triple-negative breast cancer (TNBC) generally experience a more aggressive clinical course with increased risk of disease progression and poorer overall survival. Surgery and/or chemotherapy appear to be the only available therapeutic modalities. Doxorubicin is a cytotoxic anticancer agent, but it can also stimulate immunogenic cell death, thus increasing the possibility of tumour-specific immune response. Therefore, our aim is to study the expression of cancer testis antigens (CTA) in the triple negative breast cancer (TNBC) group as well as the expression of topoisomerase 2-alpha (TOPO2A), a well defined molecular target of anthracyclins.
Material and Methods: The study includes 83 patients who underwent surgery between January 2003 and December 2009. Tissue serial TNBC sections were stained with CK5/6, CK14, EGFR, Ki-67, TOPO2A and CTA (MAGE-A1, MAGE-A10, NY-ESO and multi-MAGE-A) specific reagents. Survival time and multivariate survival analysis were also evaluated.
Results: The majority of TNBC were associated with a high histological grade (84.3%), high mitotic counts (25.9; range 2–110) and high proliferative activity, as measured by Ki-67 antigen (53.7; range 3−95). Of the 83 TNBC, 66.3% had BL immunophenotype and 48.2% BL morphology. MAGE-A1 specific staining was most frequently detectable (69.2%), followed by multi-MAGE-A (58%), NY-ESO (27.1%) and MAGE-A10 (16%) specific staining. The median value of TOPO2A positivity was 41.7% (range 5−97). A significant correlation was observed between the expression of MAGE-A10 and NY-ESO, on the one hand, and the expression of TOPO2A ($p = 0.005$, $p = 0.013$), on the other.
Conclusions: The expressions of defined CTA and TOPO2A are significantly correlated in TNBC, which might be of potential clinical relevance. These data also suggest that anthracyclin administration and CTA specific immunotherapy could be advantageously combined in the TNBC group for which therapeutic options are limited.
No conflict of interest.

1935 POSTER

Intraductal papillomas of the breast: A review of 105 cases

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Background: The assessment of papillary lesions continues to be a challenging area in breast pathology. Intraductal papillomas are subject to debate in terms of their clinical and pathological significance and management. The purpose of this study was to evaluate the clinicoradiological and pathological data of patients with intraductal papillomas of the breast.
Material and Methods: According to pathology reports from January 1, 2000 to December 31, 2010 we identified 105 cases of intraductal papillomas of breast surgically excised at our institution. For each lesion, medical records, radiological and pathological variables were reviewed.
Patients age ranged from 32 to 72 years (mean 39 years). Most of patients were in premenopausal status (73.3%).
Results: Pathological nipple discharge of serous or serosanguinous character was the most common symptom accounting for 69.5% of patients. 42 patients had palpable lumps. Majority of cases were centrally-located (89 patients).
Imaging modalities used in these patients were mammography and ultrasound. Radiology findings included mass lesions (82.6%), calcifications (7.6%) and cyst-like appearances (92.5%). Mean size of lesion on sonography was 13 mm (range 7−36 mm).
The histopathological findings of the surgically excised lesions revealed intraductal papillomas without atypia in 53 cases, atypical papillomas in 36 cases, malignant transformation was seen in 16 cases (DCIS in 14 patients and 2 invasive carcinomas).
Multiple intraductal papillomas were revealed in 13 cases, among them malignant transformation were revealed in 3 patients (23.1%).
Discordance in the imaging-histological reports was seen in 10 cases.
The upstage rate of intraductal papillomas on biopsy to malignancy on excision was 8.7%.
After a mean follow-up of 4 years no patient developed any breast malignancy.
Conclusion: We recommend that all patients with intraductal papillomas of the breast, especially with multiple lesions or when associated with atypia, undergo wide excision of the lesion with clear margins and that these patients be monitored closely with annual imaging.
No conflict of interest.

1936 POSTER

Evaluation of primary tumour and regional lymph node metastases with FDG PET/CT in breast cancer patients: Prone versus supine position

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Aim: For the staging of breast cancer, 18F-FDG PET/CT in supine position has demonstrated clinical value. To assess primary tumor response in patients scheduled to receive neoadjuvant chemotherapy (NAC) MRI is currently performed in prone position. It was postulated that additional PET/CT imaging of the thorax in prone position might also be valuable for the loco-regional assessment of these patients. The objective of this study was to compare PET/CT imaging in prone and supine position in the visualization and uptake parameters of primary tumors and regional lymph node metastases.
Materials and Methods: Between August 2010 and April 2012, 198 patients (mean age 51, range 26−81) with stage II/II breast cancer were included. Approximately 60 minutes after injection with 18F-FDG (180–240 MBq) a prone position PET/CT of the thorax was performed using a mock-up MR coil stripped from all metal parts, with a 3.00 min per bed position PET acquisition and high-resolution (2 mm^3 voxels) reconstruction. Afterwards, a standard PET/CT in supine position form skull base to thighs was performed using 1.30 min per bed position and standard reconstruction (4 mm^3 voxels). The SUVmax of FDG-avid primary tumors as well as axillary- and non-axillary lymph nodes were quantified and compared. The visual accuracy was compared for the detection of tumor multifocality and the occurrence of anatomical mismatch between CT and PET.
Results: The SUVmax values of the primary tumors (average 7.5 versus 6.4) and in non-axillary lymph nodes (average 7.6 versus 6.0) were significantly higher in prone position ($P = 0.015$ and $P < 0.001$). The measured volume of FDG tumour uptake was significantly ($P < 0.001$) larger in prone images (average 9.1 versus 6.24) with a more round form of shape. In four patients multifocality was solely visualized in prone position ($P = 0.134$). A relevant anatomical mismatch between CT and PET was more often identified on supine than on prone images and especially at the location of the non-axillary lymph nodes ($N = 4$ versus $N = 9$).
Conclusion: Optimized PET/CT imaging of the thorax in prone position leads to a sharper tumour delineation, higher quantitative SUVmax values and a more adequate loco-regional assessment in breast cancer patients. This more appropriate correlation of prone MRI and PET/CT may improve therapy response monitoring in breast cancer patients receiving neoadjuvant chemotherapy.
No conflict of interest.

1937 POSTER

Detection of occult N3-disease in breast cancer patients with PET/CT − does it affect survival?

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Background: In breast cancer the TNM classification is used for treatment planning and prediction of survival. Undetected lymph node metastases during staging workup results in a higher local recurrence rate (LRR) if left untreated. In our institute, the high positive predictive value of the FDG-PET/CT incentivized us to change the radiotherapy plan when newly N3 disease was detected in breast cancer patients scheduled for neo-adjuvant chemotherapy (NAC). The aim of the present study was to compare the event free survival (EFS), with and without newly detected N3 disease on PET/CT for breast cancer patients treated with neo-adjuvant chemotherapy.
Materials and Methods: Between September 2007 and October 2011 a total of 311 breast cancer patients with a tumour of at least 3 centimetres gave informed consent to receive a baseline PET/CT scan in the context of response monitoring to NAC. Only patients without distant metastases were included. The group was divided in a low- (T0−1N0−1 and T2N0), intermediate- (T2N1 and T3N0) and a high risk group (T2N2−3, T3N1−3, T4). Following detection of N3 FDG-avid lymph nodes on PET/CT patients were reclassified concerning risk of local recurrence. The EFS analysis

was made for patients with at least 3-year follow-up information (N = 104). Newly found distant metastases, local recurrence or death were classified as an 'event'.
Results: Of the risk groups categorized before PET-CT the EFS was 76% for the high risk group (N = 38), 84% for the intermediate risk group (N = 44) and 95% in the low risk group (N = 21). Using PET/CT information, nine patients of the intermediate- and one patient of the low risk group were upstaged to the high risk group. Of these patients who received additional radiotherapy one patient experienced an event. This resulted in an increase of the EFS to 79% for the high risk group and a negligible change for the other groups.
Conclusion: Based on conventional staging procedures and estimated risk for LRR, the EFS after three years of follow-up differed between three risk groups of breast cancer patients. Detection of occult N3 disease with PET/CT caused the upstaging for clinically unsuspected N3 patients to the high risk staging group, enabling adequate treatment with radiotherapy. If these patients would be left untreated a more elevated risk of local recurrence can be expected. Despite a trend in EFS increase the short follow-up time impeded to observe relevant change in the event free survival.
No conflict of interest.

1938 POSTER

25-hydroxy vitamin D levels in patients with breast cancer: Importance of dressing style

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Background: The aim of our study is to determine the prevalence of vitamin D deficiency as measured by serum 25-hydroxyvitamin D (25-OHD) levels in patients with breast cancer and to evaluate the correlation with life-style and treatments.
Material and Methods: This study included stage 0-III breast cancer patients (n = 170) treated with chemotherapy, radiotherapy and/or hormonal therapy at our hospital. Patients and treatment characteristics are listed in Table 1. 25-OHD levels were collected during the follow-up period between 2010–2013. The correlation between serum 25-OHD levels and the supplementation type, age, menopausal status, diabetes mellitus, usage of bisphosphonates, body-mass index, season, and dressing style were investigated. The distribution of serum 25-OHD levels was categorized as deficient (<10 ng/ml), insufficient (10−24 ng/ml), and sufficient (25−80 ng/ml). All statistical analyses were conducted with Fisher's exact test and logistic regression analysis.

Patient/treatment characteristics	Deficient/insufficient vitamin D levels	Sufficient vitamin D levels	Fisher's Exact test
Age			p = 0.127
<51 ⩾51	65 % 53.7	25 % 51	
⩾51	56 % 46.3	24 % 49	
Stage			p = 0.097
0−IIA	85 % 70.2	38 % 77.6	
IIB−IIIC	36 % 29.8	11 % 22.4	
Menopausal status			p = 0.126
Premenopausal	48 % 39.7	21 % 42.9	
Postmenopausal	73 % 60.3	28 % 57.1	
Season			p = 0.084
October–March	79 % 65.3	28 % 57.1	
April–September	42 % 34.7	21 % 42.9	
Dressing Style			p = 0.00001618
Modern	86 % 71.1	48 % 98	
Conservative	35 % 29.1	1 % 2	
Initial Vitamin D supplementation			p = 0.00001612
None or 400–1000 IU/day	120 % 99.2	39 % 79.6	
100.000–300.000 IU/month	1 % 0.8	10 % 20.4	
Time after completion of radiotherapy			p = 0.048
<9 months	69 % 57	22 % 44.9	
⩾10 months	52 % 43	27 % 55.1	
Hormonotherapy			p = 0.902
None	23 % 19	9 % 18.4	
Tamoxifen	58 % 47.9	22 % 44.9	
Aromatase Inhibitors	40 % 33.1	18 % 36.7	
Chemotherapy			p = 0.05
Yes	76 % 62.8	25 % 51	
No	45 % 37.2	24 % 49	
Trastuzumab			p = 0.165
Yes	21 % 17.4	7 % 14.3	
No	100 % 82.6	42 % 85.7	
Diabetes mellitus			p = 0.115
Yes	20 % 16.5	5 % 10.2	
No	101 % 83.5	44 % 89.8	
Body-mass index			p = 0.0071
<25 kg/m^2	42 % 34.7	27 % 55.1	
⩾25 kg/m^2	79 % 65.3	22 % 44.9	
Bisphosphonates			P = 0.0027
Yes	9 % 7.4	12 % 24.5	
No	112 % 92.6	37 % 75.5	

Results: The median age of the patients was 51 years (range, 27−79 years) and 71% of them had deficient/insufficient 25-OHD levels. Forty-two and 79 patients had deficient and insufficient 25-OHD levels, respectively. On univariate analysis, vitamin D deficiency/insufficiency was significantly inversely correlated with the use of chemotherapy, time after completion of radiotherapy, high body-mass index (⩾25), no bisphosphonates usage, and the dressing style. On multivariate analysis, none or low dose vitamin D supplementation, and decreased sun-exposure due to conservative dressing style were found as independent factors increasing risks of vitamin D deficiency/insufficiency 20.9 and 12.8 fold, respectively ($p < 0.05$).
Conclusions: The prevalence of serum vitamin D deficiency/insufficiency is high in our breast cancer survivors. Vitamin D status should be routinely evaluated for all women especially for patients with conservative dressing style.
No conflict of interest.

1939 POSTER

Thoracoscopic internal mammary lymph nodes dissection: A staging tool for internal mammary lymph nodes in breast cancer

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Background: The internal mammary lymph node status is a major prognostic factor in breast cancer. If positive, prognosis is less favourable. However, staging this regional nodal basin is not performed routinely, thus discarding additional staging information.
Methods: During the period from June 2004 to May 2007, 50 patients with operable breast cancer underwent modified radical mastectomy (MRM) or breast conserving surgery (BCS), followed by thoracoscopic internal mammary lymphadenectomy, using 3 ports through the skin incision of the MRM or the BCS.
Results: Of total number of 50 patients, the mean age of patients was 44 years (range, 27−60). 40 (80%) had medio-central tumour, 10 (20%) had lateral tumour. 35 (70%) had clinically involved axillary nodes. 16 out of 50 patients received neo-adjuvant CTH. 44 patients underwent MRM and 6 patients underwent BCS. No intra-operative complications occurred. Atelectasis was the only postoperative complication that was encountered, which occurred in 12 cases, and was treated conservatively. The average chest drainage period was 1.2 day (range, 1−2 days). The total number of IMN metastasis was 18 patients (36%). The risk of IMN metastasis was higher; in younger patients (P = 0.03), in medio-central tumours (P = 0.03), in bigger tumours (P = 0.05), with heavier metastasis of axillary LNs (P = 0.001). Knowing the IMN status helped in proper staging of patients, 7 patients showed evident stage migration after adding the IMN analysis to that of primary tumor and axillary LN. During the follow up period (the median = 22 months, range = 7 to 42 months), no patient had pleural dissemination or port-site metastasis.
Conclusions: Thoracoscopic IMN lymphadenectomy is a safe procedure, which can be done without serious additional complications or cosmetic compromise, which allows proper nodal staging, and proper treatment planning.
No conflict of interest.

1940 POSTER

Male breast cancer: A 15-year single institution experience

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Background: Male breast cancer (MBC) is rare. Although its frequency has increased in recent decades, it accounts for less than 1% of breast cancers. Unfortunately, the rarity of this condition has hampered the possibility of carrying out large randomized trials. Most of the information is therefore based on small single institution retrospective studies or by extrapolation from breast cancer trials in females. Early diagnosis is the exception and men tend to be diagnosed with breast cancer at an older age than women. The etiology, diagnosis, and treatment of breast cancer in men is similar to that of females and outcomes are similar when survival is adjusted for age at diagnosis and stage of disease. The vast majority of male breast cancers are hormonally sensitive.
Objective: To characterize the clinical and pathologic features of MBC and the overall survival in a single institution.
Methods: We retrospectively reviewed the clinical, pathological and survival data of 78 male patients with breast cancer treated in our institution, between 1997 and 2011. Overall survival was analyzed using Kaplan-Meyer curves.

Results: 78 patients were evaluated with a median age of 68 years [37−89]. Predominant histological type was ductal invasive carcinoma (57 patients, 73.1%), mostly moderately differentiated (42%). Estrogen receptor (ER) was positive in more than 50% of neoplastic cells in 58 (74.3%) patients. Progesterone receptor (PR) was positive in more than 50% of the neoplastic cells in 22 (28.2%) patients. ER e PR were positive in less than 50% of neoplastic cells in 3 and 8 patients, respectively. cErbB2 receptor was positive in only 8 patients. Stage at diagnosis was: IA in 26.9%; IB in 1.3%; IIA in 17.9%; IIB in 2.6%; IIIA in 5.1%; IIIB in 24.4%; IV in 6.4% of the patients (not available in 15.4%).
Modified radical mastectomy was performed in 36 (46%) and conservative surgery in 26 (33%) patients. As far as medical treatment is concerned, 38 patients underwent chemotherapy (49%), 37 patients underwent radiotherapy (47%) and 51 patients underwent hormone therapy (65%). Thirteen patients (17%) relapsed.
Median follow-up was 4.7 years (range 0.09–7.78), with a median overall survival (OS) of 13.34 years and a 73.3% 5-year OS (95% CI: 63.6–84.5%). One third of the patients died (n = 26) during follow-up.
Conclusion: The sample size was relevant. Overall survival was similar to the results of other published series. Prospective studies are needed to better characterize this rare disease.
No conflict of interest.

1941 POSTER

Clinical features and survival of women diagnosed with breast cancer age 40 and younger in a single Asian institute

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Background: Recent increases in breast cancer affect women around the world, especially in Asian countries. The Asian women present with the earlier age at diagnosis and higher mortality rate, compared with the older. The prognostic factors include delayed in tumour detection, short tumour doubling times, high lymphovascular invasion and poor hormonal/ErbB2 receptor expression. We examined clinical, pathological and survival data in this population, compared with their older counterparts.
Material and Methods: Records review identified 1,360 women diagnosed with breast cancer from 1998–2007. Women aged ⩽40 (n = 298) and over 40 (n = 1,062) were compared in means of tumour detection, operative procedures, tumour characteristics, adjuvant treatment and survival.
Results: Overall, most of the patients presented with palpable mass. Only half the patients underwent mammography at the time of diagnosis. Younger women had lower rates of BIRADS 4/5, compared with the older (85.4% vs. 92.6%, p = 0.02).
There was no difference in operative procedures between the two groups, in favour of mastectomy with axillary lymph node dissection. Younger women had higher rates of lymphovascular invasion (32.2% vs. 25.2%, p < 0.001) and negative oestrogen receptor status (40.3% vs. 36.4%, p = 0.002). There were no differences in adjuvant chemotherapy (81.2% vs. 78.8%), types of chemotherapy, either anthracycline- or nonanthracycline-based regimens, adjuvant hormonal therapy (68.8% vs. 62.1%) and radiotherapy (38.6% vs. 43.4%) between the two groups.
At a median follow-up of 85 months, there were no differences in 5-year disease-free survival (62.4% vs. 65.7%), distant disease-free survival (65.8% vs. 69.1%) and overall survival (69.1% vs. 74.1%) between the two groups. Pathological staging (stage 3: HR 3.85, 95% CI 2.59–5.73, p < 0.001) and nodal involvement (HR 1.60, 95% CI 1.23–2.08, p < 0.001) were predictive factors for disease recurrence and death.
Conclusions: Younger women with breast cancer have poor tumour detection and more aggressive diseases. With equivalent local and systemic therapy, however, survival is comparable with the older. Pathological staging and nodal status are predictive factors for survival outcomes.
No conflict of interest.

1942 POSTER

Treatment and prognosis of familial breast cancer patients

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Background: Hereditary breast cancer is becoming broadly recognised among professionals and patients, and we experience such cases in clinical situation more often. In spite of strong familial history of breast cancer, genetic tests for confirming diagnosis have not been adopted to those patients because these tests are not insurance adaptation in Japan. Moreover, even if they were diagnosed, it is reported that there is a gap in the treatment and surveillance in specialists against NCCN guideline about HBOCS (hereditary breast and ovarian cancer syndrome) management.
Objective: In this study we picked up 146 cases among 1007 breast cancer patients who met the testing criteria of HBOCS. They included PTEN gene variation; Cowden disease or BRCA2 gene variations. They consists of one male breast cancer patient, 55 bilateral breast cancer patients and 73 of them received operation before 40 years old. 4 patients experienced ovarian carcinoma (3 of them were serous carcinoma). Their mean follow-up period is 87 months (0–648).
Result: The rate of breast conserving mastectomy at the first operation is 58.7% (118/201). Local reccurence rate is 8.0% (16/201), distant metastasis rate is 14.4% (21/146) and mortality rate is 10.3% (15/146). 4 cases who received breast conserving mastectomy for the first operation were tended to repeat breast tumour whose intrinsic subtype differs from the first one. After performing systemic therapy, it would not be a cause of distant metastases. The rate of recurrence of familial breast cancer is almost equivalent to TN diseases of sporadic cases. However, the mortality rates of cases with distant metastasis are high, and the survival time is comparatively short.
Conclusion: Familial breast cancer tends to show multi-centric oncogenesis in many cases, and mastectomy in the first operation should be considered. Because there is no report that they tend to run into distant-metastases, initial systemic therapy is thought to be enough in conventional. But when it comes to metastatic breast cancer, more intentional therapy like PARP-1 inhibitor might be effective. We intend to focus on the patients who really need genetic screening by listening of their familial history even after operation.
No conflict of interest.

1943 POSTER

Sentinel lymph node (SLN) biopsy before neoadjuvant chemotherapy and its impact in reducing secondary lymphedema in patients with early breast cancer

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Background: Sentinel lymph node (SLN) biopsy is the standard procedure for assessing axillary status in stage I−II breast cancer patients.
The aim of our study was to select patients for axillary lymphadenectomy (AL) after the SLN biopsy followed by primary polichemotherapy (PC) in a group of patients diagnosed and treated at two hospitals in the city.
Methods: To carry out sentinel lymph node study in 50 patients with early-stage breast cancer, followed by polychemotherapy, surgery and axillary clearance (AL) only if nodes +>2 mm, radiotherapy, hormone if positive receptor/s, +/− Trastuzumab. The first 21 patients underwent (AL) to validate the technique.
Chemotherapy regimen: ADR/4EPI + CTX +/− 5FU × 4 cycles, followed by paclitaxel (P) weekly for 8 +/− Trastuzumab.
Results: Between June 2006 and October 2012 were included 50 patients with breast cancer stage IIA−IIB. The mean age was 46 years (range 21−73a). The average palpable tumor size was 3.5 cm (range 1.8 to 6.0 cm) and by ultrasound 2.0 cm (range 1.8−5.0 cm). Stage IIA: 36 (90%), CDI: 47 (93%) G1: 22(42%) ER+: 42(84%), PR+:32 (66%), HER2+:10 (20%); Ki67+:32 (64%), p53+: 31 (62%) and triple negative 6 (12%). All All 50 patients were evaluable for analysis. Median sentinel nodes removed was 2 (range 2−6). The analysis is shown in the tables. Group A (21p). Group B (29p).

Table 1.

	CLN pre PQ (−)	AL (−)	AL (+)	CLN pre PQ (+)	AL (−)	AL (+)
Group A (21p)	9 (42.86%)	9 (100%)	0	12 (57.14%)	8(38.1%)	4(19%)
Group B (29p)	20 (68.97%)	0	0	9 (31%)	7(24 %)	2(6.9)

Table 2.

	pCR	pPR isolated foci	pT <1.0 cm	pT <2.0 cm	pT >2.0 cm
Groups A-B (50p)	9 (18%)	6 (12%)	8 (16%)	18 (36 %)	10 (20 %)

The treatment was well tolerated with grade 3 and 4 neutropenia in 3 and 4 cases respectively.
Conclusions: The primary chemotherapy regimens ADR/4EPI + CTX + /-5FU-P, showed: pCR:18% and pPR:15% as isolated foci. In group B 20/29p with negative pre-chemotherapy sentinel node did not go to AL. To date, we have not seen in any axillary relapse. However there have been four distant relapses and 4 deaths related to its process base. In group B secondary lymphedema was avoided in 66% of cases.
No conflict of interest.

1944 POSTER

Outcome of patients with ductal carcinoma in situ before screening mammography

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With screening mammography the incidence of diagnosed ductal carcinoma in situ (DCIS) increases. In Slovenia it was introduced in April 2008. Register based data were analysed for 765 subjects with DCIS, diagnosed between January 1988 and August 2009. We examined the local relapses (LR) and distant metastatic relapses (DMR) after local treatment: mastectomy or breast conserving surgery followed with or without radiotherapy.
DCISs represented less than 4% of all breast cancers diagnosed in Slovenia in period 1988–2009. Median follow-up of our cohort was 9.2 years (min 0.1-max 25). Median age was 55 years (min 18-max 91), 203 (26.5%) grade were III, 283 (37%) were treated by mastectomy (69 and 36 reconstructed by autolog tissue and expander, resp.). Among 454 (60%) patients treated by breast conserving surgery, 146 (19%) and 28 (3%) had inadequate margins or uknown radicality, 217 (48%) had adjuvant radiation therapy. 75 (10%) received adjuvant hormonal therapy with tamoxifen. We found 71 (9.6%) LR, 51 (6.9%) as invasive cancers and 20 (2.6%) as DCIS, 14 patients (1.4%) developed distant metastases. 17 (2.2%) had contralateral breast cancer and 14 (1.8%) other tumor types. At median follow-up 9.2 years LR free survival was 88.6% and DMR free survival was 98.4%. We found no factor (age, grade, radicality, adjuvant radiotherapy or adjuvant hormonal therapy) to significantly correlate with LR or DMR free survival. Only nonradical surgery correlated borderline with DMR ($p = 0.068$).
The outcome of patients with DCIS is good. Distant metastases are rare. The outcome of our cohort is comparable to other reports. With introduction of screening mammography the higher incidence of DCIS is expected.
No conflict of interest.

1945 POSTER

Triple-negative breast cancer: A single-institution retrospective analysis

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Background: Triple negative breast cancer (TNBC) is a distinct entity associated with adverse outcomes. We explored our institutional results.
Methods: We retrospectively analysed our database between 2000 & 2010. The estrogen receptor (ER) & progesterone receptor (PR) status was negative by immunohistochemistry (IHC) while Her2 status was negative by IHC or confirmed negative by fluorescent in-situ hybridisation for equivocal cases. Adjuvant radiation was 50 Gy in 25 fractions after modified radical mastectomy (MRM) or 66 Gy equivalent after wide local excision (WLE). Adjuvant chemotherapy was anthracycline or taxane-anthracycline based. Treatment at relapse consisted of chemotherapy, surgery & radiation as required. Palliative chemotherapy included single agent or combination chemotherapy with paclitaxel, carboplatin, gemcitabine, ixabepilone & capecitabine. Disease free survival [DFS]) were calculated using the Kaplan Meier method. These were correlated with age, menopausal status, clinical & pathological 'T' & 'N' stage (T1 & T2 vs. T3 &T4 or N0 vs. Node positive disease), lymphovascular space invasion, extracapsular spread & type of chemotherapy. Log-rank test was used to compare survival distribution. The data was analysed using SPSS 16.
Results: 218 patients were analysed. TNBCs formed 22% of all breast cancer cases noted. Median follow up was 25.83 months (range: 1−93) Median age at presentation was 45 years (range: 27−58 years). 5 year DFS was 88.5%. Age more than 45 years ($p = 0.096$), post-menopausal status ($p = 0.058$), earlier clinical 'T' & 'N' stage ($p = 0.060$ & $p = 0.057$) & taxane chemotherapy ($p = 0.06$) showed a trend for better disease free survival. Earlier pathological 'T' stage ($p = 0.044$), taxane based chemotherapy ($p = 0.05$) and earlier pathological 'N' stage ($p = 0.001$) had significantly better DFS. Other variables did not correlate significantly with survival data.
Conclusions: Pathological T and N stage remain important predictors of survival for this disease defined on the basis of ER, PR & Her2 status. Taxanes seem to offer better disease free survival.
No conflict of interest.

1946 POSTER

Metaplastic breast carcinoma: A heterogeneous disease

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Background: Metaplastic breast carcinoma (MBC) is a rare disease which shows an aggressive clinical behavior. It is usually treated with multidisciplinary approach including radiotherapy. The aim of this study is to evaluate clinicopathologic characteristics and the multi-disciplinary treatment results of MBC patients treated in a single institute.
Material and Methods: Seventeen female patients with MBC treated in our department between June 2000 and January 2012 were identified and retrospectively evaluated. The median age at diagnosis was 46 years (range, 26−66 years). Eleven patients (%65) were in premenopausal and 6 (%35) were in postmenopausal status. Nine (53%) patients were classified as purely epithelial; 4 (24%) adenosquamous, 2 (12%) squamous, 3 (17%) adenocarcinoma with spindle cell differentiation and 8 (47%) patients were classified as mixed epithelial and mesenchymal; 5 (29%) carcinosarcoma, 2 (12%) carcinoma with chondroid metaplasia and 1 (6%) metaplastic carcinoma not otherwise specified (NOS). The median tumor size at diagnosis was 3.5 cm (range 1.5−12 cm). Six (35%) patients were treated with BCS and 11 (65%) with mastectomy. Axillary lymph node metastasis was found in 6 (35%) patients. Twelve (71%) patients had triple negative tumors. Postoperative RT and systemic adjuvant treatment was given to all patients according to stage and biological characteristics.
Results: Median follow-up time was 27 months (range, 12–151 months). At the time of this analysis, 14 (82%) patients were alive with no evidence of disease, and 1 (6%) was alive with disease. One patient died with disease. Since the other patient was lost to follow-up, the reason for death was unknown. The 3-year overall survival (OS) was 91% and 5-year 80%, and disease-free survival (DFS) rates were 76% and 76%, respectively. Recurrences were observed in 2 patients. The particular patient died with disease developed brain, lung and bone metastases 14 months after the treatment and palliated with radiotherapy and chemotherapy. She died with disease at the 26th months of follow-up. The other patient with recurrence developed local recurrence at the 15th months and distant metastases at the 19th months of follow-up. She underwent surgery and reirradiation to the chest wall and received chemotherapy. She was alive with disease at the last control which was 25th months of follow-up.
Conclusions: Despite the young age of our patients with mostly high grade tumors, larger tumor size and higher rates of lymph node metastasis, the survival outcomes in our study are more favorable compared to previously reported series. The low incidence of local failure and distant metastases in our study may be attributed to multidisciplinary approach including surgery, chemotherapy and radiotherapy to all patients. Prospective, multicentric and multi-institutional studies are necessary to find out the optimal treatment strategy in these patients.
No conflict of interest.

1947 POSTER

First analyses of radiotherapy/chemotherapy-related cardiovascular disease in breast cancer patients: A population-based study

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Background: Several studies have shown that early breast cancer (BC) treatment may increase the risk of cardiovascular disease (CVD) after $\geqslant$10 years. However, most reports are based on less contemporary treatment regimens.
The aim of this population-based study is to assess the effects of contemporary radiotherapy (RT) and chemotherapy (CT) used to treat BC on cardiovascular morbidity and mortality.
Methods: We have constructed a large population-based cohort of 5-year survivors diagnosed with BC before the age of 75 years, between

1989 and 2004 in the Netherlands (n = 70,230). Information on patient characteristics, primary and secondary malignancies, and basic treatment information were provided by the Netherlands Cancer Registry. For a subgroup detailed treatment information was collected from radiotherapy institutes, clinical trials, and regional studies. Cause of death was acquired through linkage with Statistics Netherland and data on cardiovascular morbidity through linkage with two population-based registries: the Hospital Discharge Diagnoses Registry and the Cardiac Interventions Registry.
Results: The median follow-up was 9.7 years (range 5−21 years), during which 2,411 patients died due to CVD, 1,740 underwent an invasive cardiac intervention (surgical or angioplastic), and 3,800 were hospitalized for CVD. First preliminary analyses show that compared to the general population, BC patients are not at increased risks for cardiovascular death (standardized mortality ratio 0.96 95% CI 0.92–0.99).
When comparing treatment groups within the cohort, we found that CT versus no-CT did not increase the risk of any cardiovascular event (cardiovascular death/hospitalization/surgical intervention; hazard ratio(HR)=1.02 95% CI 0.92–1.13), or ischemic heart disease (HR = 0.83 95% CI 0.69–1.00), but increased the risk of congestive heart failure (HR = 1.61 95% CI 1.24–2.09).
Compared to patients treated with surgery only, RT for left-sided BC increased the risk for any cardiovascular event (HR = 1.25 95% CI 1.15–1.35), ischemic heart disease (HR = 1.31 95% CI 1.13–1.50), and congestive heart failure (HR = 1.48 95% CI 1.22–1.78). Left- versus right-sided RT showed an increased risk for ischemic heart disease (HR = 1.23 95% CI 1.09–1.39).
Conclusion: Contemporary RT and CT used to treat early breast cancer increase the risk of CVD. Results of additional analyses focusing on radiation fields and specific systemic treatments as well as analyses focusing on history of CVD before BC will be presented at the conference.
No conflict of interest.

1948 POSTER

Impact of tumour epithelial subtype on circulating microRNAs in breast cancer

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Background: microRNAs (miRNAs) are non-coding RNAs approximately 22 nucleotides in length. They are remarkably stable in the circulation, supporting their potential as biomarkers of disease. Breast tumours are divided into epithelial subtypes based on receptor status, with basal subtype being negative for oestrogen and progesterone receptors, and Her2/neu. Basal subtype accounts for ~20% of breast cancers and due to the lack of targeted therapies has a poor survival rate. The aim of this study was to investigate the potential of circulating miR-106a, miR-191 and a novel miR, miR-A, as biomarkers of breast cancer.
Materials and Methods: Following informed patient consent, whole blood was harvested from breast cancer patients (n = 83) and healthy control individuals (n = 83). miRNA was extracted and analysed using RQ-PCR targeting a panel of miRNAs including miR-191 and miR-106a, miR-A and endogenous controls U6, miR-16 and miR-122. Any association with patient clinicopathological details was also investigated.
Results: miR-A, miR-191 and miR-106a were detectable in the circulation of all breast cancer patients and healthy controls included in the study (n = 166). miR-A was significantly up-regulated in the circulation of patients with breast cancer (Mean ± SEM; 2.05±0.06 log10 Relative Quantity (RQ)) compared to healthy controls (1.83±0.05, $p < 0.005$ log10RQ). miR-A displayed no relationship with clinicopathological characteristics. Although not significantly altered overall in breast cancer patients compared to healthy controls, miR-191 and miR-106a were significantly down-regulated in patients with basal breast cancer compared to healthy controls ($p < 0.05$). Further, both miRs displayed differential expression across epithelial subtype (ANOVA miR-191 $p < 0.05$; miR-106a $p < 0.005$).
Conclusion: These findings highlight miR-A as a potential circulating biomarker for breast cancer. Further, the data supports miR-106a and miR-191 as biomarkers for basal breast cancer. These circulating miRNAs have potential for use in conjunction with current screening techniques, and may improve the ability to more accurately detect and classify breast tumours.
No conflict of interest.

1949 POSTER

Impact of hospital surgical volume on breast cancer outcome: A population based study in the Netherlands

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Background: For some low-volume tumour types hospital surgical volume is associated with better survival. For breast cancer there is still much debate. The aim of this study is to determine to what extent the yearly surgical hospital volume determines the risk of death in breast cancer patients.
Method: Women diagnosed with primary invasive breast cancer in the period 2001–2005 were selected from the Netherlands Cancer Registry. Hospitals were grouped by their annual volume of surgery for invasive breast cancer. Cox proportional hazard models were performed including all patients with primary non-metastatic breast cancer who underwent breast surgery. Gender, age at diagnosis, morphology, grade, size (pT), number of positive lymph nodes, year of diagnosis and socio economic status (SES) were included as covariates. Follow-up was complete until the 1th of February 2012.

Table: Cox regression multivariable analyses: the relation of the number of surgical treated invasive breast cancer per hospital per year and the risk of death of patients with **non-metastatic** breast cancer in the Netherlands, 2001–2005

Variable	Number of patients	HR*	95% CI*
Number of operated invasive breast cancer per year			
150 or more	22,450	Reference	
100–149	16,272	0.99	0.95–1.03
75–99	12,125	1.02	0.98–1.06
<75	4,996	1.06	1.00–1.12**
Gender			
Female	55,509	Reference	
Male	334	1.15	0.97–1.36
Age at diagnosis		1.05	1.05–1.05
Morphology			
Ductal	41,366	Reference	
Lobular	8,458	0.92	0.88–0.96
Other	6,019	0.98	0.93–1.03
Grade			
I	9,534	Reference	
II	21,174	1.23	1.16–1.30
III or undifferentiated	16,064	1.80	1.70–1.91
Unknown	9,071	1.42	1.33–1.51
Size/pT			
T1mic (⩽0.1 cm)	227	0.88	0.66–1.18
T1a (0.1−0.5 cm)	1,594	0.70	0.61–0.80
T1b (0.5−1 cm)	7,006	0.73	0.68–0.78
T1c (1−2 cm)	21,550	Reference	
T2 (2−5 cm)	18,787	1.47	1.41–1.53
T3 (>5 cm)	1,749	1.97	1.82–2.13
T4	1,103	2.08	1.92–2.26
Unknown	3,827	2.41	2.26–2.58
Number of positive lymph nodes			
0	30,256	Reference	
Only micrometastasis	3,030	1.03	0.94–1.12
1−3	11,849	1.41	1.35–1.48
4−9	4,417	2.11	2.00–2.23
10 or more	2,200	3.30	3.10–3.51
Unknown	4,091	2.41	2.26–2.58
Year of diagnosis			
2001	11,008	Reference	
2002	10,922	0.99	0.94–1.03
2003	11,160	1.00	0.95–1.05
2004	11,388	0.99	0.94–1.04
2005	11,365	0.91	0.87–0.96
Socioeconomic status			
High	14,285	Reference	
High-middle	14,103	1.04	0.99–1.08
Low-middle	11,582	1.05	1.00–1.10
Low	15,873	1.11	1.06–1.16

*HR, hazard ratio; 95% CI, 95% confidence interval; **p = 0.052.

Results: In total 55.743 patients with invasive non-metastatic breast cancer were diagnosed during the period 2001–2005. Hospitals were grouped by volume of surgery: less than 75 (n = 19), 76–100 (n = 30), 101–150 (n = 29), 150 and more (n = 23) surgeries per year. Non-metastatic patients had a tendency to a 6% higher risk of death in a low volume hospitals

than a hospital with >150 surgeries per year (HR 1.06, 95% CI 1.00–1.12, p = 0.052). Patient and tumour characteristics like age (HR 1.05, 95% CI 1.05–1.05) and SES (lowest vs highest; HR 1.11, 95% CI 1.06–1.16), grade (low vs high, HR 1.80, 95% CI 1.70–1.91), tumour size (1−2 cm vs 2−5 cm; HR 1.47, 95% CI 1.41–1.53), and a higher number of positive lymph nodes (0 vs 1−3; HR 1.41, 95% CI 1.35–1.48 and 0 vs >10; HR 3.30, 95% CI 3.10–3.51) influenced death to a larger extend than surgical volume.
Conclusion: In the Netherlands, surgical hospital volume influences risk of death only marginally, and far less than patient and tumour characteristics. In 2011 only 9 hospitals had <75 patients per year, resulting in even more comparable risk of death between hospitals in future.
No conflict of interest.

1950 POSTER

Quality of breast cancer care in the Netherlands: Hospital variation in ipsilateral breast tumor recurrence rates

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Background: As a means of quality assurance, all Dutch hospitals are obliged to report their 5-year ipsilateral breast tumor recurrence (IBTR) rate after breast cancer surgery to the Health care inspectorate. This study assessed IBTR rates in the Netherlands answering two questions: 1) what is the IBTR rate in the Netherlands over time and 2) what is the value of the IBTR rate as indicator for comparing quality of care between hospitals.
Material and Methods: All female breast cancer patients with primary operable breast cancer (pT1−3, any N, M0) who underwent surgery, from 2003 to 2006 in 80 Dutch hospitals were selected from the Netherlands Cancer Registry. Patients were excluded in case of previous cancer, neo-adjuvant chemotherapy, or when treatment did not have a curative intent. Data on 5-year recurrence were retrieved from hospital records by specially trained registrars. IBTR rates were calculated using Kaplan Meier estimates and presented for BCS and mastectomy separately. Hospital variation was presented in funnel plots with a maximum acceptable upper limit value of 5%.
Results: A total of 31,992 breast cancer patients were selected. The overall 5-year IBTR rate was 2.51% (95% CI 2.23–2.71), which was significantly lower for BCS than for mastectomy (table 1; 1.96% and 3.23%, respectively). A decrease of IBTR rates over time was seen in both groups; in 2006 1.49% and 2.71%, for BCS and mastectomy, respectively. IBTR rates varied from 0.82% to 5.40% between hospitals. In one hospital the IBTR rate after mastectomy was significantly higher than the 5% limit.
Conclusions: Our population-based findings show that IBTR rates in the Netherlands are low and rates have improved over time. The IBTR indicator is of limited value for comparing quality between hospitals since the number of patients treated per hospital and the number of recurrences are small, causing wide CI's.
No conflict of interest.

Table 1. IBTR rates of 80 Dutch hospitals according to final surgery, and number of hospitals scoring over 5%

	No. of patients	Follow-up[a]	No. of events	IBTR (95% CI)	No. (%) of hospitals scoring >5%
Breast conserving surgery					
2003	4,159	18,669	93	2.54% (2.07–3.10)	1 (1%)
2004	4,334	19,269	84	2.21% (1.79–2.74)	2 (3%)
2005	4,551	20,541	68	1.68% (1.33–2.13)	0 (0%)
2006	4,598	20,768	61	1.49% (1.16–1.92)	0 (0%)
Total, 2003–2006	17,642	79,248	306	1.96% (1.76–2.20)	0 (0%)
Mastectomy					
2003	3,646	14,767	106	3.48% (2.88–4.20)	3 (4%)
2004	3,642	14,536	110	3.71% (3.08–4.46)	3 (4%)
2005	3,461	14,133	88	3.03% (2.46–3.72)	2 (3%)
2006	3,601	15,003	84	2.71% (2.19–3.35)	1 (1%)
Total, 2003–2006	14,350	58,442	388	3.23% (2.92–3.56)	1 (1%)

[a] Follow up time in years.

1951 POSTER

Breast cancer screening in elderly patients − a FOCUS study analysis

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Background: One third of the breast cancer patients is older than 65 years at diagnosis and this proportion is still increasing. Few studies have investigated the benefit of the mass screening program in the elderly population. The aim of this observational study was to compare characteristics of elderly breast cancer patients who had a screen-detected versus a non-screen-detected breast cancer, and to evaluate time trends of tumor stage at presentation after extension of the upper age limit of the screening program in the Netherlands to patients aged 70−75 years in 1998.
Materials and Methods: The FOCUS cohort is a detailed retrospective database of all consecutive breast cancer patients aged 65 and older who were diagnosed between 1997 and 2004 in the South-West of the Netherlands. All patients aged 65−75 were included. Differences between patients with screen-detected and non-screen-detected breast cancers were analyzed by logistic regression models. Time trends in tumor stages were analyzed in linear regression models for patients aged 65−69 and patients aged 70−75 separately.
Results: Overall, 1896 patients aged 65−75 were included. Patients with high age, nursing home residents and patients with breast cancer in their medical history were less likely to be diagnosed through the screening program (OR 0.90 (95 % C.I. 0.87–0.93) for each year of increasing age, OR 0.41 (95% C.I. 0.18–0.92) for being a nursing home resident and OR 0.22 (95% C.I. 0.18–0.92) for previous breast cancer respectively). Time trends of different stages between 1997 and 2004 showed a significant increase in early stage breast cancer in patients aged 70−75 after extension of the upper age limit to 75 years in 1998 (p = 0.01), while the number of advanced stage breast cancers did not decrease (p = 0.8). Among patients aged 65−69, the number of both early stage and advanced stage tumors did not significantly change over time.
Conclusions: In conclusion, patients of high age, nursing home residents and patients with breast cancer in their medical history were less often diagnosed through the screening program. We did not observe a statistically significant decrease of advanced stage breast cancer in patients aged 70−75 after extension of the upper age limit of the mass screening program to 75 years, while the number of early stage tumors has significantly increased. Therefore, the value of breast cancer screening in elderly patients deserves further investigation.
No conflict of interest.

1952 POSTER

Survival and contralateral breast cancer in CHEK2 1100delC breast cancer patients: Impact of adjuvant chemotherapy

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Background: Given the function of CHEK2 kinase in DNA repair, it has been hypothesized that breast cancer (BC) patients with a *CHEK2* mutation might have an increased sensitivity to chemotherapeutic agents causing double strand DNA breaks, but clinical data hereon are lacking. Therefore, we assessed the impact of adjuvant chemotherapy on contralateral breast cancer (CBC) rate, distant disease-free survival (DDFS) and breast cancer-specific survival (BCSS) in BC patients with and without a *CHEK2* 1100delC mutation.
Material and Methods: Genotyping for *CHEK2* 1100delC was performed in one hereditary non-*BRCA1/2* cohort (n = 1,220) and in two cohorts unselected for family history (n = 1,014 and n = 2,488). Kaplan–Meier survival analyses were conducted and multivariate hazard ratios (HRs) were calculated using the Cox proportional hazard method for CBC, DDFS and BCSS for carriers vs. non-carriers. All analyses were stratified for adjuvant chemotherapy.
Results: *CHEK2* 1100delC BC patients (n = 193) were younger than non-carriers (50.0 vs. 51.4 yrs.; p = 0.003) and mainly had ER positive disease (89.6% vs.73.9%, p < 0.001). *CHEK2* mutation carriers showed

an increased CBC rate (10-years incidence: 28.9% vs. 8.5%) with a multivariate HR of 3.97 (95% CI 2.59–6.07). The increased CBC rate for *CHEK2* 1100delC carriers was observed in both the group with and without adjuvant chemotherapy (HR 7.0; 95% CI 3.2–15.0 and HR 3.2; 95% CI 1.9−5.4, respectively). No significant interaction between *CHEK2* status and adjuvant chemotherapy was observed (HR 2.2, p = 0.1).
DDFS and BCSS were similar in carriers vs. non-carriers for the first six years after diagnosis (HR DDFS 1.1; 95% CI 0.83−1.4, HR BCSS 1.0; 95% CI 0.71−1.4), but diverged significantly as of six years after BC diagnosis (HR DDFS 2.7; 95% CI 1.8−3.9, HR BCSS 2.1; 95% CI 1.4−2.0). After stratifying for adjuvant chemotherapy, a significantly worse DDFS was observed beyond six years after diagnosis in both the group with (HR 4.5; 95% CI 2.4−8.6) and without chemotherapy (HR 2.3; 95% CI 1.4−3.8). No significant interaction between *CHEK2* status and adjuvant chemotherapy was observed (HR 1.5; p = 0.08). After stratifying for type of chemotherapy and for adjuvant hormonal therapy, results for DDFS were similar.
Conclusion: Compared with non-carriers, *CHEK2* 1100delC BC patients had an increased CBC rate and beyond six years after diagnosis a worse DDFS. Impact of adjuvant chemotherapy on these endpoints was not CHEK2 status dependent.
No conflict of interest.

1953 POSTER

Lower mitotic activity index in BRCA1/2-associated breast cancers detected after risk-reducing salpingo-oophorectomy

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Background: Bilateral salpingo-oophorectomy reduces breast cancer (BC) risk in BRCA1/2 carriers by about 50%, especially when performed premenopausally. It has been hypothesised that growth activity of BCs originating after risk-reducing salpingo-oophorectomy (RRSO) is lower. Therefore, we compared tumour characteristics and growth rates of BRCA1/2-associated primary BCs detected after RRSO with those of tumours originating without or before RRSO.
Methods: From a cohort containing 271 female BRCA1/2 mutation carriers with BC, 20 BRCA1/2 mutation carriers with primary BC detected at least 12 months after RRSO were selected (RRSO group). They were matched to 36 BRCA1/2 carriers with primary BC detected without RRSO (non-RRSO group) for age at BC diagnosis (± 2.5 years) and for BRCA1 or BRCA2 mutation (intended matching ratio 1:2). Pathology samples were revised for tumour differentiation grade, ER/PR and HER2 status. Breast MRIs and mammographies made at BC diagnosis as well as previous examinations were revised. Tumour growth rates, assuming exponential tumour growth and expressed as tumour volume doubling times (DT) were calculated.
Results: Median age at primary BC diagnosis was 52.0 years (range 35.0–67.0). In the RRSO group, BC was diagnosed more often by MRI than by mammography, compared to the non-RRSO group in (83% vs. 39% by MRI, P = 0.02). Tumours were smaller at diagnosis in the RRSO group (11.0 mm vs. 17.0 mm, P = 0.01). Mitotic activity index was lower in the RRSO group (12 vs. 22 mitotic counts/2 mm^2, P = 0.02) and PR-status was more often positive (median H-score=3.0 vs. 0.0, P = 0.05). No significant differences in differentiation grade, ER and HER2 status were found. Median DTs were not significantly longer in the RRSO group (DT=124 days, range 55–413) than in the non-RRSO group (DT=93 days, range 15–1317) (P = 0.47).
Conclusion: The lower mitotic activity index suggests a less aggressive biological behaviour in BRCA1/2-associated BCs developing after RRSO. When confirmed in larger series, this may have consequences for BC screening protocols for BRCA1/2 mutation carriers after RRSO.
No conflict of interest.

1954 POSTER

Pregnancy after breast cancer: Patients' characteristics and pregnancy outcomes

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Background: With the improvement of survival of young breast cancer patients (pts), the feasibility and safety of conception after breast cancer is of relevance. Evidence suggests that pregnancy after breast cancer is safe, irrespective of ER-status, but few data are available on patients characteristics and pregnancy outcome.
Material and Methods: We retrospectively extracted from our Breast Cancer Institutional database all pts <44 years, with histologically-confirmed primary breast cancer, operated on from Jan 1995 to Dec 2010.
Results: Of 2255 pts, 123 (5.4%) became pregnant after diagnosis. Of these, 69 pts underwent surgery at our Institution and are included here. Median age at diagnosis was 31 y (23−43 y). 60 pts (87%) had a pT1−2 tumor, while 37 pts (53%) had pN0 disease. 38 pts (53%), 12 (17%) and 43 (63%) had HR-positive, HER2-amplified and Ki67>20%, respectively. 11 pts (16%) had triple-negative disease. While systemic adjuvant treatment was suggested to all pts, 58 pts (84%) actually received it. 20 pts (28%) were treated with chemotherapy alone, while 38 pts (55%) received endocrine treatment +/− chemotherapy. Of 27 pts who were prescribed adjuvant tamoxifen, only 12 pts (44%) were compliant. 14/44 pts (31%) received triptorelin concomitant to chemotherapy to reduce gonadal toxicity, but none had oocytes frozen before treatment. Median time to pregnancy was 20 months (5−86 m). Pregnancy was spontaneous in 67 patients, while 3 pts underwent assisted reproduction. 44/69 pts (63%) had a term pregnancy, 14/69 pts (20%) had a first trimester miscarriage, with subsequent term pregnancies in 4 cases, while 11 pts (15%) opted for abortion. Pregnancy course was normal in 46/48 pregnancies, with 1 case of pre-eclampsia and 1 case of premature rupture of membrane. No malformations or neonatal complications were observed. 16/44 mothers (36%) breastfed their babies. With a median follow-up of 113 months, 6/69 patients had a cancer-related event, and 1/69 died.
Conclusions: Young breast cancer survivors who deliver after diagnosis are still a minority. Patients characteristics did not appear to influence the decision to proceed to pregnancy. There was a relatively high rate of non-compliance to adjuvant treatment, which calls for the adoption of tailored strategies for those women desiring subsequent pregnancy. Although a higher rate of miscarriages was observed, pregnancy and neonatal outcome were satisfactory and comparable to the general population.
No conflict of interest.

1955 POSTER

Manual injection of subcutaneous trastuzumab vs intravenous infusion for HER2-positive early breast cancer: a time-and-motion study

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Background: Within the ongoing PrefHer trial (NCT01401166, F. Hoffmann-La Roche Ltd), patients and healthcare professionals (HCPs) preferred subcutaneous (SC) trastuzumab via single-use injection device (SID) to intravenous (IV) infusion. We undertook a prospective, observational time-and-motion sub-study to quantify HCP time actively engaged in tasks related to preparation/delivery of IV and SC and the duration that patients sat in infusion chairs.
Materials and Methods: After completing (neo)adjuvant chemotherapy, patients with HER2-positive early breast cancer were randomised to

receive 4 cycles of SC trastuzumab (600 mg fixed dose via SID [Cohort 1] or manual injection [Cohort 2]) followed by 4 cycles of standard IV or the reverse sequence as part of their adjuvant trastuzumab therapy. We report interim Cohort 1+2 IV vs Cohort 2 manual SC data from 13 sites in Denmark (DK), France (FR), Italy (IT) and Switzerland (CH). Cohort 1 SC SID data were reported previously.
Following interviews with a nurse and pharmacy member at each site, generic case report forms for IV, SC and pharmacy management were tailored to reflect site practices. Estimated mean times for a single IV vs SC process (an observation: treatment room plus pharmacy task times, chair time) were calculated per country.
Data collection is ongoing and current results are based on the number of observations achieved to date: 24−58 for IV (CH−IT) and 14−65 for SC (DK−IT). Further data, including 95% CIs and the anticipated impact of a change from IV to either SC method on centre management (elicited via questionnaire), will be presented.
Results: Reduction in mean HCP time with SC ranged from 25−42% (DK−FR), and reduction in mean chair time ranged from 66−80% (IT−DK, Table).

	Mean HCP time (min)			Extrapolated mean HCP time (18 cycles, hours)			Mean chair time (min)		
	IV	Manual SC	IV-SC	IV	Manual SC	IV-SC	IV	Manual SC	IV-SC
DK	23.3	17.6	5.7 (25%)	7.0	5.3	1.7	83.0	16.8	66.1 (80%)
FR	26.1	15.1	11.0 (42%)	7.8	4.5	3.3	82.8	23.1	59.7 (72%)
IT	20.1	12.5	7.5 (38%)	6.0	3.8	2.3	62.5	21.3	41.2 (66%)
CH	26.5	18.1	8.4 (32%)	8.0	5.4	2.5	109.8	29.4	80.4 (73%)

Extrapolated chair time savings for 10 patients receiving 18 cycles each ranged from 15.5–30.1 eight-hour days (IT−DK; mean chair time*10*18/60/8).
Conclusions: Preliminary results indicate that a transition from IV to manual SC trastuzumab injection may lead to a substantial reduction in HCP time and chair time, reducing medical resource use, improving patients' care and increasing staff and centre efficiency.
Conflict of interest: *Advisory board: Angela Stefania Ribecco: Novartis. Xavier Pivot: F. Hoffmann-La Roche Ltd, Novartis, GlaxoSmithKline. Corporate-sponsored research: Angela Stefania Ribecco: F. Hoffmann-La Roche Ltd. Other substantive relationships: Douglas Millar: Employee of F. Hoffmann-La Roche Ltd. Xavier Pivot: F. Hoffmann-La Roche Ltd, Sanofi-Aventis.*

1956 POSTER

Efficacy of risk-reducing mastectomy (RRM) on overall survival (OS) in BRCA1/2-associated breast cancer (BC) patients

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Background: RRM in BRCA1/2 mutation carriers with a history of unilateral primary breast cancer (PBC) is known to reduce the risk of developing contralateral BC (CBC), but the impact on OS is insufficiently known. Therefore, we studied the efficacy of RRM on OS in BRCA1/2 mutation carriers.
Methods: From a Dutch multicenter cohort study, we identified 565 BRCA-associated PBC patients (439 BRCA1, 126 BRCA2). Eventually 190 BRCA1 and 49 BRCA2 carriers underwent RRM. To avoid overestimation of early PBC-related deaths, patients were only eligible if they were recurrence-free for at least 2 years after PBC. Contribution of person-years of observation (PYO) to the Non-RRM group started 2 years after the date of PBC diagnosis or at the date of DNA diagnosis (whichever came last) and ended on the date of death, RRM, or last contact. Contribution of PYO to the RRM group started at the date of RRM or 2 years after the date of PBC diagnosis (whichever came last) until similar endpoints as described for the Non-RRM group.
Results: Regarding PBC, no significant differences in size, nodal status, differentiation grade, hormone and Her2 receptor status were observed between the Non-RRM and RRM group. Median age at PBC diagnosis was 42 years for Non-RRM and 38 for RRM women ($p < 0.001$). Median time period between PBC and RRM was 2.1 years (range 0.01–20.2). PBC treatment included radiotherapy for 67% of Non-RRM versus 48% of RRM women ($p < 0.001$), and chemotherapy for 50% of Non-RRM versus 66% of RRM women ($p < 0.001$). Use of endocrine therapy was not significantly different (16% and 19%). More RRM women underwent risk-reducing salpingo-oophorectomy (80% versus 69%; $p < 0.001$), while ovarian cancer incidence was not significantly different (4% and 2%). With a median FU of 11.6 years after PBC diagnosis, we observed 64 CBC cases (20%) in Non-RRM women, and 4 CBC cases (2%) after RRM ($p < 0.001$). In the Non-RRM group 56 women died during 2666 PYO versus 18 women in the RRM group during 1837 PYO, yielding mortality rates (per 1000 PYO) of 21.0 and 9.8, respectively (adjusted HR 0.55, 95% CI 0.32–0.94). Fifteen years OS was 81% for the Non-RRM and 90% for the RRM group ($p = 0.006$).
Conclusions: RRM reduces CBC incidence and is associated with improved OS in BRCA-associated BC patients who are recurrence-free at least two years after PBC diagnosis. Further research is needed to identify potential prognostic factors for this survival benefit.
No conflict of interest.

1957 POSTER

Efficacy of zoledronic acid in postmenopausal Japanese women with early breast cancer receiving adjuvant letrozole: 36-month results

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Background: We reported 12-month results of upfront zoledronic acid (ZOL) therapy prevented bone loss in postmenopausal Japanese women who were receiving adjuvant letrozole confirming the Z-FAST and ZO-FAST studies results. But the examination in the long term of aromatase inhibitor-associated bone loss has not been proved in the Japanese or Asia women.
Methods: Postmenopausal women with hormone receptor positive early breast cancer (BC) patients receiving adjuvant letrozole were randomly assigned to receive either upfront or delayed-start ZOL (4 mg intravenously every 6 months) for 5 years. The delayed group received ZOL when lumbar spine (L_2-L_4) BMD decreased to less than young adult mean (YAM) − 2.0 S.D or when a nontraumatic fractured occurred. The primary endpoint of this study was to compare the changes in L_1-L_4 BMD at month 12 between the groups. Secondary endpoints, measured at other predetermined timepoints, included comparing changes in L_1-L_4, L_2-L_4 and total hip (TH) BMD and markers of bone turnover, fracture incidence, and time to disease recurrence. We report the results of 36-month interim analysis.
Results: At 36 months, mean change in L_1-L_4 BMD was 10.7% higher in the upfront group than in the delayed group (95% CI, 9.2% to 12.1%; $p < 0.001$), L_2-L_4 BMD was 10.9% higher (95% CI, 9.3% to 12.5%; $p < 0.001$), and TH BMD was 6.7% higher (95% CI, 5.3% to 8.1%; $p < 0.001$). The incidence of fracture was significantly decreased in the upfront group (upfront, 2 (2.0%) vs. delayed, 9 (9.3%), $p = 0.033$). Disease recurrence was reported in 3 upfront (3.1%) and 1 delayed (1.0%) patients. By month 36, 11 patients (11.3%) in the delayed group initiated ZOL therapy. There was no significant difference of adverse events other than fever with ZOL at the first treatment between the two groups.
Conclusion: Upfront ZOL seems to be the preferred treatment strategy versus delayed administration, as it is significantly and progressively increase BMD in postmenopausal Japanese women with early BC who were receiving adjuvant letrozole for 36 months.
Conflict of interest: *Corporate-sponsored research: ST and SN have received research support from Novartis*

1958 POSTER

Adapted physical activity effect on aerobic function and fatigue in patients with breast cancer treated in adjuvant or neoadjuvant phase (SAPA)

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Background: Research and clinical interest in the therapeutic effectiveness of exercise in breast cancer, during adjuvant or neoadjuvant chemotherapy and radiotherapy, has greatly increased. Use of cardiopulmonary exercise test (CPET) for determination of peak oxygen consumption (VO_{2peak}) provides the gold standard assessment of aerobic capacity. The main aim was to evaluate cardiopulmonary function as measured by VO_{2peak} in breast cancer patients before adjuvant or neoadjuvant chemotherapy and after adapted physical activity (APA).
Our hypothesis was that a home-based training program (aerobic and strength training) in a breast cancer population would resolved in improved cardiovascular fitness, peripheral strength, decreased fatigue and improved quality of life. We performed a phase III study, to assess the effects of a home-based physical activity training program in a breast cancer population treated by adjuvant or neoadjuvant chemotherapy versus no APA.
Methods: The programme was organised as follows: Arm A (aerobic and strength training) during the 27 weeks of treatment (chemotherapy and radiotherapy RT-CT); Arm B (control group). This study included 3 assessments phases (T0: before RT-CT; T1 (week 27) and T2: final evaluation at the 54th week). These assessments included: cardiopulmonary exercise test (CPET) including maximal oxygen uptake test (VO_{2max}), six-minute walk test (6MWT), muscular testing, pulmonary function testing, assessment of physical activity (IPAQ questionnaire), fatigue (MFI20 questionnaire), quality of life (EORTC QLQ C30), anxiety and depression symptoms (HADS) and iDEXA (total body biphotonic absorption).
Results: A total of 44 subjects were included from June 2012 to June 2013. At baseline, the average age was 53$\pm$12.1 years for Arm A versus 49.1$\pm$9.2 years for Arm B. Body Mass Index was 24.96 for Arm A and 26.62 for Arm B.
There was no significant difference in VO_{2peak} between Arm A and Arm B before RT-CT; 23.2 $ml \cdot kg^{-1} \cdot min^{-1}$ and 22.9 respectively ($P = 0.44$).
Walking distance on 6MWT of the two group assessed 515m for Arm A and 532m for group B ($P = 0.37$). The percentage of theoretical distance is similar.
Results in VO2peak, 6MWT, QLQC30, IPAQ and HADS performed after APA will presented in September 2013.
Conclusions: We hope this study provide scientific evidence of the effectiveness of rehabilitation exercise individualized and performed at home in patients with breast cancer. This type of care is now extended to other French centers.
No conflict of interest.

1959 POSTER

Evaluation of proliferation and apoptosis markers in circulating tumor cells (CTCs) of women with early breast cancer who are candidates for tumor dormancy

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Background: Clinical dormancy is frequently observed in breast cancer (BC). In the present study, we aimed to characterize CTCs in dormancy candidates (DC) with BC in terms of proliferation and apoptosis.
Material and Methods: Cytospins of peripheral blood mononuclear cells (PBMCs) were obtained from DC ($n = 122$) disease-free for $\geqslant$5 yrs and from metastatic pts ($n = 40$) on relapse that occurred $\geqslant$5 yrs after surgery. Sequential samples ($n = 27$) of 8 DC with late relapse and from 8 relapse-free ($n = 38$), were also analyzed. 10^6 PBMCs were stained with pancytokeratin antibody along with ki-67 and M30 as proliferation and apoptosis markers, respectively.
Results: CTCs were identified in 40 (32%) of 122 DC and in 15 (37.5%) of 40 metastatic patients. In all patients, ki-67(−)/M30(−) CTCs were detected. Specifically, 25 DC (61.5%) had only ki-67(−)/M30(−) CTCs, 11 (27.5%) had ki-67(+) and 8 (20%) M30(+) CTCs. Among 243 CTCs detected, 201 (82.5%) were ki-67(−)/M30(−), 14 (5.7%) ki-67(+) and 29 (11.9%) M30(+). Seven (46.6%) of 15 CTC(+) metastatic patients had ki-67(+) CTCs ($p = 0.037$) whereas 58 (41%) of total CTCs were ki-67(+) ($p < 0.001$). No M30(+) CTCs were detected. When sequential samples of the 8 DC who relapsed were analyzed, exclusively ki-67(−)/M30(−) CTCs were detected in 2 (25%) pts, ki-67(+) in 6 (75%) and M30(+) CTCs in 4 (50%). The respective numbers in the non-relapsed group were 4 (50%), 3 (37.5%) and 3 (37.5%). Moreover, ki-67(+) CTCs were more frequently observed in samples of the relapsed pts (47% vs 23.8%). Among 382 CTCs detected in all sequential samples from the relapsed group, 337 (88.14%) were ki-67(−)/M30(−), 26 (6.7%) ki-67(+) and 20 (5.1%) M30(+), whereas the respective percentages among 77 CTCs in non-relapsed pts were 78%, 6.5% and 15.8% ($p = 0.001$).
Conclusions: The great majority of CTCs detected in DC with BC express neither proliferation, nor apoptosis markers. However, the apoptotic index in CTCs is increased during clinical dormancy, whereas the proliferation index is increased on relapse. In addition, apoptotic CTCs are more frequently encountered during follow-up in DC free of relapse. The above observations suggest that monitoring proliferation and apoptosis in CTCs during clinical dormancy could be used to predict subsequent late relapse.
No conflict of interest.

1960 POSTER

Planning and memory function in breast cancer patients − an fMRI study

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Background: Cognitive function in breast cancer (BC) patients may be compromised before the start of adjuvant chemotherapy (CT). Four task-fMRI studies showed some pretreatment alterations, but had a small sample size and/or did not include cancer-specific controls. Here we report fMRI results of two tasks in a relatively large sample of BC patients scheduled to receive CT (CT+), BC patients not indicated to undergo CT (CT-) and healthy controls (HC).
Material and Methods: Baseline recruitment for this prospective study is near complete. Here, we report results from a selected sample of subjects matched on age and IQ. 33 CT+ (50.5$\pm$8.6 yrs; IQ 101.8$\pm$12.8) and 33 CT- (52.1$\pm$7.7 yrs; IQ 103.8$\pm$13.7) were assessed post-surgery, but before adjuvant treatment. 32 HC (51.4$\pm$7.5 yrs; IQ 105.9$\pm$10.6) were also tested. Each assessment included neurocognitive tests and 3T multimodality MRI. This included an fMRI version of the Tower of London (TOL) assessing planning ability. Memory encoding and retrieval was measured with of a visual paired associates task.
Results: Performance was within normal range with no significant group differences. For the TOL, CT+ showed hypoactivation of dorsolateral prefrontal cortex (DLPFC) and lateral parietal areas compared to HC. With increasing task difficulty CT+ patients showed hypoactivation of DLPFC compared to CT-. During memory encoding, inferior parietal areas where more active in the CT+ group compared to both other groups. No significant group differences were found for memory retrieval.
Conclusions: Although we found no indications for pre-treatment cognitive impairment in BC patients, we did observe differences in brain activation during planning and memory encoding, but not memory retrieval, using fMRI. This finding stresses the need for baseline assessment when studying the effects of adjuvant treatment on brain function and structure. Our follow up measurements will show whether the brain regions in which we observed baseline differences are most vulnerable to the effects of CT.
No conflict of interest.

1961 POSTER

Analysis of ANC recovery from a Phase III study of lipegfilgrastim versus pegfilgrastim in patients with breast cancer receiving doxorubicin/docetaxel chemotherapy

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Background: Lipegfilgrastim is a once-per-cycle, fixed-dose glycoP-EGylated granulocyte-colony stimulating factor (G-CSF) under review for the prevention of severe neutropenia in cancer patients receiving chemotherapy (CTx). The efficacy of lipegfilgrastim was previously demonstrated in a Phase III study conducted in CTx-naive breast cancer patients. We present here secondary efficacy endpoints related to absolute neutrophil count (ANC) decrease and recovery in lipegfilgrastim- and pegfilgrastim-treated patients.
Methods: Patients with high-risk Stage II, III, or IV breast cancer were randomized to a single 6 mg subcutaneous (s.c.) injection of lipegfilgrastim or pegfilgrastim on Day 2 of each CTx cycle. Full-dose CTx (doxorubicin 60 mg/m^2 + docetaxel 75 mg/m^2) was started on Day 1 of each cycle

for up to four consecutive cycles. Secondary endpoints included time to ANC nadir, time to ANC recovery (time from CTx administration to ANC recovery to $\geqslant 2.0 \times 10^9$/L after expected nadir), and time to recovery from ANC nadir to ANC $\geqslant 1.5 \times 10^9$/L. Times within each cycle were compared using Poisson regression and ANCOVA, with treatment, country, therapy type, and weight class as categorical variables, and baseline ANC as covariable.

Results: In the intent-to-treat population for CTx Cycle 1, the time to ANC nadir was comparable for lipegfilgrastim (n = 101) and pegfilgrastim (n = 101), with a median time of 6 days in both treatment groups in all cycles. Results were also comparable in Cycles 2−4. Time to ANC recovery was significantly shorter for patients receiving lipegfilgrastim versus pegfilgrastim in Cycles 1−2.

Mean time to ANC recovery, days±SD	Lipeg (n = 101)	Peg (n = 101)	Lipeg–Peg Least Squares Mean (95% CI)	*P-value**
Cycle 1	5.8±3.3	7.4±3.6	−1.570 (−2.547 to −0.592)	0.0018
Cycle 2	3.8±4.1	5.3±4.7	−1.349 (−2.528 to −0.171)	0.0250
Cycle 3	3.9±4.7	5.0±4.3	−1.120 (−2.317 to 0.077)	0.0665
Cycle 4	3.6±4.2	4.3±4.6	−0.458 (−1.714 to 0.799)	0.4734

*Poisson regression.

The time to recovery from ANC nadir was numerically shorter for lipegfilgrastim- versus pegfilgrastim-treated patients in all cycles, but the differences were not statistically significant.

Conclusions: In patients with breast cancer treated with lipegfilgrastim versus pegfilgrastim, time to ANC recovery was significantly shorter in Cycles 1−2 of myelosuppressive chemotherapy. Differences were not statistically significant for Cycles 3−4 and for time to ANC recovery from nadir.

Conflict of interest: *Ownership: Peter Bias, Reiner Els*sser, and Anton Buchner are all employees of Teva Pharmaceuticals and own stock in Teva*

1962 POSTER

Effect of small tumor size (⩽2 cm) on outcome of node negative breast cancer in BRCA1-associated versus matched sporadic patients

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Background: It has been suggested that tumor size has a different prognostic value in T1 BRCA1-associated compared to sporadic BCs, among others since BRCA1-associated BC mainly has a poor differentiation grade and triple-negative phenotype. To investigate this we evaluated survival of patients with small (T1), node negative (N0) BC in BRCA1 mutation carriers and sporadic patients.

Patients and Methods: We included 101 BRCA1-associated BC patients with T1N0 BC, identified through Dutch clinical genetic centers and diagnosed between 1990 and 2011. These patients were individually matched in a 1:2 ratio to 198 sporadic BC patients, selected from population-based registries, for tumor size (T1a, T1b, T1c), N0 status, year of diagnosis and birth. The Kaplan–Meier method was used to analyse 10-year breast cancer specific (BCSS) and distant disease free survival (DDFS). Cox proportional hazard models were used to compare survival between the BRCA1 and sporadic group, and to investigate the impact of tumor size (as a continuous variable) in both groups.

Results: The mean time of follow-up in the BRCA1 and sporadic group was 7.4 (range 1.1–17.5) vs. 8.2 (range 1.0–20.3) years, respectively (p = 0.082), the mean age was 41.9 years (range 23−70). BRCA1 patients more often had ER negative disease (78.7% vs. 21.1%), poor differentiation grade (74.2% vs. 34.8%), more frequently underwent mastectomy (65.3% vs. 15.2%) and were more frequently treated with chemotherapy (59.0% vs. 27.3%) than sporadic patients (p < 0.001 for all). For T1a/bN0 tumors, 10-years BCSS and DDFS in BRCA1 mutation carriers were 100% and 92% versus 95% and 85% in sporadic patients (p = 0.427 and p = 0.318). For T1cN0 tumors, 10-years BCSS and DDFS in BRCA1 mutation carriers were both 81% versus 87% and 85% for sporadic patients (p = 0.134 and p = 0.352). Overall, no univariate differences were observed between BRCA1 and sporadic patients regarding BCSS (HR 1.55 [95% CI 0.69–3.47]) and DDFS (HR 1.12 [95% CI 0.56–2.25]). Within the BRCA1 group, tumor size yielded HRs for BCSS and DDFS of 1.26 (95% CI 1.04–1.53) and 1.15 (95% CI 1.00–1.33), while the association was just not significant in the sporadic group (HRs 1.10 [95% CI 0.98–1.23] and 1.05 [95% CI 0.97–1.14]).

Conclusion: T1a/bN0 tumors in BRCA1-associated BC have a favorable prognosis. Also, in T1N0 BRCA1-associated BC, tumor size is a prognostic factor, supporting the value of BC detection at small size.

No conflict of interest.

1963 POSTER

Cognitive function and cerebral white matter in breast cancer survivors 10 years after treatment

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Adjuvant chemotherapy (CT) for breast cancer (BC) is associated with cognitive problems and alterations in brain structure and function. In a previous study we found detrimental effects on brain white matter of patients exposed to high-dose adjuvant CT (Hi-CT) compared to patients who only received radiotherapy (RT), 10 years post-treatment. In the current study, we extended our measurements to BC survivors who received conventional-dose adjuvant CT (Con-CT) ⩾10 years earlier and healthy controls (HC). Our aim was to compare neurotoxicity profiles of different treatment strategies.

Twenty Con-CT (5 cycles 5-fluorouracil, epirubicin, cyclophosphamide [FEC], 60.5±5.7 yrs) and 20 HC (58.9±3.9 yrs) were assessed using neurocognitive tests and 3T MRI (Diffusion Tensor Imaging (DTI) and 1H-MR Spectroscopy (MRS)). Data were compared to previously reported results in 17 Hi-CT (4xFEC + 1x high-dose cyclophosphamide, thiothepa, carboplatin, [CTC], 57.1±5 yrs) and 15 RT only patients (58.2±5.8 yrs). All patients were exposed to RT. All CT patients received endocrine treatment for 2−5 yrs. Cognitive status was evaluated with an overall performance score for each participant (Mahalanobis Distance [MhD].

The MhD was significantly lower for the RT group vs. HC, indicating worse overall cognitive performance. However, although the Hi-CT group showed higher MhD values (41.7) compared to CON-CT (37.2), RT only (30.4) and HC (10.6), other groups differences did not reach statistical significance. DTI revealed significantly higher mean diffusivity (MD) values in the Hi-CT vs. Con-CT group in several anterior and posterior areas in the brain. The Hi-CT group also had significantly larger MD values than the RT only group in similar brain areas, albeit to a lesser extent. A higher MD was also found in the RT only group vs. the HC group in anterior brain areas. 1H-MRS showed that, compared to other treatments, Hi-CT was associated with a reduction of N-acetyl aspartate (NAA).

Our findings suggests that the cognitive performance (expressed in an overall distance score) in BC survivors ⩾10 years post-treatment doesn't show a clear dependency on treatment type, possible due to a limited sample size. Our imaging findings do suggest widespread negative Hi-CT effects on WM compared to other treatments as evidenced by increased MD and lower NAA, the latter being suggestive of impaired axonal function. The effects of RT only are less pronounced and warrant further investigation.

No conflict of interest.

1964 POSTER

Breast cancer molecular profile according to BMI and menopausal status

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Background: Several studies have shown a positive association between body mass index (BMI) and the development of estrogen receptor (ER)-positive breast cancer. However, correlation of BMI, menopausal status and molecular subtypes has not been established yet.

Material and Methods: Overall 1,004 patients with early breast cancer (EBC) were recruited for this study. Clinical and tumor characteristics such as age, menopausal status, weight, height, tumor size (T), grading, ER, progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2) status, were prospectively collected. BMI was categorized into three groups (low: ⩽25; intermediate: 26−30; high: >30) and associations between BMI and clinicopathological variables were performed by $\chi 2$ test.

Results: Overall 615 (61.3%) pre-menopausal and 389 (38.7%) post-menopause women were enrolled. Among premenopausal patients (Table 1), high BMI correlates with increased ER and lower HER2 expression and less aggressive tumor subtypes as luminal A. In the same patients group, women with low BMI were more likely to develop a Luminal B, HER2 like or TN breast cancer. No correlation was observed between tumor phenotypes and BMI among postmenopausal women.
Conclusions: Among premenopausal patient, high BMI is associated with less aggressive and more endocrine sensitive EBC. This is consistent with the hypotheses that higher estrogen exposure of breast tissue in women with higher BMI may drive growth of these cancers. If further confirmed, our data suggests that weight control in this subset of women may help to prevent cancer development.
No conflict of interest.

Table 1.

Clinical and molecular characteristics	BMI − premenopausal							p-value
	⩽25		26−30 N (%)		>30 N (%)		Total	
	N	%	N	%	N	%		
Er								0.004
Pos	153	76.1	145	89.5	183	80.6	481	
Neg	48	23.9	17	10.5	44	19.4	109	
PgR								0.2
Pos	144	71.6	129	79.6	167	73.6	440	
Neg	57	28.4	33	20.4	60	26.4	150	
Her2								0.01
Pos	38	19.5	13	8.4	37	16.6	88	
Neg	157	80.5	141	91.6	186	83.4	484	
Molecular subtypes								.01
Luminal A	115	59.0	114	74.0	143	64.4	372	
Luminal B	23	11.8	9	5.8	18	8.1	50	
HER2	14	7.2	2	1.3	12	5.4	28	
TN	32	16.4	13	8.4	29	13.1	74	
Normal breast	11	5.6	16	10.4	20	9.0	47	

1965 POSTER

Intimacy and sexual health care program for breast cancer patients

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Background: Based on study results we aim at efficiently elaborating a multidisciplinary health care program related to intimacy and sexual health. This study has a twofold objective, i.e. 1) listing the effects of breast cancer and its treatment on the sexual functioning, and 2) determining the professional assistance women expect to receive at the hospital.
Material and Methods: 139 follow-up breast cancer patients (up to 5 years) have been asked to complete surveys. 73 women who did not want to participate, have been requested to indicate the reason for their refusal. The survey package comprised a Distress Barometer, HADS, a questionnaire on breast cancer, intimacy and sexual health, FSFI and SSFS for women.
Results: Up to 44% of the respondents shows lower sexual arousal, however 22% of them suffer from this problem. There are also problems concerning sexual excitement and pain. Women with depressive complaints report significantly more sexual dysfunction.
55% of the respondents shows a different experience of sexuality and intimacy. Being together, caressing and cuddling are experienced as more important than kissing and having sexual contact. Sexual satisfaction is significantly lower after cancer.
47.7% needs professional assistance in finding answers to their questions on sexual functioning. 73.8% believes that more intramural attention is to be paid to the patient's perception of sexuality.
Conclusions: This study already suggests emerging tendencies. Breast cancer and its treatment have a clear effect on the patient's intimacy and sexual health. The majority of the women would like to receive more information. They want to receive an information leaflet, spontaneous discussions on this topic during contacts with health care professionals at the hospital and information sessions with companions. They want to talk (in decreasing order of importance) with the gynaecologist, the oncologist, the sexologist and the psychologist.
However some limitations should be considered. The study was based on a small number of participants. Also further research is necessary into the implementation of a multidisciplinary health care program related to intimacy and sexual health. More knowledge of the expectations and information need of health care professionals can be added.
The elaboration of a health care program is deemed necessary and strongly advisable and needs to involve medical, sexological and psychosocial health care professionals.
No conflict of interest.

1966 POSTER

ER/PR/HER2 receptor discordance between primary tumors and corresponding axillary metastases in curatively resected node positive breast cancer patients

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Background: ER/PR/HER2 status of the primary (P) breast cancer (BC) and corresponding distant metastases may show discordance in part to the change in biology. This discordance may change the ultimate treatment decisions and oncologic outcomes. Today, we only use the receptor status of the PBC while deciding the treatment options for node positive disease. Currently, there are no recommendations regarding the receptor status examination of axillary lymph nodes (ALN) which may have clinical importance. We, therefore, aimed to analyze the ER/PR/HER2 receptor status change in P & A tumor tissues of 107 node positive BC patients who were treated with adjuvant chemotherapies + radiotherapy ± trastuzumab in our institution.
Material and Methods: After approval by the local ethics committee, P and corresponding A tumors were synchronously reevaluated using routine immunohistochemical procedures. Patient's files and hospital electronic database system were checked for clinical data, and phone calls were made as needed. Relation of clinical and pathological variables with receptor discordance and its effects on survival were analyzed.
Results: A very high rate of receptor concordance between P&A was seen. PA receptor discordance for ER, PR and HER2 were, 8%, 11.4%, and 6.2%, respectively. ER&PR changes may have caused treatment decision change in 1% of the patients. HR discordance was mostly seen in patients having ⩽30% ER or PR in the P tumor. No discordance that may cause treatment decision change was seen in terms of HER2. A negative but weak correlation between absolute PR change and tumor diameter & grade were seen. Receptor discordance had no effect on both survival parameters.
Conclusions: We detected a very high receptor concordance between P BC and corresponding A metastases. On the other hand we particularly detected the HR subgroup, which had the most HR discordance between P&A. Neither the discordance in individual receptors per se nor the discordance in defined HR groupings had an effect on survival which might have been a matter of small sample size. In the light of our findings we think that, HR discordance in patients having ⩽30% ER or PR in the P tumor and the efficacy of specific hormonal treatments in this group of patients are points that warrants further investigation.
No conflict of interest.

1967 POSTER

High prevalence of additional contralateral and ipsilateral malignant findings by MRI in patients with invasive (ducto)lobular breast cancers

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Background: In patients with invasive lobular cancer, preoperative MRI detects additional contralateral or ipsilateral malignant findings in up to 50% of patients. Invasive breast cancer comprises a spectrum of histological changes with purely lobular cancer on one side and purely ductal cancer on the other, with many mixed lesions in between ('ductolobular cancer'). The role of preoperative MRI in these lesions with such mixed differentiation had not been evaluated.
Patients and Methods: All patients diagnosed with breast cancer containing a lobular component of any proportion between Jan 2008 and Oct 2012 were prospectively offered preoperative MRI. MRI findings were compared to findings on conventional imaging (mammography and ultrasound). Clinically relevant additional findings on MRI (defined as ⩾5.0 mm discrepancy in tumour size, additional ipsi- and contralateral lesions) were verified histologically and reviewed by an expert breast pathologist.
Results: Of all 155 patients diagnosed with (ducto)lobular cancer, 109 (70%) patients underwent preoperative MRI. In 44 patients the lobular component comprised 1−30% of the cancer, in 17 patients it comprised

31−70% and in 47 patients it comprised 71–100%. Preoperative MRI detected 95 additional findings in 69 (63%) patients.Further work- up revealed contralateral breast cancer in 10 patients (9%), additional ipsilateral malignant foci in 20 patients (18%) and more extensive disease in 22 (20%) patients. On the patient level, MRI led to the detection of additional malignant findings in 54/109 (50%) patients. The probability of detecting relevant additional findings did not increase with the proportion of the lobular component (i.e. 48% for 1−30% lobular component, 53% for 30 −70% and 49% for 70–100%, p = 0.526).
Conclusion: In breast cancer patients presenting with lobular differentiation at core needle biopsy, preoperative MRI leads to the detection of clinically relevant additional finding in a substantial amount of patients irrespective of the proportion of the lobular component. Therefore, preoperative MRI should be part of the routine work-up of this selected patient category.
No conflict of interest.

1968 POSTER

Identifying the different courses of cognitive functioning across time in patients with breast cancer treated with chemotherapy

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Introduction: Results of existing studies suggest the existence of subgroups within patients with breast cancer (BC) who are treated with chemotherapy with regard to problems with cognitive functioning. Therefore, the aims of this study were to (i) examine cognitive functioning across time in BC patients compared to patients with a benign breast disease (BBD) by evaluating the group means across time, (ii) identify longitudinal development classes for cognitive functioning in BC patients treated with chemotherapy, (iii) describe the sociodemographic and clinical characteristics of the resulting groups, and to compare the groups on their psychological functioning across time.
Methods: BC patients who were scheduled to receive adjuvant chemotherapy (N = 86) and a control group of women with a benign breast disease (BBD) (N = 95) participated in the study. BC patients completed validated questionnaires and a neuropsychological test battery before chemotherapy started, three months and one year after ending chemotherapy (and at comparable moments for the BBD group).
Results: Concerning verbal memory BBD patients stayed stable across time, while it declined in BC patients three months after ending chemotherapy but increased at one year after ending chemotherapy (though they remained below their baseline verbal memory functioning) (p = 0.033). Three longitudinal developmental classes were identified: 'consistently high/average/low cognitive functioning'. This last group had a higher age, lower educational level, and less often salaried work/retirement compared to the other subgroups. Furthermore, they scored worse on state anxiety and depressive symptoms three months after ending chemotherapy compared to the other subgroups.
Conclusion: Verbal memory is affected in BC patients treated with chemotherapy. Three subgroups can be defined within the BC patients: 'consistently high/average/low cognitive functioning'. Further research with a larger sample size is warranted to examine the vulnerability of this last subgroup to develop problems with cognitive functioning after BC treatment.
No conflict of interest.

1969 POSTER

Metformin use correlates with molecular subtype of invasive breast carcinoma

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Background: Metformin has anti-proliferative effects in primary breast carcinoma (BC) tumors. Gene set analysis revealed in BC patients without diabetes mellitus (DM) reduced expression of p53, BRCA1 and cell cycle pathways after treatment with metformin for two weeks. Our aim was to find out if long lasting use of metformin correlates with histologic type and molecular subtype of BC.
Material and Methods: A chart review of 253 patients (mean age 67 y.) with operable invasive BC and DM was done. Altogether 128 patients were on metformin, while 125 were not receiving metformin. They were surgically treated at our institute from 2005–2011. Control group consisted of 320 patients with invasive BC without DM (mean age 59 y.), who were consecutively surgically treated at our institute in 2006. Data on clinical and histopathology factors were collected. Subtypes were classified by immunohistochemical surrogates as luminal A (estrogen receptor [ER]+ and/or progesterone receptor [PR]+, HER2−), luminal B (ER+ and/or PR+, HER2+), HER2 (ER−, PR−, HER2+), triple negative/basal (ER−, PR−, HER2−). Contingence tables and non-parametric tests were used for statistical analysis.
Results: There was a trend for higher rate of ductal type of BC in patients with DM on metformin in comparison to those not receiving metformin (90% vs. 82%, p = 0.09). Patients with DM on metformin, with DM not on metformin and control group had different molecular subtype of BC (p = 0.01): luminal A subtype was found in 78%, 83% and 71%, luminal B in 12.6%, 9% and 11%, HER2 in 0.8%, 1.6% and 8%, triple negative/basal like subtype in 8.6%, 6.4% and 10%, respectively. Patients' age, body mass index, tumor diameter and pathological tumor stage were statistically different in patients with DM on metformin, DM not on metformin and patients without DM. There was no statistical difference in presence or mean number of metastatic regional lymph nodes.
Conclusion: Metformin use correlates with molecular subtype of BC in diabetics on metformin in comparison to diabetics not on metformin and patients without DM.
No conflict of interest.

1970 POSTER

Correlation between quality-of-life (QoL) and muscolo-skeletal (MSKs) symptoms in early breast cancer (BC) patients (pts) during treatment with aromatase inhibitors (AIs): Preliminary results of a single-institution, prospective study

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Background: AIs are the milestone adjuvant treatment for postmenopausal early BC pts. Non-steroidal AIs induce a significant oestrogen deprivation, responsible in approximately 40% of the pts for MSKs and for discontinuation in 25%. Median time to arthralgia onset is 6 months. This study shows the preliminary data about the impact of AIs-related muscolo-skeletal events on QoL and their correlation with quantitative (NRS Pain Scale) and qualitative (Trigger-Points − TRPs) Items.
Patients and Methods: QoL has been evaluated by using SCL 90-r for psychological symptoms, SF-36 for the self-perception of the health status and COPE-NVI for evaluation of coping. All the questionnaires have been self-administered with the support of a dedicated psychologist at baseline (T0) and at 3 (T1), 6 (T2), 12 (T3) and 18 (T4) months thereafter. Presence and intensity of pain were measured by NRS 11-points scale and by Trigger Points (TGPs) evaluation at the same intervals, as well as 17-OH-Vitamin D and oestradiol blood levels. Pearson correlation analysis was used to calculate correlations between Pain Scale, Physical Synthetic Index of Sf-36 and NRS/TRPs scores. Wilcoxon's Test was used to compare baseline scores with subsequent ones.
Results: From September 2011 to February 2012, 60 early BC pts entered the study. Exclusion criteria included severe osteoporosis or other comorbidities that contraindicate therapy with AIs and documented diagnosis of psychosis and cognitive deterioration. Median age was 68 years (43−88). Seven (11.7%) pts had previously received adjuvant chemotherapy, in 4 cases with taxanes. For the present preliminary analysis, 30 pts have been considered, for whom T0 and T1 measurements were available. At baseline, 22 pts (73.3%) had a NRS score >0; pain was mild (NRS 1−4) in 3 pts (13.6%), moderate (NRS 5−7) in 5 (22.7%) and severe (NRS>7) in 4 of them (18.1%). At T1 evaluation, we did not observed any difference in the total number of pts with pain (18 vs 14), whereas a significant increase in the number of pts with mild pain (9, 56.2%) was reported, whereas MSKs symptoms were present in 6 pts (20%). At T0, 26.7% of the pts had a TRPs score $\geqslant$1. No significant difference was reported for TRPs evaluation between baseline and T1. At baseline, 76.7% of the pts presented a deficiency of 17-OH-Vitamin D (median: 20.35 ng/mL, range: 3−59.9 ng/ml). No modifications have been observed at T1 regarding Vit D levels. At baseline, there was a statistically significant correlation between Physical Pain Scale of SF-36 and NRS Pain score (p = 0.001) and between Physical Synthetic Index of SF-36 and NRS Pain Score (p < 0.001) No differences have been found for SF-36 scales between T0 and T1. On the contrary, for COPE-NVI, at T1 there was a statistically significant reduction in terms of avoidance strategies (p = 0.002) and a significant increase in problem solving (p = 0.02). No differences have been observed in terms of NRS score (p = 0.97).
Conclusion: During the first 3 months of AIs, there are no modification in terms of qualitative and quantitative pain score evaluation, except for mild

pain. The more time since BC surgery has passed, the more pts seem to use better strategies to cope their cancer condition.
Conflict of interest: *Advisory board: Novartis*

1971 POSTER

Inconsistent selection and definition of local and regional study endpoints in breast cancer trials

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Background: In breast cancer research, results are reported using study endpoints. Most are composite endpoints (e.g. disease-free survival), consisting of several components (e.g. regional recurrence or death), in turn consisting of specific events (e.g. recurrence in supraclavicular lymph node). Inconsistent selection and definition of study endpoints may limit mutual comparison of study outcomes, resulting in unjustified conclusions. This study aims to determine which local and regional endpoints are used in breast cancer studies, and how these endpoints and their components are defined.
Methods: A PubMed search was performed for breast cancer studies (e-)published in 2011 in *Annals of Surgery, Annals of Surgical Oncology, British Journal of Surgery, Journal of Clinical Oncology, Journal of the American Medical Association, Lancet, Lancet Oncology, New England Journal of Medicine,* and *Radiotherapy & Oncology*. Articles using endpoints with a local or regional component were included and definitions were compared.
Results: From 44 articles, 23 different endpoints with a local or regional component were extracted. Most frequently used were disease-free survival (n = 25 articles), recurrence-free survival (n = 7), local control (n = 4), locoregional recurrence-free survival (n = 3), and event-free survival (n = 3). Different endpoints were used for similar outcomes. Of the 23 endpoints, 5 were not defined at all, the remaining 18 at least partially. Of these, 17/23 contained a local and 13/23 a regional component. The events included in the local and regional components were not specified in 57% and 54% respectively. If provided, definitions of local components were inconclusive with respect to inclusion of carcinoma *in situ* and recurrence in surgical scar, and inconsistently included skin- and chest wall recurrences. In regional components, skin- and chest wall recurrences were inconsistently included and specific nodal sites that were considered regional recurrences were either not provided in the article, or varied between different studies.
Conclusion: In breast cancer studies, many different endpoints with a locoregional component are used. Endpoint definitions are often not provided or incomplete with respect to the included events. Additionally, events included in the components of these endpoints vary between studies. This limits transparency and may cause unjustified conclusions.
No conflict of interest.

1972 POSTER

Transforming follow-up: Patients as true partners in a major multi-disciplinary change project

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Background: A multi-disciplinary working group was established within the Oxford University Hospitals NHS Trust to develop and implement a radically transformed breast cancer follow-up pathway. This new pathway aims to be in line with Cancer Survivorship principles, to generate a safe framework within which patients can be supported in self-management, and to ensure limited resources are used in the most effective ways to improve patient outcomes.
Materials and Methods: The working party included representatives of patients, service commissioners, charitable partners, primary care physicians (GPs), multi-disciplinary hospital specialists (breast nursing, surgery, imaging, oncology, administration, management and patient liaison) and university research partners. In addition to regular group meetings there were separate facilitated patient focus groups, GP education meetings, imaging and IT discussions, nursing team meetings and oncology education sessions. Open days for patients also provided opportunities for wider public comment.
Results: A radically shortened follow-up path was developed; patients are discharged from routine hospital follow-up 6 months after the completion of hospital-based therapy (surgery, chemotherapy, biological therapy, radiotherapy). This has been implemented from early 2013. The pathway includes formal preparation for discharge during the 6 months following treatment completion: a holistic needs assessment is carried out in a nurse-led clinic, with attention to individual information needs, and signposting to supportive programmes run by cancer charity partners (Breast Cancer Care and Maggie's Centre). After discharge patients with problems can self-refer directly to a new rapid review service, a specific recommendation from our patient representatives. A dedicated e-mail help-line for GPs has also been set up, and a mechanism established to call patients for all routinely required breast imaging for at least 5 years from diagnosis, with results sent promptly direct to the patient and their GP.
Conclusions: Implementing dramatic change in established practice is challenging. Early collaboration and full engagement with all parties including patients makes the likely success much higher. At the end of the planning phase all members of the group acknowledged how much they had learnt from each other, how this had changed the pathway developed, and how this would influence their future practice in a positive way. This work has given us a robust template for meaningful patient involvement in the transformation of established cancer pathways, and is already being used to implement similar changes in other cancer clinics and in neighbouring hospitals.
No conflict of interest.

1973 POSTER

Clinical impact of breast specific gamma imaging on the management of patients with indeterminate breast lesions

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Background: Mammography, combined with ultrasound (US), remains the mainstay for breast cancer detection but has its limitations in certain situations like dense breasts. Although MRI can be used as an adjunct modality, its major limitation is the poor specificity. Molecular breast imaging techniques, such as breast-specific gamma imaging (BSGI), are increasingly being used as adjunctive diagnostic techniques to mammography and ultrasound. In this study we tried to determine the possible impact of BSGI on the management of the breast patient population especially the group with indeterminate breast lesions. For this group national guidelines advocate repeated imaging within 1 year which keeps the individual patient in uncertainty for that long period.
Method: Data were analysed from all patients who where referred for BSGI in the period from January 2011 until August 2012 presenting with indeterminate breast lesions, defined as breast lesions classified as BI-Rads 3 on mammography, ultrasound and/or MRI. In these patients a BSGI scan was performed and images classified according to the functional grading system as defined by the Society of Nuclear Medicine. These findings were registered and if necessary further analysis was performed and recorded. Pathologic analysis after second look ultrasound or BSGI guided biopsy was performed in case of upstaging. If biopsy was not conducted, follow-up imaging after 1 year was used as the reference standard.
Results: In total 55 patients were included in the study. The prevalence of malignancy in this group was 5 patients (9.1%) In 10 patients resulted in upstaging, of whom 4 showed a malignancy = 40%. In 17 the BI-Rads classification remained 3 and follow-up took place. Repeated imaging showed one malignancy within 1 year. In the remaining 28 patients the suspicion level was downgraded tot BI-Rads 1 or 2 and after repeated imaging no further pathology was demonstrated.
Sensitivity for the BSGI scan in this study is 80%, specificity 88%. The positive predicted value is 40% whereas its negative predictive value 98%.
Conclusion: Breast-specific gamma imaging could play an important role in the management of patients with indeterminate findings in the breast, mainly due to its high negative predictive value. Positive findings need to be confirmed by histology. But if downstaging takes place the individual patient can be successfully reassured and repeated imaging is not necessary.
No conflict of interest.

1974 POSTER

Incidence of bone pain in patients with breast cancer treated with balugrastim or pegfilgrastim: An integrated analysis from the phase II and III studies

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Background: Balugrastim is a once-per-cycle, fixed-dose human recombinant protein composed of human serum albumin and granulocyte-colony stimulating factor (G-CSF) developed as an alternative to pegfilgrastim (Neulasta®) for the prevention of severe neutropenia in cancer patients receiving chemotherapy (CTx). All G-CSF products have the potential to cause bone pain, which is generally transient in nature and mild to moderate in intensity. Using data from a Phase II and a Phase III study in patients with breast cancer receiving CTx, we compared the incidence of bone pain-related (BPR) symptoms in patients treated with balugrastim versus those treated with pegfilgrastim and the relation to G-CSF treatment and CTx.
Methods: All patients received CTx (doxorubicin 60 mg/m^2 + docetaxel 75 mg/m^2) and at least one subcutaneous injection of balugrastim 30, 40, or 50 mg or pegfilgrastim 6 mg on Day 2 of each cycle for up to four cycles. The incidence and severity of treatment-emergent adverse events (TEAEs) were recorded up to 30 days after the last dose of study medication. BPR TEAEs comprised the preferred terms arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, and pain in extremity. All BPR TEAEs designated by the investigator as related to G-CSF or CTx treatment were defined as TEAE drug reactions (TEADRs).
Results: No BPR TEAEs were serious or led to study discontinuation. A relationship was observed between balugrastim dose and the number of patients experiencing G-CSF-related BPR TEADRs. These TEADR rates were 0.0%, 8.1%, and 12.5% for balugrastim 30 mg (n = 10), 40 mg (n = 335), and 50 mg (n = 104) groups, respectively (pooled rate of 8.9%, N = 449), compared with 6.1% for the pegfilgrastim group (N = 262). CTx-related BPR TEADRs were experienced by 10.0%, 17.0%, and 23.1% of patients in the balugrastim 30, 40, and 50 mg groups, respectively, resulting in a pooled rate of 18.3% for all balugrastim doses compared with 14.1% of patients in the pegfilgrastim group.
Conclusions: The incidence and severity of G-CSF-related bone pain symptoms were low and comparable between the pooled balugrastim and pegfilgrastim treatment groups. The incidences of CTx-related bone pain symptoms were comparable between the pooled balugrastim and pegfilgrastim treatment groups and as expected for patients with breast cancer.
Conflict of interest: *Ownership: Anton Buchner, Steve Barash, Hedva Voliovitch, Tamar Erez, Nicole Lang, Noa Avisar, are all members of Teva pharmaceuticals.*

1975 POSTER

Controversial issues in early stage breast cancer: ESMO and Jules Bordet Institut collaborative survey

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Background: Knowledge of early-stage breast cancer represents a dynamically evolving field. However, several clinical issues remain unresolved and the use of recent advances remains heterogeneous. This survey explored the current clinical practice in the management of early-stage breast cancer patients, identified areas of controversies and interrogated how treating physicians implement newest advances.
Methods: We conducted a 27-item survey. Multiple choice questions captured demographic characteristics of the participants and addressed multiple issues of clinical management. We followed a 2-stage dissemination of the survey: paper distribution at selected breast cancer track sessions at ESMO 2012 Congress, and dedicated mailing messages to ESMO members with interest in breast cancer. Descriptive statistical analysis was applied as well as logistic regression analysis exploring potential associations between the demographic characteristics of the participants and the replies provided. To this end, we defined what we considered as correct answers according to the level of evidence from the literature.
Results: A total of 512 physicians from 79 countries participated in the study, with 465 (91%) fully completed questionnaires. The majority of the participants were ESMO members (66%), medical oncologists (86.5%), working in multidisciplinary teams (91.6%). Heterogeneous results were captured, as the following: 40.9% of the participants consider no genetic test useful for adjuvant treatment decisions; 15.3% consider PET-CT a useful imaging modality for staging; 68.8% consider that postmenopausal patients with hormone receptor positive disease should always be offered an aromatase inhibitor as part of their adjuvant therapy; 78.7% prefer to administer trastuzumab concurrently with the taxane component of chemotherapy; and 27% would consider bevacizumab in the neoadjuvant setting. The logistic regression analysis did not identify any strong predictor of the probability to give a reply fully compatible with the literature evidence.
Conclusions: This study captures the clinical practice and the implementation of newest advances in early stage breast cancer across an extended number of treating physicians, with significant individual differences. Areas of controversy were detected and they deserve further exploration for the generation of 'tailored' educational tools, with the final goal being the standardization of the treatment of early-stage breast cancer.
No conflict of interest.

1976 POSTER

Comparison of Axillary nodal status between clinical, PET scan and pathological staging in breast cancer

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Background: Axillary lymph node dissection in breast cancer patients poses significant morbidity. Even though sentinel lymph node can determine the earliest metastases and guide in avoiding axillary dissection, still it is an invasive procedure. We have studied the sensitivity and specificity of PET scan in determining the axillary nodal metastases.
Materials and Methods: All breast cancer patients non metastatic at presentation were evaluated. Patients who found to have distant metastases/supraclavicular nodes during workup were excluded. Over a period of one year 45 patients without any distant metastases at presentation were worked up with 18-FDG PET scan. Those who had distant metastases or N3 disease were excluded. The clinical axillary nodal was then compared with PET scan status of the axillary nodes. All the 45 patients then underwent modified radical mastectomy and axillary nodal clearance from level I–III. Standard histopathological examination was carried out in all the patients and this pathological N status was compared with clinical and PET scan results.
Results: The above results were then analyzed with Bayesian statistical analyzer. The sensitivity and specificity of clinical examination alone in detecting pathological nodes was 54%and 74% respectively whereas that with PET scan was 83% and 82% respectively. Two of the false positive PET patients were with h/o autoimmune disease.

PET and Path. N status Clinical Vs pathological N status

	pN+	pN−	Total
Clinical			
cN+	14	5	19
cNo	12	14	26
Total	26	19	45
PET scan			
Positive	19	4	23
Negative	4	18	22
Total	23	22	45

Conclusion: 18-FDG PET scan has high sensitivity and specificity in detecting pathological axillary nodes compared to clinical examination alone. Future studies comparing sentinel lymphnodes and PET scan are required to find their exact specificity. Results in patients with autoimmune disorders have to be interpreted with caution.
No conflict of interest.

1977 POSTER

Correlation and prognostic significance of lymphangiogenesis and vascularity in breast cancer

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Background: Prognostic markers predict the clinical course and subsequent outcome in cancer patients. Lymph node metastasis is the most

important prognostic marker in breast cancer and lymphatic microvessel density (LMVD) along with lymphatic vessel invasion (LVI) can serve as a proxy prognostic marker to lymph node involvement. Tumour vascularity is the key factor responsible for tumour growth and metastasis which can serve as a prognostic marker. Color Doppler ultrasonography parameters of vascularity can be measured by resistivity index (RI), pulsatility index (PI) and maximum flow velocity (Vmax). The correlation between lymphangiogenesis and angiogenesis in breast cancer has not been studied till date.
Methods: We studied the correlation of LMVD and LVI by immunohistochemistry using D2−40 antibody with colour Doppler ultrasonography findings in 30 early invasive breast cancer patients. The patients were classified as low or high category (lymphangiogenesis and vascularity) based on their mean value. The LMVD, LVI and colour Doppler parameters were correlated with each other and also with other clinico-pathological parameters.
Results: The mean ± Standard Deviation (SD) of age was 44.40±10.37 years. The mean±SD of LMVD, RI, PI and Vmax were 8.37±2.59, 0.89±0.12, 2.42±0.12 and 20.80±8.27 respectively. There was a significant correlation between LMVD with RI (r 0.596; p 0.001) and PI (r 0.573; p 0.001), LVI with RI (r 0.418; p 0.022) and between LMVD and LVI (r 0.503 p 0.022). Tumour size, number of positive lymph nodes, grade of tumour and receptor status correlated with RI, PI, LMVD and LVI (p value <0.05) but not with Vmax.
Conclusion: The result of present study supports the positive correlation between lymphangiogenesis (LMVD and LVI) using D2−40 antibody and RI and PI by Doppler study in breast cancer. Further these parameters also correlate with clinico-pathological parameters.
No conflict of interest.

1978 POSTER

Overexpression of P53 is prognostic for aromatase inhibitor (AI) resistance in early stage postmenopausal patients with ER-positive breast cancer: A retrospective analysis in AI-treated patients

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Background: Studies have demonstrated that P53 overexpression is a significant factor in predicting resistance to 3rd generation aromatase inhibitors (AI) in hormone-sensitive recurrent or advanced breast cancer, however, the prognostic significance of P53 in early stage breast cancer is uncertain.
Patients and Methods: Patients who received aromatase inhibitors (n = 293) with complete baseline data in the Cancer Hospital of Fudan University, Shanghai, China between 2000 and 2006 were included. All patients were postmenopausal with positive ER and/or PgR tumors. The clinicopathological factors included the following: age, hypertension, DM, TNM stage, histology grade, vascular invasion, lymph node status, P53 status, PR, HER2/neu, chemotherapy and radiotherapy. The expressions of PR, p53 and HER2 were evaluated by immunostaining. The disease-free survival (DFS) was compared. Survival analysis was performed using Kaplan–Meier method. Cox proportional hazards models were used to evaluate the prognostic value of P53 expression for DFS. The p-values less than 0.05 were regarded as significant.
Results: The median follow-up was 72 months (range, 6–140 months). Only 4 of 12 variables analysed remained significantly prognostic for survival in the Cox proportional hazards model. These included age (HR = 1.988, 95% CI = 1.511–2.617, P < 0.005); pathological stage (HR = 2.270, 95% CI = 1.399–3.681, P =0.001); histological grade (HR = 2.328, 95% CI = 1.312–4.133, P =0.004); and P53 expression (HR = 1.729, 95% CI = 1.038–2.880, P =0.035). The 5-year disease free survival rate in P53 positive and P53 negative patients were 78% and 89%, respectively.
Conclusion: This retrospective analysis demonstrates that P53 overexpression correlated strongly with AI resistance in early stage postmenopausal patients with ER-positive breast cancer patients who were treated with AI and confirmed the relevance of previously described prognostic factors. If validated by larger studies, the p53 overexpression may become a key factor in determining treatment strategies for postmenopausal hormone-sensitive disease.
No conflict of interest.

1979 POSTER

Sleep disturbances and changes in the urinary metabolite of melatonin (aMT6s) levels in patients with breast cancer undergoing lumpectomy

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Background: Sleep disturbances and changes in self-reported discomfort and melatonin secretion are common in the postoperative period. We aimed to study the distribution of sleep stages in the pre- and postoperative period and evaluate changes in the secretion of the melatonin metabolite aMT6s and subjective parameters of sleepiness, pain, general well-being and fatigue in patients undergoing breast cancer surgery.
Materials and Methods: Twelve patients, 30−70 years, undergoing a lumpectomy were included in the study. PSG monitoring was made the night before surgery (PREOP), the night after surgery (PO1) and approximately 14 days after surgery (PO14). Recordings were scored as awake, light sleep (stage 1 and 2), slow wave sleep (stage 3 and 4) and rapid eye movement (REM) sleep. Sleep stages were analyzed as percent of total sleep time. Self-reported discomfort was assessed using questions about the level of fatigue, general well-being and pain and sleepiness was assessed by Karolinska Sleepiness Scale. Urinary aMT6s was measured by a radioimmunoassay.
Results: Table 1 shows sleep data. There was significantly decreased REM sleep on PO1 (5.9% of total sleep time) compared with the night before surgery (18.7% of total sleep time) (p < 0.005). Patients had fewer episodes of REM sleep on PO1 compared with PREOP (p < 0.005). An increase in light sleep was observed on PO1 (68.4% of total sleep time) compared with the night before surgery (55.0% of total sleep time) (p < 0.05). No significant changes in total sleep time, sleep latency, sleep period or total time awake were found. The observed sleep changes were normalized after two weeks. No significant changes were found in pain, general well-being, fatigue or sleepiness. aMT6s night secretion showed a non-significant trend towards a decrease from PREOP to PO1 (p = 0.09) and a normalization on PO14 (p < 0.05 between PO1 and PO14).
Conclusion: Patients with breast cancer undergoing a lumpectomy had significantly disturbed sleep architecture the night after surgery and these changes were normalized after two weeks.
Trial registration: Clinicaltrials.gov identifier: NCT01171508
No conflict of interest.

Table 1. Sleep data

	PREOP	PO1	PO14	Wilcoxon P-value
Sleep latency (min)	23(4−58)	19(0−29)	21(2−107)	
Sleep period (min)	439(286–491)	434(352–471)	412(343–469)	
Number of awakenings	25(16−38)	23(5−30)	29(13−47)	*<0.05 † <0.05
Awake (min)	106(64–255)	114(75–236)	100(25–184)	
WASO (min)	80(28–237)	104(49–216)	54(21–161)	‡ ⩽0.05† <0.05
TST (min)	320(189–428)	332(182–405)	353(194–403)	
LS in % of TST	55.0(43.1–66.1)	68.4(42.7–94.4)	60.0(49.3–70.6)	*<0.05
SWS in % of TST	21.1(15.1–41.1)	24.5(0.0–53.8)	20.8(13.6–26.0)	‡ ⩽0.05
REM in % of TST	18.7(15.6–32.3)	5.9(0.0–12.8)	20.9(15.8–25.9)	*<0.005 † <0.005
REM episodes	7(3−16)	3(0−4)	6(3−13)	*<0.005 † ⩽0.005

Values are median (range). P-values (Wilcoxon Signed-Rank test) ⩽0.05 are shown.
WASO = Wake after sleep onset; TST = Total sleep time; LS = Light sleep; SWS = Slow wave sleep; REM = Rapid eye movement.
*PO1 vs. PREOP; †PO14 vs. PO1; ‡PO14 vs. PREOP

1980 POSTER

Lack of circadian variation and reduction of heart rate variability in women with breast cancer undergoing lumpectomy

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Background: Changes in the autonomic nervous system with increased sympathetic tone may be a cause of postoperative short-, and long-term cardiovascular complications. Heart rate variability (HRV) is assessed by Holter-monitoring as a measure of autonomic tone and has not been investigated in patients with breast cancer undergoing surgery. We aimed to investigate evening- and night-time HRV after lumpectomy.
Material and Methods: Twelve patients were included in this descriptive study. HRV was measured the night before surgery (PREOP), the night after surgery (PO1) and 14 days after surgery (PO14) from 1900 h-0700 h.

For calculation of HRV, time domain parameters (SDNN-standard deviation of all NN intervals around the mean NN for the period of measurement, pNN50-percentage of beats where the change from one beat to the next is more than 50msec, rMSSD-root mean square of successive differences) were used. We analyzed the variation of the overall time period and the circadian variation between evening and night (sympathetic vs. parasympathetic tonus).

Results: Table 1 shows mean heart rate and time domain parameters (SDNN, pNN50, rMSSD) for overall time-period 19−07 on PREOP, PO1 and PO14. Mean heart rate increased from PREOP to PO1 ($p < 0.001$) and also increased between PREOP and PO14 ($p < 0.05$). SDNN ($p < 0.001$) and PNN50 ($p < 0.001$) decreased from PREOP to PO1. There was also a significant decrease between PREOP and PO14 for both parameters ($p < 0.005$ and $p = 0.05$ respectively). SDNN increased from PO1 to PO14 ($p < 0.005$). rMSSD decreased from PREOP to PO1 ($p < 0.001$). A circadian variation was found in the mean heart rate for all 3 monitoring periods ($p < 0.005$). Circadian variation was also present on PREOP for pNN50 ($p \leqslant 0.05$) and rMSSD ($p < 0.05$). This variation was missing for both PO1 and PO14.

Conclusion: Patients had a shift of autonomic tone with reduced parasympathetic activity and lack of circadian variation 14 days after lumpectomy.

Trial registration: Clinicaltrials.gov identifier: NCT01171508

No conflict of interest.

Table 1. Mean heart rate and time domain parameters (SDNN, pNN50, rMSSD) for overall time-period 19−07 on PREOP, PO1 and PO14

	PREOP	PO1	PO14	Repeated measures test
Mean heart rate	68 (49–110)[a]	72 (51–105)	70 (49–101)[c]	<0.001
SDNN (ms)	44 (20–164)[a]	36 (9–166)[b]	42 (9–112)[d]	<0.001
pNN50 (%)	6.4 (0–42.1)[a]	1.5 (0–52.0)	3.5 (0–38.5)[c]	<0.001
rMSSD (ms)	29 (11−94)	23 (7−99)	26 (7−79)	<0.05

Values are median (range). P-values (Wilcoxon Signed-Rank test and Friedman analysis of variance) $\leqslant 0.05$ are shown. Comparisons were made between PO1 versus PREOP, PO14 versus PREOP and PO14 versus PO1. Only significant changes are depicted in the table.

[a] p <0.001, PO1 vs. PREOP.
[b] p <0.005, PO14 vs. PO1.
[c] $p \leqslant 0.05$, PO14 vs. PREOP.
[d] p <0.005, PO14 vs. PREOP.

1981 POSTER

Prognostic value of Ki67LI in HER2 negative luminal (HNL) early breast cancer (EBC): A single institution experience with long follow up

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Background: Several studies have emphasized Ki67LI biologic and prognostic value and its potential application of its assessment in routine practice, particularly to define prognostic subgroups of luminal/hormone receptor-positive (HR+) tumors.

Methods: Ki67LI was identified by immunohistochemical staining in 3760 EBC pts treated from 1995 to 2008 in our institution. Median age was 61 y. The relationship with clinic-pathological parameters and the prognostic significance of KI67LI were investigated in all EBCs and in HER2 negative luminal (2380 HNL) cases stratified on homogeneous grading (594 G1, 1282 G2, 504 G3).

Results: Median Ki67LI values were 22% in all cases, 20% in HNL and 10, 20 and 35% in different HNL grading group (HNL-GG). Ki67LI >22% (1873 pts) was significantly ($p < 0.001$) associated with younger age, ductal type, greater size, positive N, poor G, absent or low ER /PR level, positive HER-2 status, triple negative subtypes. Local and Distant Relapses were 138 (7.3%) and 355 (18.9%) in < or >22% Ki67LI respectively. Median time to first event was 31.7 ms in >22% *vs* 50.1 ms in <22% Ki67.

At median f-up of 77 months EFS and OS were 91.9 and 92.1% in <22% *vs* 78.9% and 81% in >22% Ki67 respectively ($p < 0.001$).

Prognosis in term of DFS and OS was consistently worse for >22% compared to <22% Ki 67 in all clinical-pathological subsets, except in negative ER Group. In multivariate analysis, KI 67mantained an independent prognostic significance for DFS and OS.

In HNL, EFS and OS were 93.7 and 92% in <20% *vs* 81.7 and 83.3% in >20% Ki67($p < 0.001$). Using median ki67LI value for different homogenous HNL-GG as cutoffs, we stratified these populations in low and high risk. The results are shown in the table.

Conclusions: Our study confirms prognostic value of Ki67LI in EBC, associated with other clinical-pathological characteristics. Cutoffs are different into HNL-GG. They can cathegorize at least two biological entities in every grading group providing additional prognostic information in planning therapies and outcome prediction.

No conflict of interest.

Subgroup	EFS	P	OS	P
G1		0.043		0.114
High (Ki67>20%)	91.7%		92.7%	
Low (Ki67<10%)	96.0%		96.0%	
G2		<0.001		0.012
High (Ki67>20%)	84.2%		87.5%	
Low (Ki67<20%)	93.7%		90.6%	
G3		0.053		0.036
High (Ki67>35%)	70.9%		76.4%	
Low (Ki67<35%)	83.2%		80.7%	

1982 POSTER

Comparative study of the follow-up of long-term survivors of breast cancer in primary-care versus specialist attention

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Background: We sought to describe the long-term breast cancer survivors evolution according to type of care provided (primary or specialized follow-up), measuring the impact on health outcomes, cost, quality of life and satisfaction.

Material and Methods: Retrospective cohort study with disease-free patients followed in Oncology for at least 5 years. Using personal survey, the type and cost of follow-up, events, quality of life and satisfaction were analyzed, depending on whether they had been referred for primary care or followed in Oncology.

Results: 98 women were interviewed, 60 from primary care and 38 from specialized care. No differences in the diagnosis of metastases and new primary tumors were found. 0.98 (0.48) visits per patient and year were conducted in primary care and 1.11 (0.38) in specialized ($p = 0.19$). In primary, 44.6% were scheduled, and 55.4% were unscheduled. In specialized, 94.6% were scheduled, and 5.4% were unscheduled ($p = 0.0001$). The primary follow-up costs were lower, with 112.86 € (77.54) vs 184.61 € (85.87) per patient and year ($p = 0.0001$). No differences in quality of life were observed. 80% of patients expressed a preference for specialized, 10% for primary and 10% were indifferent. Women were more satisfied with specialized in all dimensions of the questionnaire.

Conclusions: Adherence to follow-up protocol was high in both areas. Specialized care visits were mainly scheduled and almost half of primary care visits were unscheduled. In our setting, primary care is more efficient than specialized, but women express greater satisfaction and prefer specialized follow-up.

No conflict of interest.

1983 POSTER

Guidelines for time-to-event endpoints' definitions in cancer randomized controlled trials (RCTs) for breast cancer − results of the DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials)

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Background: With the necessity of reducing randomized clinical trial (RCT) duration, cost and number of patients, surrogate endpoints are increasingly being used as replacement for overall survival (OS) in cancer RCTs. However, most of these endpoints currently lack of standardized definition enabling a comparison of RCT results. Some recommendations have been proposed for specific cancer sites but they do not rely on a formal consensus methodology. The objective of the DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials) is to provide guidelines to standardize definitions of time-to-event (TTE)

endpoints in RCTs for different cancer sites. We present results for Breast cancer (BC) (similar abstract submitted for Sarcoma and GIST).
Methods: We relied on the modified Delphi consensus method, a validated formalized consensus process for the development of practice guidelines. International experts with various backgrounds and expertise were involved. First, the coordinating committee, a group of statisticians and epidemiologists involved in the design and conduct of RCTs, led a comprehensive literature review to identify the existence of guidelines or TTE endpoints and clinical events of interest. The steering committee, which included additional medical experts prepared the questionnaire based in part on Hudis et al. proposal (JCO 2007) and sent for rating to an independent expert committee.
Results: The consensus process involved two rounds of rating (31 experts) and one in-person meeting (Chicago 2012). Each expert had to rate on a 1−9 scale if s/he agreed to include clinical events (e.g. death from BC) in the definition of TTE endpoints (e.g. progression-free survival). Consensus was reached for 57% of the events after the rounds of rating and was finalized at the meeting for the remaining events except one. Guidelines for the definition of 11 TTE endpoints were established (e.g. disease-free survival, time-to-progression, etc) in adjuvant or metastatic settings.
Conclusions: The DATECAN guidelines should help standardize definitions of commonly used TTE endpoints. They should (i) facilitate the comparison of RCTs, (ii) improve the quality of trial reporting and (iii) improve the quality of future RCTs. These guidelines will be presented at ASCO'13. However, communicating about these recommendations at ESMO/ECCO is also a key step towards wide scale dissemination and implementation of these guidelines.
No conflict of interest.

1984 POSTER

Expression of androgen receptor in breast cancer in younger age with special relation to molecular subtypes and response to anterior chemotherapy

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Background: Breast cancer, a heterogeneous disease comprises different tumour subtypes associated with varied clinical characteristics. Prognostic factors including age, tumour size, histological subtype and grade, lymph node status and the expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) currently assist routine clinical management. Breast cancer in younger age BCYA (under 40 years old) has different clinicopathological characteristics than in the elderly, a more aggressive phenotype with a larger tumor size, more lymph node involvement, and advanced stages. Despite adjuvant treatment recurrence, metastasis and death were still higher than in elderly patients. In the present study an attempt has been made to evaluate AR expression in BCYA and response to taxane and/or anthracycline based standard chemotherapy regimen.
Materials and Methods: Between May 2011 and Sept 2012, 116 breast cancer patients were enrolled. Tissue sections were immunostained for ER, PR, Her2 Neu and AR. n = 35 patients with BCYA were sub-grouped. n = 24 patients were subjected to neoadjuvant taxane and/or anthracycline based chemotherapy according to standard treatment guidelines. Clinical response was evaluated using revised RECIST guidelines (version 1.1).
Results: Mean age of presentation was 36.1 years (20−40 years) with 22/35 (62.9%) BCYA AR+ve. In particular, AR expression was commonly observed in luminal A 9/11 (81.8%) and B 5/7 (71.4%) cancers, but was less frequently seen in HER2 cancers 6/11 (54.5%). Despite being defined by the absence of ER, PR and Her2 neu expression and being considered hormonally unresponsive, 2/6 (33.3%) of TNBC expressed androgen receptor. 24/35 (68.6%) BCYA were given NAC, 12/24 (50%) were AR positive. BCYA AR+ve showed better response to NAC as 10/18 (55.5%) were partial or complete responders compared to 2/6 (33.3%) showing stable or progressive disease.
Conclusion: Expression of AR is seen in approximately two-third of BCYA, with positively stained BCYAs showing to have better response to chemotherapy; providing further evidence that BCYAs represent a heterogeneous group. As AR is confirmed as biologically relevant in breast cancer, it is possible that hormonal manipulations targeting it could be useful in treatment but large sample size is needed to deduce the final statement.
No conflict of interest.

1985 POSTER

Clinical impact of breast specific gamma imaging on the surgical management of patients with proven breast cancer

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Background: Mammography, combined with ultrasound (US), remains the mainstay for breast cancer detection, MRI can be used as an adjunct modality for surgical planning but its major limitation is the poor specificity. Molecular breast imaging techniques, such as breast-specific gamma imaging (BSGI), are increasingly being used as adjunctive diagnostic techniques to mammography and ultrasound. In this study we tried to determine the possible impact of BSGI in assisting surgical planning.
Method: Data were analysed from all patients who where diagnosed with invasive breast cancer and planned for surgical treatment the period from January 2012 until April 2013. Patients who obviously had an indication for a mastectomy where excluded as no BSGI scan was performed in these patients. After diagnosis a BSGI scan was performed and the results were analyzed. If necessary additional imaging and if indicated biopsy was performed. Depending on these additional results the surgical strategy was altered.
Results: In total 232 patients were diagnosed with breast cancer in this study. In 186 a BSGI scan performed of which 39 demonstrated a mismatch with the conventional imaging. In 18 patients =9.7% additional cancer sites, 7 ipsilateral and one contralateral or a larger tumor area in 7 patients were demonstrated and proven by biopsy. In 3 patients conventional imaging remained equivocal and the malignancy was only demonstrated with BSGI scan. In these patients surgical management was altered. In 10 patients additional lesions could not be proven on second look imaging. In 2 of those patients malignancy could only be proven by BSGI guided biopsy. On the other side BSGI failed to visualize 11 lesions, which were detected on conventional imaging. These consisted of grade 1 invasive carcinomas in 5 patients, ductal carcinoma in situ in 5 patients and a <5 mm grade 2 invasive tumor in one patient. The sensitivity and specificity of BSGI in this study were 46% and 93% respectively.
Conclusion: Breast-specific gamma imaging could play an important role in the management of patients with proven malignancy of the breast by detecting synchronous lesions that altered patient surgical management. Its high specificity makes it a better additional tool for surgical planning than the MRI.
No conflict of interest.

1986 POSTER

Retrospective multivariate analysis of risk factors of breast cancer in a high-risk population using a logistic regression model

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Background: Breast cancer (BC) is the most common malignancy among women in western society, and its prevalence varies widely in different Countries. Several risk factors (RF) have been reported, but none was able to give reliable epidemiological information on clinical outcome for each patient population. The aim of this study was to provide information about relationship between BC and different RF to be considered at the time of diagnosis in women residing in a high-risk region of Italy.
Patients and Methods: The study included 375 BC cases (median age 60 years, range 26−89) and 1,261 population-based age-matched controls. All patients lived in the same urban area and underwent clinical breast examination spontaneously. Patients with other or previous cancer were excluded. The following parameters were considered: age, family history of BC, menstrual and reproductive factors (age at menarche, menstrual pattern, number of births and abortions, age at first birth, lactation), use of oral contraceptives and hormonal replacement therapy, smoking, alcohol consumption, occupational and sedentary activity, body mass index (BMI).
Results: Univariate analysis showed significant differences ($p < 0.01$, Student's t-test and chi-squared test) between cases and controls in: (1) age at menarche (12.3±1.6 vs. 12.7±1.5 years) and menopause (49.5±4.1 vs. 47.3±5.3 years), (2) number of births (1.4±1.1 vs. 1.8±1.3) and age of first birth (25.2±4.3 vs. 24.4±3.6 years), (4) estrogen replacement therapy (43.9±30.3 vs. 33.7±28.1 months), (5) smoking (5.9% vs. 12.5%), and (6) alcohol abuse (5.7% vs. 2.3%). Multivariate analysis using a logistic regression model showed that only

four independent parameters correlated with BC: age at menarche (years), number of births, lactation, and estrogen replacement therapy. Odds ratio for BC calculated from the observed vs. predicted values obtained using the logistic regression function was 5.05 (95% CI 3.6−7.1), while the OR of single variables was <3 (95% CI 1.51–4.32).
Conclusions: The results display that the prolonged (>3 years) use of estrogen replacement therapy, is strongly related to the onset of BC. However, in this study, many classical parameters did not result useful as RF, suggesting that to correctly select the high risk population both different primary RF and other environmental and external factors should be considered for each patient.
No conflict of interest.

1987 POSTER

Validation and calibration of breast cancer nomogram for predicting risk of ipsilateral breast tumour recurrences in asian population with ductal carcinoma in situ after local excision

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Background: Over a quarter of screen detected breast cancers in Singapore are ductal carcinoma in situ (DCIS). At our centre, DCIS is commonly treated with wide excision followed by adjuvant radiotherapy, i.e. breast conservation therapy (BCT). The primary concern of BCT is the risk of ipsilateral breast tumour recurrences (IBTR). The aims of our study are to review the outcomes of DCIS treatment in our patients and to evaluate a recent nomogram for predicting IBTR from Memorial Sloan-Kettering Cancer Centre (MSKCC) in our Asian population.
Methods: Chart reviews of 716 patients with pure DCIS treated from 1992 to 2011 were performed. Univariable Cox regression analyses were done to evaluate the effect of the ten prognostic factors of the MSKCC nomogram on IBTR. NCCS nomogram was generated based on multivariable Cox regression via reduced model selection by applying the stopping rule of Akaike's information criterion to predict IBTR free survival. The abilities of NCCS nomogram and MSKCC nomogram to predict IBTR of individual patients were evaluated with bootstrapping of 200 sets of resamples and NCCS dataset, respectively. An adequacy index was used to quantify the percentage of the variation explained by a subset of predictors (NCCS nomogram and MSKCC nomogram separately) compared with the information contained in the full set of predictors (both NCCS and MSKCC nomogram) by means of log likelihood. Harrell's c-index was calculated for each nomogram to evaluate the concordance between predicted and observed responses of individual subjects.
Results: The study cohort was followed up for a median of 70 months. Over 95% of patients received adjuvant radiotherapy. The 5-year and 10-year actuarial IBTR free survival rates for the cohort were 95.5% and 92.6% respectively. In the multivariable analysis, independent prognostic factors for IBTR include use of adjuvant endocrine therapy, presence of comedonecrosis and younger age at diagnosis. These factors formed the basis of our NCCS nomogram. Similar C-index (NCCS: 0.696; MSKCC: 0.687) and adequacy index (NCCS: 81.1%; MSKCC: 79.4%) of the nomograms suggests similar power of the NCCS nomogram in predicting IBTR despite including fewer predictors.
Conclusion: Local results of DCIS treated with BCT are comparable to published studies. External validation of the MSKCC nomogram on our cohort of Asian patients demonstrates predictive power similar to that of the NCCS nomogram which uses fewer prognostic factors.
No conflict of interest.

1988 POSTER

p53 protein expression in early breast cancer (EBC) and its correlation with molecular features

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Background: The p53 gene is located on chromosome 17p13 and encodes a 53-kDA nuclear phosphoprotein that is essential in regulation of the cell cycle. It has been suggested that wild type p53 is a 'guardian of the genome' preventing proliferation of cells with genetic damage. Alterations in this gene are reported in nearly a third of all EBC and loss of p53 function seems to result in a more aggressive disease and worse clinical outcome. The prognostic and predictive role of p53 in EBC is still uncertain and the rate of p53 mutations vary depending upon the subtype.
The aim of our study was to correlate p53 expression with known prognostic factors.
Materials and Methods: In this retrospective study p53 immunohistochemical detection was performed in a series of consecutive patients (pts) with EBC over a period of 1 year. Prognostic factors such as hormonal receptors, HER-2 status and ki67 index were simultaneously measured; p53 was defined mutated with a nuclear staining >10%. Molecular subtypes were classified accordingly to St. Gallen 2011 criteria.
Results: From January 2012 to December 2012 p53 was measured in 287 pts, with a median age of 60 yrs (range 32−88): 223 pts (81%) had p53 $\leqslant$10% while 64 pts (19%) had p53 >10%. A significant correlation was found with ER negativity and Ki67 index.
The table shows the relationship between p53 expression and molecular subtypes.

	p53 $\leqslant$10%	p53 >10%	p value
Luminal A	*65 (95%)*	*4 (5%)*	*p < 0.0001*
Luminal B HER2−ve	*141 (87%)*	*22 (13%)*	*P < 0.0001*
Luminal B HER2+ve	*14 (61%)*	*9 (39%)*	*ns*
HER2+ve	*4 (40%)*	*6 (60%)*	*ns*
Triple Negative	*9 (41%)*	*13 (59%)*	*p < 0.0002*

Conclusions: Our study supports findings that p53 expression is highly linked to tumour subtypes, being significantly low in Luminal A and Luminal B-HER2−ve tumours and high in Triple Negative ones. According to these data the role of p53 as a prognostic factor should be reconsidered in EBC.
No conflict of interest.

1989 POSTER

Incidence of bone pain in patients with breast cancer treated with lipegfilgrastim or pegfilgrastim: An integrated analysis from the phase II and phase III studies

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Background: Lipegfilgrastim is a once-per-cycle, fixed-dose glycoPEGylated granulocyte-colony stimulating factor (G-CSF) being developed as an alternative to pegfilgrastim (Neulasta®) for the prevention of severe neutropenia in cancer patients receiving chemotherapy (CTx). All G-CSF products have the potential to cause bone pain, which is generally transient in nature and mild to moderate in intensity. Using data from the Phase II and III studies in patients with breast cancer receiving CTx, we compared the incidence of bone pain-related (BPR) symptoms in patients treated with lipegfilgrastim versus those treated with pegfilgrastim and the relation to G-CSF treatment and CTx.
Methods: All patients who received CTx (doxorubicin 60 mg/m^2 + docetaxel 75 mg/m^2) and at least one subcutaneous injection of lipegfilgrastim or pegfilgrastim were included in the analysis. BPR TEAEs comprised the preferred terms (PT) arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, and pain in extremity. All BPR TEAEs were defined as TEAE drug reactions (TEADRs), except those specifically assessed as 'not related'.
Results: See the table.

Table: All TEAEs by SOC and PT

	Number of patients (%)*	
	Lipegfilgrastim 6 mg (N = 151)	Pegfilgrastim 6 mg (N = 155)
All BPR TEAEs	38 (25.2)	34 (21.9)
Arthralgia	7 (4.6)	4 (2.6)
Back pain	3 (2.0)	2 (1.3)
Bone pain	24 (15.9)	22 (14.2)
Musculoskeletal chest pain	1 (0.7)	0 (0.0)
Musculoskeletal pain	1 (0.7)	1 (0.6)
Myalgia	16 (10.6)	9 (5.8)
Pain in extremity	0 (0.0)	1 (0.6)

*Patients could be counted more than once and only categories with $\geqslant$1 patient reporting a TEAE are listed.

For BPR TEADRs by PT, 28/151 (18.5%) of the lipegfilgrastim patients experienced 64 events, whereas 26/155 (16.8%) of the pegfilgrastim patients experienced 57 BPR TEADRs; this difference was not statistically

significant. None of these BPR TEADRs were serious or led to study discontinuation and all resolved.
Conclusions: Overall, there were no significant differences in all BPR TEAEs between treatment groups. The incidence and severity of treatment-related symptoms of bone pain by PT were low and comparable between lipegfilgrastim and pegfilgrastim.
Conflict of interest: *Ownership: Peter Bias, Reiner Els*sser, and Anton Buchner are all employees of Teva and own stock in Teva Pharmaceuticals*

1990 POSTER

Prognostic impact of Ki-67 in Croatian women with early breast cancer (single-institution prospective observational study)

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Background: Review of available literature revealed scarcely published data on prognostic factors in Croatian women suffering from early breast cancer. Here we present single-institution data on proliferation marker Ki-67 in patient cohort with primary operable breast cancer treated in Breast cancer unit of University Hospital Center Zagreb during years 2002 and 2003.
Materials and Methods: From initial 215 patients (pts.) 6 were excluded from the analysis when proved to be initially metastatic, or lost to follow-up, giving final total number of 209 pts. Median age at diagnosis was 56 years (min 30, max 87). Median follow up is 9.38 years (min 8 months, max 10.4 years). 135 pts. were menopausal at diagnosis. All pts. were diagnosed by pathohistological examination of extirpated tumor including immunohistochemistry (IHC) for estrogen (ER) and progesterone (PR) receptor, as well as Her-2 and Ki-67 determination. Her-2/neu confirming methods were FISH or CISH for suspected amplification (++ by IHC). Adjuvant therapy followed according to TNM stage and accepted ESMO guidelines, with exception of adjuvant trastuzumab, which was not reimbursed by health insurance at that time. Pts. are grouped according to Ki-67 expression (cut-off value 14% − percentage of positive nuclei per hundred tumor cells), grade, stage and ER/PR/Her-2 profiles (five breast cancer subtypes according to St. Gallen recommendations). Kaplan–Meier curve with log-rank test, Kruskal-Wallis or Mann-Whitney test with Bonferroni correction were used for univariate, and Cox regresion analysis for multivariate models.
Results: Overall survival (OS) singificantly differs in Ki-67 positive vs. negative group (positive >14%, OS=77.9 vs. 62.2, $p = 0.023$). Accordingly, pts. that died during follow-up have significantly higher Ki-67 value (16 vs. 9.67, $p = 0.003$). Ki-67 value correlated with histologic grade (10 vs. 16.8 vs. 38.9% in grades I to III, respectively − $p < 0.001$, $\chi^2 = 15.204$). Kruskal-Wallis analysis confirmed non-equity of Ki-67 among grade-groups, but non-parametric test between I and II grade failed to reach statistic significance. Tumor grade had prognostic impact on OS (after 10 years, 90.1vs.77.7 vs. 57.4 in grades I to III, respectively − $p = 0.006$) and on disease free survival (DFS) as well. Stratification according to five molecular intrinsic subtypes of breast cancer, using ER/HR/Her-2 and Ki-67 (luminal A (1) and B (2), Her-2 enriched luminal (3) and non-luminal (4) and (5) triple-negative) revealed significantly lower Ki-67 expression in luminal A-like and significantly higher in luminal B-like group than Her-2 enriched and triple negative-like groups ($P<0.005$). In multivariate regresion analysis Ki-67 expression did not reveal significant impact on OS and DFS of patients stratified in aformentioned subtype-like groups.
Conclusion: Ki-67 alone had prognostic value on OS at 10 years follow-up in our cohort, whereas DFS was not significantly affected by Ki-67. Ki-67 level and tumor grade showed correlation, mostly significant, but tumor grade appeared to have stronger prognostic value than Ki-67. After grouping in molecular intrinsic-like subtypes of breast cancer according to IHC measurements of ER/PR/Her-2/Ki-67, Ki-67 differed significantly between luminal A and B-like and the rest of subtypes, but no significant difference in OS and DFS between groups was observed.
No conflict of interest.

1991 POSTER

Breast cancer: Value of evaluation exams 5 years after the diagnosis and treatment

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Background: The aim of this study was to analyze the diagnostic value of evaluation exams in asymptomatic patients, 5 years after the diagnostic and treatment of invasive breast cancer.
Methods: Retrospective study of patients with the diagnosis of invasive breast cancer during 2005 and that were submitted to evaluation exams before being referenced to surveillance in primary health care. We analyzed the diagnosis rate of metastatic disease after these exams in each stage. For each diagnostic test (BS, LUS, CXR), we analyzed the diagnosis rate of metastasis defined as the number of patients with diagnosis of metastatic disease after an imaging technique divided by the total number of patients tested. In addition, sensitivity and specificity were calculated. We considered as clinically significant, diagnostic rates superior to 1%.
Results: Of the 751 patients admitted in 2005, 228 had been submitted to BS, LUS, CXR five years after being diagnosed and treated for their breast cancer. 226 were female. The median age was 57 years (23−90 years). The most frequent histological type was invasive ductal carcinoma (80.7%); 90.5% had positive hormone receptors; the HER-2 was unknown in the majority of cases. *The most frequent stage was stage II* (110 patients). The re-staging exams had diagnosed metastatic disease in 8 patients (3.5%): 3 patients in stage II (1.32%) and 5 in stage III (2.19%). BS was carried out in 199 patients, LUS in 186 patients and CXR in 188 patients. BS detected skeletal metastases in 2% of patients, LUS detected liver metastases in 0.53% of patients and CXR detected lung metastases in 0.52% of patients. The median overall survival after the diagnosis of metastasis was 25.2 months.
Conclusions: These findings suggest that a complete re-staging work-up to detect metastases in asymptomatic patients five years after the diagnosis and treatment of breast cancer is unnecessary in stage I.
In stages II and III, the prevalence of metastatic disease with these exams was superior to 1%, which indicates a possible benefit in doing evaluation exams in these patients routinely.
No conflict of interest.

1992 POSTER

Survival analysis of breast cancer patients in Northwest Iran

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Introduction: In Iran, breast cancer (BC) is ranked first among malignancies of women, comprising 24.4% of all neoplasms with a crude incidence rate of 17.81 in the year of 2006. However, studies specifically describing the clinicopathologic features, stages, and age distributions of BC in Iran are limited; thus, it is difficult to predict the present and future patterns of BC and carry out the most appropriate preventive and therapeutic measures to decrease the burden of the disease in Iran. Some studies in southern Iran about survival pattern of BC found three- and five-year overall survival rates of 76% and 58% respectively. The aim of this study was to determine the survival rate and prognostic factors of BC in northwest Iran.
Methods and Patients: A cohort study of 271 patients recruited from 1376−87, in Tabriz, northwest of Iran. In this study we analysed the age, tumour diameter, nodal status, hormone receptor status, pattern of metastasis and survival rate of breast cancer patients who referred to a university clinic in Tabriz, the city in the northwest of Iran and compared it with the results of other cities in Iran and other countries.
Results: Mean age was 48(26−82), 116 were ER and PR positive, 104 and 103 were negative. In fifteen years follow up 52 patients died. 14 patients were below 40 years old. 109 patients were premenopause, 83 post-menopause, and 43 unknown. 36.1% had tumour>4 cm and 9.5% <2 cm. 18.6% had N1, 14.4% N2, 12.8% N3, 16.7% unknown, 27.5% negative, 53.5% positive. 51.1% with metastasis, (26.6% nonskeletal, 24.5% skeletal, 1.4% both).
Life table analysis showed one, three, five, seven and ten years overall survival of 96, 86, 81, 79, and 76% respectively. It showed statistically significant correlation of survival with age less or above 40 years. Patients less than 40 years old had one, three and five years survival of 82, 74, and 65 % while patients over 40 had 95, 86, and 83% respectively (log rank=0.22). Diameter of the tumour had minimal effect to survival (T>4 cm had lower survival, $P = 0.08$).
Discussion: Two studies have previously reported 5-year overall breast cancer survival rates in Tehran and these were 60% and 62%. Our study shows similar results and denotes that Iran has considerably poorer survival than European countries and the United States.
Age less than 40 may be a prognostic factor in northwest Iran.
No conflict of interest.

1993 POSTER

HER-2/neu status in Syrian women with breast carcinoma

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Background: Her-2/neu is a member of epidermal growth factor receptors (EGFR) implicated in the pathogenesis of breast cancer. Her-2/neu is known to be overexpressed in 30% of breast cancers, furthermore it is considered as an important prognostic factor.
Objective: The study is aimed at determining the prevalence of Her-2/neu overexpression in Syrian women diagnosed with breast cancer and to assess both progression free survival and overall survival rates.
Material and Methods: The study is a retrospective one where we collected data from 10355 Syrian women diagnosed with breast cancer during the period 2007 through 2012 at Al Bairouni University Hospital in Damascus (Syria). Paraffin samples were reviewed by a central lab and another reference lab using both immunohistochemistry staining and fluorescence in situ hybridisation (FISH), [Hercep test (DAKO Inc)]. Both Her-2 (++ and +++) were checked again by FISH to determine Her-2/neu gene status.
Results and Discussion: 4013 out of 10355 were Her-2 positive (2+ and 3+) representing 38% of patients with a mean age of 42 years old at diagnosis, in the other hand the remaining 62% were Her-2 negative (0 and +1). A further investigation showed that Her-2 by FISH is positive in 2822 out of 4013 forming 70% of the positive group as follows: 1413/2344 (2+ patients) versus 1409 /1669 (3+ patients), in other word 16% of (3+) patients by immunohistochemistry showed to be negative by FISH. Of the 2822 patients, 1920 patients (68%) progressed with a median progression event of 19 months while the survival was 28 months in median.
Conclusions: The prevalence of Her-2/neu in Syrian women having breast cancer in this study is 27%. The study reflects the distribution of real Her-2/neu gene expression among the Syrian women diagnosed with breast cancer because Her-2 amplification was detected by FISH in all patients, further the sample covered 6 years and more than 10,000 patients. Finally, Her-2/neu overexpression accompanied with a bad prognosis in light of short progression and overall survival time.
No conflict of interest.

1994 POSTER

Progesterone receptor status and Ki-67 index provide prognostic value for early relapse in luminal B/HER2 negative breast cancer patients

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Background: Few studies has documented early relapse in luminal B/HER2 negative breast cancer. We examined prognostic factors of early relapse among these patients to improve treatment decision.
Patients and Methods: Total 399 patients with luminal B/HER2 negative breast cancer were included in the study. After 2 years of median follow-up, Kaplan–Meier curves were applied to estimate disease free survival (DFS) and overall survival (OS), while Cox proportional hazards regression to identify prognostic factors.
Results: Absence of progesterone receptor (PR) expression was associated with higher tumour grade (p<. 001) and higher Ki-67 index (p=. 008). PR absent tumours received more chemotherapy than PR present group (p=. 005). Multivariable logistic regression suggested absence of PR was strongly related to higher tumour grade (p <.001). After a median follow-up of 2 years, 17 patients (4.3%) had early relapses while 6 patients(1.5%) died. In univariate models, PR absence group was associated with poor DFS (HR = 3.679, 95% CI 1.369–9.882) when compare with PR present group. Furthermore, patients within high Ki-67 index group (>30%) had a reduced DFS (HR = 3.125, 95% CI 1.085–8.999) when compare with low Ki-67 index group($\leqslant$30%). In multivariate analysis, absence of PR expression was significantly associated with a reduced DFS (HR = 3.774, 95% CI 1.214–11.738) when compare with PR present group.
Conclusion: PR absence might be a prognostic factor for early relapse in luminal B/HER2 negative breast cancer,while high Ki-67 index may also suggest higher risk of early relapse.
No conflict of interest.

1995 POSTER

Do all node positive breast cancer patients undergoing axillary clearance need staging?

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Background: Currently all patients who undergo axillary node clearance (ANC) with node positive disease are routinely imaged as part of their staging investigations at our institution. It is well reported that axillary node status, and particularly the absolute number of positive nodes, is the most important prognostic factor in breast cancer. Our study addresses the question of whether routine imaging is necessary in patients with a low burden of node positive disease.
Methods: We collected data for all patients who underwent full ANC from 1st January − 31st December 2011. Patient parameters, number of lymph nodes retrieved and final number of positive nodes were recorded. Imaging investigations were examined for the presence of metastatic disease. We compared the number of positive lymph nodes and lymph node ratio (LNR) between those with and without metastatic disease. A P value <0.05 was considered significant.
Results: Eighty patients (79 female, 1 male) underwent full ANC during the study period. Mean age was 61.4 years (38−86 years). Sixty-nine (69) out of the 80 patients were found to have one or more positive lymph nodes after full ANC. These node positive patients underwent routine imaging with one or more of the modalities as follows: chest X-ray with liver ultrasound scan (37/69 patients), CT chest/abdomen/pelvis (35/69 patients), and isotope bone scan (27/69 patients).
Four out of the 69 (5.8%) node positive patients were found to have metastatic disease which was detected by routine imaging. Patients with metastatic disease were found to have significantly higher numbers of positive lymph nodes (average 18.3 vs 3.7, $P = 0.019$) and significantly higher average LNR (0.87 vs 0.31, $P = 0.003$) than patients without metastatic disease.
Conclusion: Imaging investigations should not be routine for patients with a low burden of node positive breast cancer. This should be reserved for those with a large number of positive nodes (or high LNR) or in patients with symptoms suggestive of metastatic disease.
No conflict of interest.

1996 POSTER

The association of nipple discharge color with malignant breast pathology

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Background: Nipple discharge usually has a benign cause. However, unilateral single duct nipple discharge is associated with an increased risk for underlying malignancy. To date, there is no consensus whether the color of nipple discharge independently indicates the risk of malignancy. Therefore, we sought to assess the relationship between the color of discharge and the risk of malignancy.
Materials and Methods: A retrospective study was performed in patients with unilateral single duct nipple discharge from the database of the Canisius Wilhemina ziekenhuis Nijmegen, who underwent a diagnostic microdochectomy between 1993 and 2012. All patients presented with no abnormalities on clinical and radiological examination. Nipple discharge colors and aspects of interest were classified as bloody/brown, white, yellow, green, serous, purulent and clear. Multiple logistic regression was performed to assess the relationship between color of nipple discharge and malignancy accounting for age. Statistical significance was set at $p < 0.05$.
Results: 173 patients with a median age of 52 y (range 19−84) were included. The median age of patients with breast carcinoma was 66 y (range 23−78), while patients with a benign diagnosis had a median age of 51 y (range 19−84). Histologic examination revealed an underlying (in situ or invasive) breast carcinoma in 21 (12.1%) patients. In addition, 17 (9.8%) patients were diagnosed with a lesion associated with a propensity to progress to breast cancer. Malignancy was associated with bloody/brown discharge in 76.2% of cases (OR 1.71; 95% CI 0.56–5.17). None of the other colors were significantly associated with malignancy either. Patients >60 y had an increased risk (OR 3.6; 95%-CI 1.42–9.20) of being diagnosed with malignancy versus patients $\leqslant$60 y (OR 0.28; 95%-CI 0.11–0.71).
Conclusions: Uniductal unilateral nipple discharge is a sign of underlying malignancy in a substantial proportion of cases. While the majority of patients diagnosed with breast cancer presented with bloody/brown discharge, its association with malignancy is not strong enough to distinguish high risk patients. The presence of the other colors couldn't exclude malignancy or identify low risk patient groups either. Therefore,

patients with unilateral single duct nipple discharge without radiological abnormalities should always be offered invasive diagnostic procedures like microdochectomy to search for underlying malignancy.
No conflict of interest.

1997 POSTER

Quality of life after mastectomy: What about moroccan patients?

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Introduction: Breast cancer is the first cancer that affects the Moroccan woman and it's a public health problem.
In recent years, great interest was shown for the consequences of breast cancer and its treatment methods on the quality of life of patients.Mastectomy is widely regarded as a destructive experience in the life of a woman. It leads to women of all ages a disturbance of the body image and femininity. The aim of our work is to study the impact of psycho-pathological quality of life among women attending the National Institute of Oncology,in Rabat, Morocco for localized breast cancer who underwent mastectomy in the estimated components self, family and sexual satisfaction.
Materials and Methods: This is a prospective study evaluating the quality of life in patients after mastectomy for localised breast cancer.
A questionnaire was developed to assess the quality of life of these patients in terms of body image and sexual satisfaction.
Results: Our study included 113 patients, the average interval between mastectomy and the questionnaire was 17 months, the average age of our patients was 49.ans, 58% are young (<50 years) and 67% of them are married, 79.% of patients live in urban areas, and the illiteracy rate was 58%.
The majority of our patients are housewives. The right breast was slightly affected by the mastectomy in 53% of cases. 33% of patients surveyed showed their preference for a lumpectomy to conserve their body image.
Denial of postoperative mutilation interested 60 patients, there was still persistent in 9% of cases. The anxiety and fear of death were found in half of our patients. Symptoms presented during the interrogation were dominated by: pain at the scar in 46% of cases and intramammary chronic pain in 51% of cases. In addition, 35% of patients had a fear of touching their cicatrice and46% of women reported a disturbance in body image.
Feelings of depression has affected half of the patients, and only 9% of them have a consultation with a psychiatrist, clinical signs frequently found were: insomnia in 42% of cases, loss of appetite in 49 % and weight loss in 30% of cases.
Loss of interest in pleasurable activities usually was found in 46% of cases, and fear of prolonged exercise has been described in 91% of cases.
Regarding the fear of going to Moorish Bath, it was found in half of the patients, the major cause was the fear of people's eyes.
On the sexual plane, 30% of the patients had sexual dysfunction, which are increased to 77.% Of them; against sexual satisfaction by concerned 53% of patients. 47% of women have shown their desire mastectomy breast reconstruction, either immediate or delayed (after treatment).
Conclusion: Our study demonstrates the importance of exploring further dimension of self-esteem when suffering from a serious disease like breast cancer. Moroccan women especially young, had mental suffering after mastectomy.
No conflict of interest.

1998 POSTER

Patients' perceptions on breast cancer clinical trials

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The Dutch Cancer Society (KWF) and the Breast Cancer Study Group (BOOG) believe that design and execution of clinical trials could be improved when patients become actively involved. A qualitative study is conducted − involving breast cancer patients, health care providers, researchers and stakeholder organizations − to explore possibilities for active patient involvement in breast cancer clinical trials.
The study started with consultation of 52 stakeholders (of which 27 patients). Then an advisory committee of 6 female breast cancer patients was established. Facilitated by a researcher they produced during three meetings an advisory report, based on the data from the consultation, on possibilities for active involvement clinical trials. In a dialogue meeting with different stakeholders, feasibility and preconditions for successful implementation of the advice were discussed.
Based on the results of the consultation and advisory committee three potential forms of patient involvement were formulated: (1) appointment of an advisory committee of patients who monitor the entire process of clinical trials (from design to follow-up), (2) inclusion of a patient (representative) in the research team as an equal member, and (3) involvement of individual patients for different aspects in a clinical trial. Within each phase of a clinical trial (design, information and recruitment, treatment, and follow-up and feedback) several aspects were identified in which patients' input from the three different levels could have additional value, e.g. contribution to questionnaires, outcome measurements, logistics, patient information, sharing experiences, feedback.
Active patient involvement of (ex)breast cancer patients in clinical trials is promising. The BOOG and BVN are started implementing the results of this study by conducting an advisory committee.
This project is a collaboration between the Dutch Cancer Society, the Dutch breast cancer trialists group and the Dutch breast cancer patient organization, and is performed by the Athena Institute, VU University Amsterdam.
No conflict of interest.

1999 POSTER

A survey of the patient's experience of participation in a clinical study at the Netherlands Cancer Institute

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Background: The purpose of this study is to make an inventory of patient experience participating in clinical studies during the primary systemic therapy for breast cancer. The ultimate aim is to use this insight to improve active participation and patient experience in future studies within our institute.
The Netherlands Cancer Institute is currently running a large-scale study monitoring various clinical aspects during the primary systemic therapy for breast cancer. The purpose is to evaluate the response of the tumour to neo-adjuvant therapy and to adjust the treatment regime if the response appears to be unfavourable.
There is, at present, no clear picture of how patients experience participation in this research program. As a result, the reasons for not taking part or dropping out during the course of the study are not known. A better understanding of these reasons would help to improve practices with regard to patient inclusion and help to improve patient experience.
Material and Method: The research involves collecting data from 80 patients who were treated with primary systemic therapy for breast cancer during the year 2011 and who were asked to participate in the PETscan study. The research population is sub-divided into the following groups:
1. Non-responders: patients who were asked to participate in the study but refused.
2. Responders: patients who were asked to participate in the study and accepted. This group was further divided into two sub-groups:
2.1. **Compliers:** a sub-group who completed the clinical study;
2.2. **Non-compliers:** a sub-group who did not complete the clinical study.
Data has been collected from interviews with patients from each group. Data in the form of individual patient characteristics has been collected from patient files and will be correlated with the data from the interviews. The following questions will be addressed: What reasons are given by the patients for their (non)response and (non)compliance? Are there any background differences between (non)responders and (non)compliers?
Results: Collecting and processing the results of this research will be completed by the end of May 2013 and will be presented at the ECCO.
Conclusion: A preliminary evaluation of the data generated suggests that patient experience will have an impact upon the way that research procedures are conducted.
No conflict of interest.

2000 POSTER

BRCA 1−2 Ashkenazi mutations in Argentinian patients at high risk of hereditary breast cancer

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Background: BRCA1−2 Ashkenazi Mutations (AM) have been found in Hispanic populations with non direct Jewish ancestry. There is no data about their frequency in argentinian patients (pts) with breast cancer at high risk of hereditary breast ovarian cancer syndrome (HBOCS). The AM tests were the only ones available in our country by the time of the study

design. The purpose of this study was to evaluate the frequency of the three AM in BRCA 1 and 2 genes in a selected population of women with breast cancer at high risk of HBOCS.
Material and Methods: From September 2009 to may 2011, breast cancer pts from a research collaborative group who full-filled inclusion criteria for HBOCS were evaluated. After genetic counseling consultation and informed consent, data about patient-tumor characteristics and family history were obtained and direct DNA sequencing from a blood sample was performed searching for the 3 Ashkenazi mutations 185delAG- BRCA1exon 2; 5382insC-BRCA1 exon 20 and 6174delT-BRCA2 exon 11.
Results: 97 pts were tested. Median age at diagnosis was 27 years (23−50). 70% ⩽40 years, 29% < than 35, 41% between 35−40 and 30% between 41−50. 7% (7 pts) had ashkenazi ancestry, 32% a 1º relative with breast/ovarian cancer before age of 50, 42% a 2º relative with breast/ovarian cancer before age of 50. Clinical presentation was bilateral in 11%, localized disease 79%, locally advanced 17% and metastatic 4%. 75% had conservative surgery and 21% a mastectomy. Sentinel node biopsy was performed in 22% and an axillary disection in 78%. 48% of the pts had positive lymph nodes. Median tumor size was 2 cm (0.2−10 cm). Invasive ductal carcinoma 83% and lobulillar 10%. Hystologic grade III 54%. Estrogen and progesterone receptors were positive in 64% and 61% of the pts respectively. Her 2 positive 26%. Triple Negative 14%.
Mutational analysis performed at the central laboratory was negative in 99% of the pts (n 96). The only positive patient had Ashkenazi ancestry and a BRCA 1 185delAG heterozygous mutation was found.
Conclusions: In a highly selected population of Argentinian pts with HBOCS the study of the 3 founder AM showed to be unuseful, even in the Ashkenazi subgroup of patients.
No conflict of interest.

2001 POSTER

Role of tumor cellularity in the assessment of response to neoadjuvant chemotherapy treated locally advanced breast cancer

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Background: Breast cancer is the most common invasive malignancy in women worldwide. The advent of neoadjuvant chemotherapy has radically changed the management of locally advanced breast cancer and complete response is reported to have significantly improved disease free survival. Traditionally, clinical response has been assessed by tumor size. In this study, an attempt has been made to see if tumor cellularity could be a better prognostic factor and also to see what impact the correlation of tumor size with cellularity has on the response assessment in locally advanced breast cancer patients.
Materials and Methods: 37 patients of locally advanced breast cancer treated by neoadjuvant chemotherapy during the period of December 2008 to May 2009 were selected for the study and from their case records, tumor size, clinical response and demographic details were gathered. Tumor cellularity was assessed prior to chemotherapy in core needle biopsy sections and matched with subsequent mastectomy specimens. Tumor size and cellularity were then correlated with the different treatment response groups and statistically analysed using the SPSS 13.0 software.
Results: After neoadjuvant chemotherapy, the tumor size and cellularity was found to be significantly reduced in the breast carcinomas ($p < 0.05$, paired t test). The relative changes in cellularity were highly variable between individual patients and different clinical response groups, particularly in the partial response and no response categories. The product of cellularity and size dramatically changed the distribution of residual tumor pathology causing a shift towards complete response.
Conclusions: The current study shows that the product of tumor size and cellularity may be a better prognostic indicator of clinical response in neoadjuvant chemotherapy treated locally advanced breast cancer patients and would enable a new definition for clinical response in the future.
No conflict of interest.

2002 POSTER

Traditional Chinese acupuncture for treatment of chemotherapy and hormonal therapy adverse events in breast cancer patients

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Background: Adverse events from chemotherapy and hormonal therapy are frequently reported by breast cancer patients. Some side effects are difficult to control with best supportive care. Acupuncture has demonstrated to improve chemotherapy-related nausea/vomiting but its efficacy remains uncertain for other symptoms (Garcia MK, J Clin Oncol 2013).
Methods: 118 women with advanced or early breast cancer receiving chemotherapy or hormonal therapy at our Oncology Department were treated with acupuncture. A total of 1.180 acupuncture sessions were retrospectively reviewed. Each session lasted about 1 hour to allow relax both the patient and acupuncturist. Acupuncture was administered in a clinic outside the hospital, quiet and cozy. The program was divided in two sections. The first section sought to treat chemotherapy-related side effects such as nausea, vomiting, constipation, asthenia, dyspepsia and sensory neuropathy. This included two acupuncture sessions after the cycle of chemotherapy and then one session weekly up to maximum 10 sessions. The second section aimed to improve climacteric syndrome due to hormonal therapy, in particular hot flushes, tachycardia, anxiety or depression, insomnia and arthralgie. The treatment consisted of 10 weekly sessions of acupuncture.
We evaluated the severity of symptoms using a scale from 0 to 10, at baseline, in mid and at the end of treatment.
Results: The majority of patients obtained a significant reduction of severity of symptoms after the acupuncture, as shown in the Table. The scoring was at least halved for most of symptoms. Many patients did not require additional supportive care.

	Score (media) depending on time of the treatment		
	Baseline	Mid-treatment	At end of treatment
Chemotherapy-related adverse events			
Asthenia	8.5	6.07	5.07
Dyspepsia	7.5	4	1
Sensory neuropathy	7.72	5.6	4.7
Vomiting	6	0	0
Nausea	8.83	4.33	2.16
Constipation	8.2	5	4.4
Symptoms of climacteric syndrome			
Insomnia	8.31	5.18	3.81
Arthralgie	8.6	4.6	3.8
Tachycardia	8	4.5	2.5
Anxiety or depression	8.63	6.13	5.13
Hot flushes	7.5	1.5	1.5

Conclusions: We think that acupuncture is a promising complementary treatment to manage chemotherapy toxicities and climacteric syndrome. It may avoid the use of supportive therapies and their side effects. In addition, acupuncture has no adverse events related and it may prevent reductions or delays of anticancer treatment preserving its efficacy.
No conflict of interest.

Table (abstract 2001). Categorization of the change in tumor cellularity, tumor size (cm), and tumor size multiplied by cellularity according to clinical response and residual tumor stage

Variable	No.	Change in tumor cellularity			Tumor size (cm)		Tumor size × cellularity		
		Median	Range	Mean±SD	Median	Mean±SD	Median	Range	Mean±SD
CR	7	−0.25	6.24 (−0.58, 5.66)	0.66±2.22	4.9	5.5±2.1	1.09	39.7 (−34, 5.7)	−3.7±13.5
PR	16	0.12	6.47 (−0.92, 5.56)	0.41±1.49	1.3	1.88±1.7	−0.08	15.2 (−11.1, 4)	−0.74±3.2
NR	6	0.39	2 (−0.92, 1.12)	0.26±0.8	−0.05	−0.03±0.18	0	0.39 (−0.3, 0.09)	−0.03±0.14
PD	8	0.15	2.8 (−0.6, 2.28)	0.41±0.95	−0.55	−0.7±0.83	0.12	3.3 (−0.79, 2.5)	0.12±0.97
Tumor stage									
T3	20	0.33	6.6 (−0.92, 5.6)	0.68±1.7	−0.65	−0.96±1.84	0	36.4 (−33.9, 2.5)	−1.9±7.2
T4	17	−0.11	2 (−0.92, 1.12)	0.01±0.49	−1.3	−2.4±2.63	0.01	7.2 (−3.2, 4)	0.34±1.7

SD: standard deviation; CR: complete response; PR: partial response; NR: no response; PD: progressive disease.
Change in cellularity defined as (% tumor cellularity in core needle biopsy − % tumor cellularity in mastectomy specimen)/(% tumor cellularity in core needle biopsy). Negative values indicate lower cellularity at resection compared with the core needle biopsy specimens.

2003 POSTER

Cognitive functioning before adjuvant chemotherapy for breast carcinoma

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Background: The influence of chemotherapy on cognitive functioning has not been adequately described yet, and results of previously published studies provide equivocal results. Moreover, some studies show that cognitive decline may be present before introducing chemotherapy. The aim of the study is to assess and to compare cognitive functioning of patients starting different regiments of adjuvant chemotherapy for breast cancer.
Material and Methods: 66 patients with breast cancer qualified to neoadjuvant chemotherapy with AC (n = 41, mean age=54±8) or AC followed by T (n = 25, mean age=49±11) participated in the study.
Each patient was participated in a clinical interview, numerical rating scales to assess fatigue, sleep, mental and physical self-efficiency, depression and anxiety assessment using the Modified Hospital and Anxiety Depression Scale (HADS − M) and distress using the Distress Thermometer. The evaluation of cognitive functioning was carried out using the Trail Making Test A and B (TMT A &B) and the Stroop Color-Word Interference Test (SCWIT) and the Digit Symbol Substitution Test (DSST).
Results: It was found that patients qualified to AC performed significantly slower than patients qualified to AC followed by T in the TMT A ($z = -2.28$, $p = 0.023$), the TMT B ($z = -2.07$, $p = 0.039$) and second part of the SCWIT ($z = -3.17$, $p = 0.002$). In AC followed by T group significant negative correlation ($r = -0.42$, $p = 0.03$) between mental self-efficiency and time of performing TMT B was found. In this group significant positive correlation ($r = 0.4$, $p = 0.04$) between depression and time of performing SCWIT part 1 was found. In both groups significant positive correlations between distress, depression and anxiety were found.
Conclusions: Our results indicate that some aspects of cognitive functioning, such as psychomotor speed, attention or executive functions may differ in patients starting different regiments of adjuvant chemotherapy for breast cancer. Further analyzes will be performed.
No conflict of interest.

2004 POSTER

Post-mastectomy radiotherapy: Before or after reconstruction? A systematic review of the literature

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Background: The aim of this review is to investigate whether a difference exists in complication rate and satisfaction with cosmetic outcome between radiotherapy (RT) before or after breast reconstruction for autologous and implant reconstructions separately.
Methods: PubMed was searched for the period between January 2000 and December 2012. Of the 37 eligible studies, the type and incidence of complications were recorded, and if mentioned patient and physician satisfaction with cosmetic outcome. We calculated the weighted mean including confidence intervals for the incidence of complications and cosmetic outcome overall, and also per subgroup: 1) RT followed by autologous reconstruction; 2) RT followed by implant; 3) autologous reconstruction followed by RT; 4) implant followed by RT. Forrest plots were made for the most relevant complications.
Results: The reported data showed a large variation in complication rates (8.7%-70.0%) and acceptable cosmetic outcome (41.4%-93.3%). No significant differences were found in complication rate and cosmetic outcome, between the weighted means of the four subgroups. If the analyses were confined to studies that directly compared two groups (group 1/2 vs group 3/4), we found that overall, complications occurred less if RT was followed by reconstruction (OR 0.60 [0.38–0.96]. This was mostly ascribed to the subgroup of patients with an implant reconstruction (OR 0.22 [0.10–0.48] (Table). However, serious complications such as flap or implant failure occurred more if RT was followed by reconstruction (OR 5.02 [0.62–40.89] and OR 3.08 [1.62–5.86]), respectively. No significant difference was found for both patient and physician satisfaction regarding cosmetic outcome.
Conclusions: Reconstruction should be performed after RT, to minimize the total number of complications. However, to minimize the incidence of serious complications, it seems like RT given after reconstruction is better. Timing or type of reconstruction results in no statistical difference regarding cosmetic outcome.
No conflict of interest.

Table: Odds Ratio (OR) and 95% confidence intervals RT first versus reconstruction first. OR < 1: favours RT first; OR > 1 favours reconstruction first.

Study	OR RT first/reconstruction first	
	Autologous	Implant
Adesiyun (2010)	1.39 [0.52–3.76]	0.21 [0.05–0.88]
Lee (2010)	1.10 [0.42–2.85]	0.14 [0.03–0.62]
Carlson (2008)	0.64 [0.17–2.41]	
Anderson (2009)		0.32 [0.09–1.14]
Overall per type of reconstruction	1.07 [0.58–1.96]	0.22 [0.10–0.48]
Overall	0.60 [0.38–0.96]	

2005 POSTER

Clinical outcomes of the association trastuzumab–locoregional breast radiotherapy: A prospective monocentric study

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Background: Trastuzumab and adjuvant breast radiotherapy (RT) have individually proved their oncologic efficacy in terms of disease-free and overall survival. The aim of our study is to assess the clinical outcomes of the concurrent administration of trastuzumab to locoregional breast RT.
Material and Methods: Prospective monocentric study of 308 patients (pts) treated between 2000 and 2009 by trastuzumab administered concurrently to normofractionated adjuvant RT for localized breast cancer. Trastuzumab was delivered every three weeks for one year (8 mg/kg at the first infusion, then 6 mg/kg). Survival data were defined as the time from the histological diagnosis of breast cancer until the occurrence of the first event (locoregional or distant recurrence, or death). Locoregional or distant recurrence-free and alive pts were censored at the date of their last known contact. Survival and interval rates as well as their confidence interval (CI) were calculated using the Kaplan–Meier method. Multivariate analyses were performed using the Cox model.
Results: Median follow-up was 50 months (13–126). Median age at diagnosis was 52 years (25−83). The clinical tumour size at diagnosis was: T0 or T1 in 131 pts (43.4%), T2 in 122 pts (40.4%), and T3 or T4 in 49 pts (16.2%). A clinical lymph node involvement was observed in 132 pts (42.9%). Lumpectomy was performed on 189 pts (61.4%) and total mastectomy on 105 pts (34.1%). The median dose of trastuzumab was 6145 mg (1845–29180). Anthracycline- and taxane-based regimens were administered to 280 (90.9%) and 293 pts (95.1%), respectively. Hormonotherapy was prescribed to 157 pts (51.0%).
At 48 months, locoregional control rate was 95% 95% CI [92;98], distant control rate 93% [90;96] and overall survival rate 98% 95% CI [96;100]. Locoregional and distant recurrences were reported in 16 (5.2%) and 20 pts (6.5%), respectively. The main sites of locoregional and metastatic recurrence were the treated breast in 10 pts (3.2%) and the central nervous system in 5 pts (1.6%), respectively. In multivariate analysis, the clinical lymph node involvement at diagnosis and the absence of the hormone receptors expression were significantly associated with an increased risk of locoregional recurrence.
Conclusions: In this prospective study, the concurrent administration of trastuzumab to adjuvant breast RT leads to favourable outcomes in terms of locoregional and distant control. Further follow-up is needed to confirm these results.
No conflict of interest.

2006 POSTER

Five year outcomes of the hypofractionated three-dimensional conformal simultaneous integrated boost irradiation in breast conserving therapy

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Background: In 2005, we adopted three-dimensional conformal radiotherapy with a hypofractionated simultaneous integrated boost (3D-CRT-SIB)

technique as standard after breast conserving surgery. The aim of this report was to present the 5-year clinical outcomes of a large consecutive series of women with invasive breast cancer treated with 3D-CRT-SIB irradiation after breast conserving surgery and second to study prognostic factors for any recurrence.
Material and Methods: This retrospective study was composed of a consecutive series of 752 invasive breast cancer patients (stages I−III) treated with 3D-CRT-SIB as part of breast conserving therapy, from January 2005 to January 2008. Patients were irradiated with 28 fractions of 1.8 Gy to the whole breast and 2.3 Gy (76%) or 2.4 Gy (in case of focal irradicality) to the surgical bed. Median age was 58.4 (range 26−84) years. Survival curves, including the unadjusted 5-year actuarial rates of local control (LC), distant metastases free-survival (DMFS), and overall survival (OS) were estimated with the Kaplan–Meier method. Multivariate Cox proportional hazard analysis was used to investigate prognostic factors of any recurrence.
Results: Median follow-up was 60 (range 3−93) months. In total, 7 (1%) patients had an isolated in-breast recurrence, of which 5 were invasive and 2 pure DCIS histology. The unadjusted 5-year actuarial rates of LC, DMFS, and OS were 98.9% (95% CI 98.1–99.7), 94.2% (95% CI 92.4–96.0), and 93.3% (95% CI 91.3–95.3), respectively.
Patients with triple negative tumours (i.e., oestrogen receptor negative, progesterone receptor negative, and human epidermal growth factor receptor negative) and with larger tumours (>2 cm) were at higher risk of recurrent disease, compared to patients with receptor positive breast cancer (HR 2.0, 95% CI 1.0−4.0) and small tumours (HR 2.5, 95% CI 1.4−4.5). Furthermore, patients with more than 3 positive lymph nodes developed more recurrent disease, than patients with few or no positive lymph nodes (HR 2.7, 95% CI 1.2−6.0, N0 as reference group).
Conclusions: The use of the hypofractionated 3D-CRT-SIB as part of breast conserving therapy results in excellent 5-year local control rates. Triple negative tumours, tumours of >2 cm, and >3 positive lymph nodes were associated with recurrent disease.
No conflict of interest.

2007 POSTER

Multi-centre prospective randomised trial on breast conservative surgery (BCS) with and without whole breast irradiation (WBI) in postmenopausal women aged 55−75 and low in-breast-recurrence (IBR) risk: Analysis after 9 years medium follow-up − RT 55−75 Study Group

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Breast conserving therapy (BCT) including postoperative WBI has become treatment of choice for most patients with early stage breast cancer. The question whether WBI is mandatory in all patients still remains a heavily debated matter in BCT. In January 2001 a randomized prospective multi-centre study was launched to further explore the question. Until December 2005, 749 postmenopausal from 11 centres all over Italy were enrolled in the study. Patients aged 55−75, with completely excised unifocal infiltrating breast cancer up to 25 mm and widely clear margins, 0−3 positive axillary lymph-nodes, no extensive intraductal component or lymph-vascular invasion were eligible and were randomised between BCS + WBI (Arm 1: 373 pts) or BCS alone (Arm 2: 376 pts). Baseline characteristics were fairly well balanced between the two arms. Treatment allocation was centralized and stratified per site. All patients were included in efficacy analyses, which were conducted on intention-to-treat basis. All time events were computed from the date of randomization and Kaplan–Meier method was used for survival analysis with 95% confidence interval. Log rank test (alpha=0.05) was applied to evaluate the difference between the two arms. 50 % of the patients were aged 65 yrs or older, 88% had pT1, 85% pN0, 92% ER +ve, 87% G1 or G2 disease. EIC or LVI was absent in all cases. 87 % received adjuvant endocrine therapy alone.15 % adjuvant chemotherapy alone or in combination with hormonal treatment. Primary end-points of the study were to assess the cumulative incidence IBR and overall survival (OAS) after BCS with or without WBI. After median follow-up of 9 years, 12 IBR (3.4%) were observed in arm 1 and 16 (4.4%) in arm 2. OAS was 81.4% in arm 1 and 83, 7% in arm 2. There was no statistically significant difference regarding IBR and death in the two treatment groups. These data are promising and suggest that WBI after BCS can be omitted in selected patients without increased risk of IBR and death.
No conflict of interest.

Treatment arm	Type of disease progression					
	No	Distant	Local		Contralateral BC	Total
			Other quadrants	Index quadrant		
BCT+WBI (Arm 1)	329 88.20%	26 6.97%	5 1.34%	7 1.88%	6 1.61%	373
BCT alone (Arm 2)	327 86.97%	28 7.45%	9 2.39%	7 1.86%	5 1.33%	376
Total	656	54	14	14	11	749

2008 POSTER

Skin and oesophageal toxicities of the association trastuzumab-locoregional breast radiotherapy: A prospective monocentric study

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Background: Trastuzumab and breast radiotherapy (RT) both expose the treated patients (pts) to an increased risk of cardio-vascular events. However, the adverse effects regarding the other healthy organs are less well-known. The aim of our study is to assess the skin and oesophageal toxicities of concurrent trastuzumab with adjuvant RT in breast cancer.
Material and Methods: Prospective monocentric study of 308 pts treated between 2000 and 2009 by concurrent trastuzumab to normofractionated locoregional RT for localized breast cancer. Trastuzumab was delivered every three weeks for one year (8 mg/kg at the first infusion, then 6 mg/kg). All toxicities were described using the *Common Terminology Criteria for Adverse Events* v3.0. Clinical assessment was performed weekly during RT, and, after the completion of the irradiation, every 6 months for 5 years, then annually.
Results: Median follow-up was 50 months (13–126). Median age at diagnosis was 52 years (25−83). Anthracycline-, taxane- and 5-fluorouracil-based chemotherapy regimens were administered to 280 (90.9%), 293 (95.1%), and 242 pts (78.6%), respectively. Median dose of trastuzumab was 6145 mg (1845–29180).
RT treated the mammary gland and the chest wall in 193 (62.7%) and 115 pts (37.3%), respectively. The internal mammary nodes (IMN) were irradiated in 227 pts (73.7%). Median delivered doses were: 50 Gy (41−55) to the breast, 50 Gy (43−52) to the chest wall, 66 Gy (41−77) to the tumour bed, and 46 Gy (40−52) to the IMN.
In the 6 months following the initiation of RT, acute epithelitis was reported in 305 pts (99.0%), with 226 (73.4%) grade 1, 67 (21.8%) grade 2 and 12 (3.9%) grade 3 skin reactions. Acute oesophagitis was observed in 31 pts (10.1%): 26 (8.4%) grade 1, 4 (1.3%) grade 2 and 1 (0.3%) grade 3.
With a median time of 23 months (1−54) since the completion of RT, the first clinical assessment regarded 286 pts (92.9%). Among them, grade 1 late skin fibrosis was described in 53 pts (18.6%), grade 2 in 20 pts (7.0%); grade 1 telangiectasia in 14 pts (4.9%) and grade 2 in 10 pts (3.5%). Grade 1 mammary pain was observed in 39 pts (13.7%), grade 2 in 8 pts (2.8%), and grade 4 in 2 pts (0.7%; no grade 3 reported). Grade 1 late oesophagitis occurred in 1 patient (0.3%).
Conclusions: In this prospective study of pts treated by concurrent trastuzumab with locoregional breast RT, the skin and oesophageal toxicities remained mild. Further follow-up is warranted to verify these results.
No conflict of interest.

2009 POSTER

An objective assessment of cosmetic outcome after intraoperative radiotherapy or external beam radiotherapy for early breast cancer in patients from a randomized controlled trial

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Background: Non-inferiority between the novel technique of TARGIT (Intra-operative radiotherapy with Intrabeam ®) and conventional whole-breast external beam radiotherapy (EBRT) in women with early breast cancer, in terms of the primary outcome measure of risk of local relapse within the treated breast, has been demonstrated in the international randomised contolled TARGeted Intraoperative radioTherapy (TARGIT) trial. The very low recurrence rates have increased the importance of cosmesis as an outcome after breast conserving treatment with both surgery and radiotherapy. This study was performed to determine if the single high dose of TARGIT leads to impaired cosmesis, compared with a fractionated dose of radiotherapy given as EBRT.
Material and Methods: BCCT.core software is a validated, objective assessment tool for the evaluation of cosmetic outcome from frontal digital photographs. Images were analysed at baseline (before TARGIT or EBRT) and yearly thereafter for up to five years. The analysis produces a composite score (Excellent, Good, Fair, Poor) based on symmetry, colour and scar.
Results: 342 patients from two centres participating in the TARGIT Trial were assessed. All were over 50 years old with a median age at baseline of 64 years (IQR 59 to 68). Scores were dichotomised into Excellent and Good (EG), and Fair and Poor (FP). There were statistically significant increases in the odds of having an outcome of EG for patients who received TARGIT group relative to those who received EBRT group at year 1 (OR=2.07, 95% CI 1.12 to 3.85, p = 0.021) and year 2 (OR=2.11, 95% CI 1.0 to 4.45, p = 0.05).
Conclusions: This objective assessment of aesthetic outcome in patients from a randomised setting demonstrates that those treated with targeted intraoperative radiotherapy have a superior cosmetic result compared with those patients who received conventional whole-breast external beam radiotherapy.
No conflict of interest.

2010 POSTER

Analysis of different clinical target volumes of whole breast after breast-conserving surgery based on three-dimensional CT and four-dimensional CT images

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Background and Purpose: The four-dimensional CT (4D-CT) has more information of tumour movement comparing with three-dimensional CT (3D-CT) during the whole respiratory. However, the workload of target delineation for the whole breast was heavier and the capacity of workload on the target delineation was increased greatly. In order to identify the necessary of the 4D-CT used for simulation in the IMRT of the whole breast after breast-conserving surgery, this study investigated the difference of the clinical target volumes of whole breast (CTVs) based on 3D-CT and the 4D-CT for patients after breast-conserving surgery.
Materials and Methods: Thirteen patients after breast-conserving surgery underwent 3D-CT simulation scans followed by 4D-CT simulation scans of the thorax during free breathing. Then data sets for 3D-CT and 4D-CT scans were transferred to Eclipse treatment planning software. The clinical target volumes (CTVs) of whole breast were manually delineated on the registered images of the 3D-CT, 4D-CT and maximum intensity projection (MIP) images by a radiologist under the same delineation criteria. And all the CTV delineated on the 10 phases of the 4D-CT images were fused into an internal target volume (ITV). The CTV_0, CTV_{20}, CTV_{50}, CTV_{MIP}, CTV_{3D} were defined on 0%, 20%, 50%, MIP and 3D-CT images. The volumes of the CTV, the matching index (MI) and the degree of inclusion (DI) were compared respectively.
Results: There was no difference in the CTV delineated by the same radiologist no matter based on 3D-CT or 4D-CT (P >0.05). The volume demonstrated no significant difference between CTV_{3D} and CTV_0, CTV_{20}, CTV_{50}, CTV_{MIP} (P >0.05). The difference of the MI and DI between CTV_{3D} and CTV_0, CTV_{20}, CTV_{50} was not statistically significant as well. The volume of ITV was larger than that of CTV_{3D} and CTV_{MIP}, the DI of ITV in CTV_{3D} and CTV_{MIP} Vs. DI of CTV_{3D} and CTV_{MIP} in ITV were significant as well (P <0.05).
Conclusions: The 3D-CT and MIP showed limited target movement information and it would not be a reliable clinical approach to replace 4D-CT by 3D-CT and MIP images when the clinical target volume of the whole breast was been delineated. It was more reasonable to construct ITV of whole breast based on 4D-CT after breast-conserving surgery.
No conflict of interest.

2011 POSTER

Breath hold and volumetric IMRT for accelerated partial breast irradiation (APBI)

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Purpose/Objective To investigate the effect of using volumetric modulated arc therapy (VMAT) and/or voluntary moderately deep inspiration breath-hold (vmDIBH) for patients treated with external beam APBI.
Materials and Methods: For three left-sided breast cancer patients, two CT-scans were acquired, in free breathing (FB) and in vmDIBH. On each scan, five tumour volumes were contoured: upper-inner, lower-inner, central, upper-outer, and lower-outer. For each tumour location 3D conformal radiotherapy (3D-CRT) and VMAT plans both in FB and vmDIBH were made. The prescribed dose was 38.5 Gy given in 10 fractions, two fractions per day. Dose parameters for the planning target volume (PTV), heart, lungs, ipsilateral (IL) non-involved and contralateral (CL) breast were assessed and compared.
Results: VMAT dose conformity was significantly better compared to that of 3D-CRT (conformity index =0.8±0.1 vs. 0.6±0.1). The PTV volume covered with 95% of the prescribed dose increased from 94.6% for 3D-CRT to 98.7% for VMAT. IL breast receiving ⩾50% of the prescribed dose was on average reduced by 30% with VMAT compared to 3D-CRT. For dose to heart and ipsilateral lung, the tumours were grouped: 1) inner and central location, and 2) outer location. For group 1, the mean heart dose decreased from 2.1±1.8 Gy for 3D-CRT(FB) to 1.0±0.9 Gy with VMAT(FB), and 0.6±0.5 Gy for VMAT(vmDIBH). The heart V5 Gy was reduced to 2.3% with VMAT(vmDIBH) compared to 14.9% and 3.8% with 3D-CRT(FB) and 3D-CRT(vmDIBH). For group 2, the mean heart dose was 0.2−0.5 Gy for all techniques. The heart V5 Gy was 3.2% in 3D-CRT(FB) plans, while no heart received 5 Gy in VMAT(vmDIBH). VMAT(vmDIBH and FB) resulted in significant reduction of the ipsilateral lung dose: V5 Gy = 8.8±7.6% vs. 24.2±1.7% for 3D-CRT(FB). VMAT showed a slight but acceptable increase in the maximum CL breast dose (from 0.8 to 4 Gy), with the mean dose always below 1 Gy.
Conclusions: APBI with VMAT offers improved PTV dose conformity and delivers lower doses to the ipsilateral breast and lung compared with 3D-CRT, at the cost of a slightly higher but acceptable dose to the contralateral breast. VMAT shows the largest reduction in heart dose for patients with tumours in the inner and central parts of the breast. Combining VMAT and vmDIBH only slightly reduces the heart dose further.
No conflict of interest.

2012 POSTER

Screening patients for deep inspiration breath hold to reduce cardiac doses for adjuvant left breast irradiation

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Background: When delivering radiotherapy to left-sided breast cancers, deep inspiration breath hold (DIBH) using active breath control (ABC) can significantly reduce radiation dose to heart and coronary arteries in selected patients. Currently, at our institution a cutoff of heart V50% >10cc is used to determine which patients require ABC. This dose-volume measurement requires generation of a radiation plan to select patients for ABC, delaying the second ABC CT simulation. The purpose of this study is to determine if simple 2-D measurements of the heart at the time of CT simulation can adequately screen patients for ABC. This would facilitate a streamlined process that minimizes delays for left-side breast radiation.
Materials and Methods: This study evaluated CT simulation scans from 50 randomly selected left-sided breast cancer patients treated with tangent RT alone from November 2009 to August 2012 (era when ABC was standard), where 50% of these patients were treated with ABC and 50% were not. On each CT dataset, a tangential line was drawn between the medial

and lateral tattoo and the following heart measurements were recorded by a blinded observer at 2, 3, 4, and 5 cm below the tattoos: (1) maximal heart distance (MHD) perpendicular to this line and (2) heart length (HL) along this line. The first 20 cases were measured by 2 observers to test interobserver variation. Correlation between each measurement and heart V50 (from the delivered RT plan) was calculated using linear regression. T-test was used to evaluate the association between heart measurements and ABC use. Predictive models were created using two strategies; (1) using a step wise approach utilizing the most significant factor and (2) using principle component analysis.
Results: 49 patients were analyzable as the heart dose from one patient was not available. Analysis of the first 20 patients shows the heart measurements between the two observers were similar with a correlation coefficient of 0.93 for the MHD and 0.94 for HL. For the 49 patients, the HL at 2 cm had the highest association with V50 (R^2 = 0.45; p < 0.0001). The other values that were significantly associated with V50 were HL at 3 cm (R^2=0.37; p= <0.0001), MHD at 2 cm (R^2=0.25; p = 0.0003), MHD at 3 cm (R^2=0.23; p = 0.0006) and HL at 4 cm (R^2=0.17, p = 0.0035). The predictive model using the most significant variable (HL at 2 cm) gave an adjusted R^2=0.4385 (P<0.0001). Adding other variables into the predictive model did not improve the adjusted R^2.
Conclusions: The results of this study suggests that a simple 2-D heart measurement, heart length across a line connecting the 2 tattoos at 2 cm, shows moderate correlation with the irradiated heart volume in the delivered RT plan. Although the correlation was modest, this may serve as an easy screening tool to select patients who may benefit from ABC. Appreciating the limitations of our retrospective study, validation of this predictive model is ongoing.
No conflict of interest.

2013 POSTER

Irradiation of the internal mammary nodes in breast cancer patients with morphologically verified metastasis at this zone

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Objective: Detection of regional lymph nodes involvement is an extremely important step in the diagnosis and treatment of breast cancer. As with axillary lymph node metastases, parasternal lymph nodes metastases are an important prognostic factor.
Goal: To detect metastasis in the internal mammary lymph nodes (IMN) and to find out the best way of radiation therapy at this zone.
Material and Methods: Retrospective study of 1125 patients with breast cancer who underwent thoracoscopic internal mammary lymphadenectomy in 1998–2008 was performed. Metastases were found in 204 of 1125 cases (18.3%), representing 33.9% of all cases of regional metastases (n = 601). Only patients with metastasis had radiation therapy at IMN zone. Standard regimen (2 Gy x 25, total 50 Gy) underwent 87 patients (42.6%) − Group A, hyperfractionated regimen (3 Gy x 13, total 39 Gy) − 80 patients (39.2%) − Group B, no radiation − 37 patients (18.1%) − Group C.
Results: No difference in overall survival was registered in all three groups. Median disease free survival was significantly worth in Group C (5.5 years) in comparison with Group A (7.8 years) and Group B (not achieved).
Conclusion: We believe that the thoracoscopic internal mammary lymphadenectomy should be a part of the diagnostic process in patients with breast cancer. Irradiation of IMN leads to better disease-free but not to overall survival at 8.1 years median follow up. Hyperfractionated regimen could be safely used for breast and IMN irradiation.
No conflict of interest.

2014 POSTER

Case selection for targeted intraoperative radiotherapy (TARGIT)

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Background: The TARGIT-A randomised trial compared a risk-adapted approach using targeted intraoperative radiotherapy (TARGIT) with whole breast external beam radiotherapy (EBRT) after lumpectomy for early breast cancer. At the San Antonio update, it was suggested that the preferred option is to give TARGIT concurrently with lumpectomy (prepathology). In this analysis we describe patient and tumour factors that may help select patients for TARGIT based on the results of an *a priori* statistical analysis plan.
Methods: In this large international trial, 3451 patients (age>=45, unifocal invasive ductal carcinoma, size $\leqslant$3.5 cm) from 33 centres in 10 countries were randomly allocated to either TARGIT or EBRT. Primary outcome was ipsilateral breast recurrence and secondary included mortality. Before unblinding for this analysis, we hypothesised that progesterone receptor (PgR) status, as an expression of a functionally active oestrogen receptor (ER), is a surrogate for radiation responsiveness and could predict a difference between the outcome for local control in the two randomised groups and pre-specified a detailed analysis by PgR status. We also assessed whether a Cox proportional hazard model including age, margin status, tumour grade, ER, PgR, HER2, vascular invasion and node positivity was consistent with our results.
Results: For PgR positive cases, there was no significant difference in the primary outcome of Ipsilateral breast recurrence between TARGIT and EBRT (2.3%(1.3−4.3) vs. 1.5%(0.75−3.0) p = 0.51, while in PgR negative cases there were significantly more local recurrences after partial breast irradiation using TARGIT: 7.0%(3.5–13.6) vs. 0.5%(0.1−3.7) p = 0.017. By contrast, age, margin status, tumour grade, tumour size, vascular invasion, node positivity, ER and Her2 status were not found to be significant predictors. Even age younger than 50 or grade 3 cancers had similar outcome with TARGIT or EBRT. Exploratory analyses in conjunction with the timing of TARGIT, revealed that when TARGIT was given concurrently in PgR positive cases (n = 1625) the results were (TARGIT vs. EBRT): ipsilateral breast recurrence 4 vs. 5, 5-year risk 1.4%(0.46−3.9) vs. 1.2%(0.48−2.9) HR 0.82(0.22–3.06), and overall mortality 18 vs. 31, 5-year risk 3.3%(1.83–6.04) vs. 6.4%(4.3−9.6) HR 0.60(0.34–1.08).
Conclusions: It appears that progesterone receptor status is useful in selecting cases for using the TARGIT concurrently with lumpectomy for breast cancer. Progesterone receptor negative patients may fall in the cautious or unsuitable category and progesterone receptor positive cases are in the suitable category for partial breast irradiation with TARGIT.
Conflict of interest: *Other substantive relationships: Carl Zeiss (travel to meetings and honoraria).*

2015 POSTER

Late toxicities and outcomes after one year of adjuvant radiotherapy associated with concurrent bevacizumab in patients with non-metastatic breast cancer

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Background: Few data are available regarding the safety of the concurrent combination of bevacizumab (BV) with adjuvant locoregional radiotherapy (RT) for breast cancer, especially in terms of late toxicity. The aims of this study were to determine late toxicities and outcomes among patients with non-metastatic BC treated with this combination.
Materials and Methods: In our multicenter prospective and descriptive study, we analyzed toxicities of adjuvant RT in patients with non-metastatic BC receiving concurrent BV. Early and late toxicities were assessed by the Common Terminology Criteria for Adverse Events (v3.0). Evaluation was done 12 months after the end of RT. All patients provided written informed consent before enrollment.
Results: Among patients enrolled in our study from October 2007 to August 2010, evaluation at 12 months was available for 63 patients. Mean age was 51 years. Among tumors, 17% were luminal BC, 24% HER2+ and 70% triple negative. A total of 56 patients had an invasive ductal carcinoma. Nineteen patients were stage I (30%), 21 patients stage II (33%) and 22 patients stage IIIB (35%) without patients stage IV (no data for one patient). A total of 23 patients (37%) received neoadjuvant chemotherapy plus BV followed by surgery then RT whereas 40 patients (63%) had surgery followed by adjuvant chemotherapy plus BV then RT. A total of 28 patients (44%) achieved post mastectomy RT and 35 patients (56%) had a whole breast RT with a boost in the surgical bed. Lymph node RT was performed in 42 patients (67%) with internal mammary chain RT in 25 patients (40%). Concurrent trastuzumab with RT and BV was performed in 15 patients (23%). Mean time of BV treatment was 10.2 months (2−13)

and mean total dose of BV was 15085 mg (960–28080). One year after the end of the RT, the most common late toxicities were grade 1−2 pain (11%), grade 1 arm lymphedema (6%), grade 2 arm lymphedema (2%), grade 1 fibrosis (5%). No patients were identified to have ⩾ grade 3 late toxicity. One patient had a grade 1 arterial hypertension and one patient had a grade 1 ventricular extrasystoles. An asymptomatic grade 2 left ventricular systolic dysfunction occurred in one patient. One year after RT and concurrent BV, overall survival was 100% and no locoregional or metastatic relapse were reported.

Conclusions: Our results indicate that concurrent BV with loco-regional RT provide acceptable late toxicities after one year in patients with non-metastatic BC.

No conflict of interest.

2016 POSTER

Intraoperative radiotherapy using the Intrabeam® device as intraoperative boost in breast conserving therapy − a single institution experience after the first 200 cases

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Background: The concept of breast conserving therapy in breast cancer consists of a segmental resection followed by whole breast irradiation with a dose of 50 Gray. The expected local recurrence rate in 5 year follow-up is 7.6%, after adding a boost irradiation of the index region with a dose of 10 to 16 Gray 4.3%. The boost irradiation as an intraoperative procedure using the Intrabeam® device showed a further decrease of local recurrence rates down to 1.75% in 5 year follow up. In our study we investigated the influence of this procedure on the duration of the operation, the postoperative hospitalisation and the cosmetic results.

Methods: We collected the data of the first 200 patients treated with the Intrabeam® device during breast conserving therapy in our institution since April 2010. 60 (30 %) of the 200 patients had been treated with neoadjuvant chemotherapy +/− Trastuzumab. After the end of the whole breast irradiation we collected data concerning the satisfaction of the patients and their doctors with the cosmetic outcome. To investigate the influence on the duration of the operation and the hospital stay, we then compared the data of the first 200 patients treated with the Intrabeam® with the data of 200 patients, who had breast conserving therapy, before we started using the Intrabeam® but who would have been feasible for intraoperative radiotherapy.

Results: The data concerning the satisfaction with the cosmetic result are described in table 1.

Table 1. Satisfaction with the cosmetic results after completion of the whole breast irradiation (in %)

	Excellent	Good	Satisfying	Acceptable	Poor	Inacceptable
Patients	6	63	23	6	2	0
Gynecologists	9	59	27	2	3	0

The average duration of the surgical procedure was 99.61 min in the cohort with intraoperative radiotherapy. We could see a learning curve between the first 100 and the second 100 cases. In the first 100 cases the time duration was 104.29 min, in the second 100 cases this time was markedly shorter with 94.93 min. The average duration of the operation in the cohort without intraoperative radiotherapy was 67.07 min. The average prolongation of the duration of the surgical procedure was 32.54 min.

The hospital stay differed moderately with 2.2 days without and 3.3 days with intraoperative radiotherapy. The reason for the prolongation in most of the cases was a need for a later removal of the drainage in the intraoperatively radiated patients.

Conclusions: Intraoperative Radiotherapy with the Intrabeam® device is easy to integrate into daily clinical practice. The prolongation of the duration of the surgical procedure of about half an hour and of the hospital stay of one day are absolutely tolerable if seen in relation to the expected better local control. The satisfaction with the cosmetic result in 92% of the patients and 95% of the physicians is an indicator, that intraoperative radiotherapy doesn't lead to a compromise in the oncoplastic approach.

No conflict of interest.

2017 POSTER

Comparison of the volume and localization of internal gross tumor volume and planning target volume delineated by clips and seroma based on 4DCT scan for external-beam partial breast irradiation after breast conserving surgery

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Background: To explore the volume and localization of internal gross tumor volume(IGTV) and planning target volume delineated separately by metal clips, seroma, both clips and seroma based on four-dimensional computed tomography (4DCT) during free-breathing(FB).

Material and Methods: Fifteen early-stage breast cancer patients after breast-conserving surgery were recruited for EB-PBI. The gross tumor volume formed by clips, seroma, both clips and seroma were defined as GTVc, GTVs and GTVc+s, respectively. GTVc, GTVs and GTVc+s were delineated by one radiation oncologist on the ten sets CT images. The IGTVc, IGTVs, IGTVc+s were combined by GTVc, GTVs and GTVc+s on ten sets CT images, respectively. The PTVc, PTVs, PTVc+s were formed by adding 15 mm margin to IGTVc, IGTVs, IGTVc+s, respectively. The IGTV and PTV volume and the distance between the center of IGTV/IGTV, PTV/PTV were recorded. Dice similarity coefficient(DSC) of IGTV/IGTV, PTV/PTV were calculated.

Results: The volume of IGTVc+s was significantly larger than IGTVc and IGTVs($p < 0.05$), and the volume of PTVc+s was significantly larger than PTVc and PTVs($p < 0.05$). DSC of PTVc/PTVs, PTVc/PTVc+s, PTVs/PTVc+s were significantly superior to IGTVc/IGTVs, IGTVc/IGTVc+s, IGTVs/IGTVc+s. DSC of IGTVc/IGTVs (0.56 ± 0.14) was significantly inferior to IGTVc/IGTVc+s (0.76 ± 0.12) and IGTVs/IGTVc+s (0.69 ± 0.15). The difference among DSC of PTV/PTV was not statistically significant($F=0.408$, $p = 0.668$). DSC of IGTVc/IGTVc+s, IGTVs/IGTVc+s, PTVs/PTVc+s were negatively correlated with their centroid distance($r<0$, $p < 0.05$).

Conclusion: The volume of IGTVc+s was significantly larger than IGTVc and IGTVs, and the volume of PTVc+s was significantly larger than PTVc and PTVs. DSC of PTV/PTV was significantly superior to IGTV/IGTV. The spatial mismatch of IGTVc/IGTVc+s, IGTVs/IGTVc+s, PTVs/PTVc+s were negatively correlated with their centroid distance.

No conflict of interest.

2018 POSTER

Changes in tumor shadows and microcalcifications on mammography image analysis in elderly patients with stage I/II breast cancer following KORTUC II, a new radiosensitization treatment

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Background: We have employed non-surgical therapy using a novel enzyme-targeting radiosensitization treatment, Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, Type II (KORTUC II) for patients with early-stage breast cancer treatment. KORTUC II can convert low linear energy transfer (LET)-radioresistant tumors into radiosensitive tumors on the basis of the radiosensitizing action of one of its components, hydrogen peroxide.

The purpose of this study was to examine changes in tumor shadows and microcalcifications on mammography (MMG) in elderly patients with breast cancer following KORTUC II treatment.

In addition to MMG, positron emission tomography-computed tomography (PET-CT) was performed to detect both metastasis and local recurrence.

Material and Methods: Patients with breast cancer but no clinical evidence of distant metastasis were enrolled in the KORTUC II trial.

Radiation therapy (RT) with 4 MV X-ray. Hypofractionated RT was administered using a tangential field approach: the total dose was 44 Gy administered as 2.75 Gy/fraction.

The new radiosensitizer was injected into the breast tumor tissue twice a week under ultrasonographic guidance.

Therapeutic effects of KORTUC II were evaluated in terms of the changes in size of tumor shadows and microcalcifications shown on the monitor before and after KORTUC II. Changes of tumor density on MMG were also analyzed using image analysis software image-J. PET-CT was also performed during follow-up to detect both metastasis and local recurrence.

Results: In all 14 patients in this study, tumor shadows on MMG completely disappeared within several months after KORTUC II treatment. Microcalcifications also disappeared or markedly decreased in number.

As a result the image analysis that disappearance of the tumors was also confirmed by the profile curve of tumor density on MMG following KORTUC II treatment; density fell and eventually approached that of the peripheral mammary tissue in 3 months following KORTUC II treatment.

These 14 patients have so far shown neither local recurrence nor distant metastasis also on PET-CT with a mean follow-up period of approximately 72 months at the end of October 2012.
Conclusion: We concluded that breast-conservation treatment using KORTUC II followed by aromatase inhibitor is a promising therapeutic method for elderly patients with breast cancer, in terms of avoiding any surgical procedure. Moreover, MMG is considered to be useful for evaluating the efficacy of KORTUC II.
No conflict of interest.

2019 POSTER

Actual dose delivery of vmDIBH in breast cancer patients is at least as good as in free breathing

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Purpose: Different breathing movement management techniques have been described which effectively spare the heart in tangential breast irradiation. The easiest and cheapest way is voluntary moderately deep inspiration breath hold (vmDIBH), but reproducibility, and thus actual dose delivery, of this method is unclear. The aim of this study is to determine whether the 2D measured delivered transit dose during vmDIBH is comparable to the dose delivered during free breathing (FB).
Material and Methods: Data of 30 patients irradiated during vmDIBH and 29 patients irradiated in FB were analyzed. Patients were irradiated to a total dose of 42.7−50 Gy in 16−25 fractions using a forward IMRT technique and a Shrinking Action Level protocol (α=10, n = 3) for set-up verification. 2D transit EPID dosimetry for the tangential fields was performed on various days, resulting in 580 measurements in 16 vmDIBH patients and 257 measurements in 15 FB patients. The measured transit dose was compared with a predicted transit dose by calculating percentage of pixels exceeding gamma criteria, using 5% as the dose-difference criterion and 5 mm as the distance-to-agreement criterion. The percentage of pixels exceeding 10% was determined for each measured fraction, for both latero-medial and medio-lateral beams. Mean values of this parameter for vmDIBH patients were compared to FB patients. Measurements exceeding 10% gamma were visually classified in translations (set-up error/organ motion) or other causes (breast shape, rotation). The translation classification is assumed the only cause of differences in measured dose between vmDIBH and FB.
Results: The percentage of pixels exceeding gamma criteria was 12.2% (+/−10.9) in vmDIBH patients and 10.9% (+/−10.1) in FB patients ($p > 0.05$). The percentage of fractions that exceeded the 10% gamma criteria was 44 +/− 11% (1 SD) in vmDIBH patients and 36 +/−11 % (1 SD) in FB patients. In both patient groups, 11.0% of the measured abnormalities were caused by translations.
Conclusion: Dose delivery in breast cancer patients irradiated during vmDIBH, as verified *in vivo* with 2D EPID dosimetry, is as accurate as in patients irradiated during FB.
No conflict of interest.

2020 POSTER

Dosimetry and toxicity among patients treated in the prone versus dorsal position with intensity modulated radiotherapy (IMRT)

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Background: Since 2011, all adjuvant breast cancer patients are treated with fixed-angle IMRT or VMAT at the Champalimaud Cancer Center (n = 369). The standard fractionation scheme has become 16 × 2.66 Gy or 15 × 2.7/3.2 Gy with integrated boost. Plans show excellent target coverage, also in lymph node areas (48% of our patients), low maximum dose (Dmax average, 107.28%) and good dose homogeneity (median 1.05). With a minimum of 6 months' follow-up, the treatment was very well tolerated, including women with large breast volumes. In the first patients pneumonitis was observed (8 cases at 6 months), probably due to a large low dose bath (V5>70%). Since the introduction of a stricter dose constraint for V5 only one new case (large breasts) has been observed. To reduce further the pulmonary dose, a prone board (CIVCO Horizon) was introduced.
Methods and Materials: All patients, since January 2013 (n = 47) were planned in both dorsal and prone position with full fixed angle IMRT. Treatment was mostly performed in dorsal position but all patients underwent at least one conebeam scan in prone position to evaluate the reproducibility.
Results: IMRT resulted in good target coverage and homogeneity in both dorsal and prone position. In means of lung and heart exposure not all patients benefitted from prone position. For the left sided patients, often, more heart dose was required for PTV coverage without exposure of the contralateral breast. Delineation of lymph node regions and boost was often debatable among doctors. For treatment repositioning in prone was more difficult, needing more tattoos, security margins and daily conebeam scans.
Conclusion: Altogether, hypofractionated breast full fixed angle IMRT results in homogeneous dosimetry and yields a confirmed benefit in terms of toxicities. The extra benefit of prone position is moderate and not only anatomy dependent. Prone positioning needs daily imaging and extra tattoos to be as reproducible as the dorsal treatment. Further investigation is needed to harmonize target definition and improve reproducibility of prone irradiation before accepting prone IMRT as a standard of care.
No conflict of interest.

2021 POSTER

Adjuvant radiotherapy for skin-sparing mastectomy versus conventional mastectomy − retrospective comparative analysis from a single institution

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Background: The Skin-Sparing Mastectomy (SSM) advocates the preservation of the skin and allows immediate breast reconstruction with better cosmetic results and higher patient satisfaction. Although the widespread of SSM technique, there is still some concern if native skin preservation could increase the risk of local recurrence in breast cancer.
Endpoint: *Primary endpoints*: To evaluate the recurrence-free survival (RFS) of patients submitted to SSM and conventional mastectomy (CM) and its impact on adjuvant radiotherapy decision.
Secondary endpoints: To assess the rates of distant recurrence and complications/loss of the prosthesis with different techniques.
The endpoints were also studied according to the following variable: age, tumor grade histology, angiolymphatic invasion (ALI), margins status, stage, nodal involvement, and associated treatments.
Materials and Methods: From January 2009 to December 2010 260 patients were submitted do mastectomy at Barretos Cancer Hospital, Brazil. All the records and chart were retrospectively evaluated. Adjuvant radiation therapy was defined according to physician discretion, although there was no recommendation to change the approach for SSM.
The chi-square test was used for comparison between variables and. Kaplan–Meier and long-rank test were used to evaluate outcomes and the confidence interval adopted was 95%.
Results: The median follow-up was 32.4 months. Two years RFS for all patients was 94.4% and there was no statistically difference between RFS according to mastectomy approach (SSM =100% vs MC =93.2%, $p = 0.053$). Pathological and clinical stage, tumor grade histology, tumor size, nodal involvement, angiolymphatic invasion, adjuvant and neoadjuvant chemotherapy were prognostic factor for RFS.
Complications were more frequent in SSM (26.7% vs. 3.7%, $p < 0.001$).
Skin sparing mastectomy was not associated with different criteria for adjuvant radiation therapy when compared with the institutional protocol for CM.
Conclusion: In our experience SSM does not appear to result in higher local recurrence in 2 years when compared to CM. Radiation oncologist did not change their criteria to define RT despite of mastectomy technique.
No conflict of interest.

2022 POSTER

Acute and late toxicity with hypofractionated radiation therapy for early breast cancer compared to conventional radiotherapy

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Background: The purpose is to evaluate toxicity and cosmetic outcome in breast cancer survivors treated with hypo-fractionated radiotherapy (HFRT) and to identify risk factors for toxicity. For comparison, a group of 65 patients with similar characteristics and consecutively treated with conventional fractionation was retrospectively selected.
Materials and Methods: From April 2010 and September 2012, 240 women with early breast cancer were treated with HFRT, after conserving surgery. The patients received 40.05 Gy in 15 fractions. The boost to the tumour bed was administered with a total dose of 9 Gy in 3 consecutive fractions in 74 women due to young age (<50 yrs) or to positive margins. Eligibility criteria were: T<5 cm, age>18 years, no indication to lymph nodal RT (<3 positive lymph-nodes). Physician-rated toxicity and

cosmetic outcomes were prospectively assessed during yearly follow-up after radiotherapy.
Results: In the HFRT group, the mean age was 69 years. 11% and 32% patients were affected by diabetes mellitus and hypertension, respectively. 13% had tumours that were 2 cm or larger in diameter; pTis = 17%, pT1a= 6%, pT1b= 23%, pT1c=41%, pT2=13%; 10% had oestrogen-receptor-negative disease and 29 % had high-grade disease. Pre-operative chemotherapy was administered in 10 patients; adjuvant systemic therapy and hormone therapy were given in 24 patients, while 11 and 205 patients received chemotherapy or hormone therapy alone, respectively. The mean follow-up was 19 months (range 6−32 months). The median time from surgery was 29 days, with overall median treatment duration of 22 days. By the end of RT 18% of the patients treated with HFRT developed no toxicity, while 55.7% showed grade 1 and 13.3% grade 2 acute skin toxicity. Only one patient experienced a grade 3 acute skin toxicity. In the control group, early G1 reactions were observed in 24 patients (42%); 19% of patients showed G2 acute toxicity and only one patient developed G3 acute reaction. Late toxicity was assessed after 6 months from RT completion in 120/190 patients in the HFRT and in 51/65 patients in the standard RT group. Late toxicity according to the RTOG criteria was observed in 9 patients (7.5%) in the HFRT group and in 4 patients (8%) in the conventional fractionated radiation group. The difference was not statistically significant. Cosmetic result was assessed and scored at the RT end and 6 months later: at last follow up, 71% of women in the control-group as compared with 68.8% of the women in the HFRT group had a good or excellent cosmetic outcome. The boost and chemotherapy resulted predictive factors of radiation-induced toxicity ($p < 0.03$). We don't found any significant association between cosmetic outcome and the examined variables.
Conclusions: Our results confirm the feasibility of the HFRT in patients with breast cancer. If compared with conventional RT group, the HFRT not seems to increase the late toxicity. Long-term follow up is needed to confirm this finding.
No conflict of interest.

2023 POSTER

A comparative study on the displacement of surgical cavity center defined separately by clips and seroma based on 4DCT scan for external-beam partial breast irradiation

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Background: To compare the displacement of surgical cavity center delineated by metal clips and seroma based on the four-dimensional computed tomography (4DCT) in the free-breathing(FB) state for external-beam partial breast irradiation(EB-PBI) after breast conserving surgery.
Material and Methods: Fourteen breast cancer patients after breast-conserving surgery were recruited for EB-PBI. All of the metal clips in the cavity were delineated on each of the 10 respiratory phase. All of the metal clips were marked as the geometry. The gross tumor volume formed by the clips and the seroma were defined as GTVc and GTVs, respectively. The centra displacements of the geometry, GTVc, GTVs and the selected boundary metal clips in the left-right(LR), anterior-posterior(AP)and superior-inferior(SI) were measured and compared. Three dimensional displacement vectors of the geometry, GTVc and GTVs were calculated.
Results: The displacements in the LR, AP and SI directions were 2.20 mm, 1.80 mm and 2.70 mm for geometry center; 0.90 mm, 1.05 mm and 1.20 mm for GTVc center; 0.80 mm, 1.05 mm and 0.80 mm for GTVs center. For every center the displacements in the LR, AP and SI directions don't have significant difference (X2=3.837, 2.051, 3.647, P = 0.147, 0.359, 0.161). In the three dimensional directions, the displacements of the geometry were larger than GTVc and GTVs ($P<0.05$). The displacement of GTVc was larger than the GTVs center in SI direction ($Z = -2.048$, $P = 0.041$). The displacement of the three cavities were larger than the four selected clips.
Conclusion: In the FB state,the centra displacements of the geometry resulted from the respiration movement were larger than GTVc and GTVs,and also larger than the four selected boundary metal clips in three directions, but there was no significant difference between GTVc and GTVs.
No conflict of interest.

2024 POSTER

Mastectomy with immediate reconstruction: A challenge to the radiation oncologist? Dosimetric analysis

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Background: Most women with breast cancer will receive radiotherapy (RT) as part of their treatment, with benefit in both local control and survival. The purpose of this study was to evaluate the impact of immediate breast reconstruction (IBR) in postmastectomy radiotherapy dose distributions in the reconstructed breast, heart, lungs, and contralateral breast. Also, to evaluate the changes made in the standard opposed tangents treatment planning to adequate the target coverage and if there was any difference between IBR with tissue expanders (EXP) or prostheses (PRO).
Materials and Methods: Forty-eight patients submitted to IBR with either EXP or PRO. All patients were treated with 50 or 50.4 Gy (1.8 to 2 Gy/day) with 3-dimensional conformal RT, initially planned with opposed tangents and 'field-in-field' technique for better dose homogeneity. Volume delineation was made according to the Radiation Therapy Oncology Group recommendations. Dosimetric variables related to target coverage and organs at risk (OAR) doses were analyzed. PTV coverage was evaluated according to the ICRU 50 and 62 recommendations, with a 5 mm margin beneath the skin surface. OAR dose constraints were established according to 'QUANTEC'. The mean values of the studied variables were compared between patients with EXP and PRO (Student-t test) with the significance level set at 5% ($p \leqslant 0.05$).
Results: Among the 48 studied patients, 34 were reconstructed with PRO and 14 with EXP. In all situations CTV and PTV coverage was considered adequate. However, 6 (12.5%) patients had their treatment planning modified in order to achieve a proper coverage of the target. The major reason was inclusion of internal mammary nodes (IMN) in the treatment (4 patients). The group with PRO presented higher CTV mean doses (D90 = 48 Gy versus 47 Gy in EXP) and lower lung doses when compared to EXP ($p \leqslant 0.05$). Nevertheless, there was a higher proportion of patients with lymph nodes irradiation in the EXP group. All the OAR dose constraints were kept below the recommended limits.
Conclusion: Proper target coverage was achieved in all patients, despite the fact that, in a small proportion of cases, the standard opposed tangents planning had to be modified. PRO seems to be better than EXP regarding 'breast' coverage. The lower lung doses the PRO group were possibly related to the lesser IMN irradiation.
No conflict of interest.

2025 POSTER

Acute skin toxicity in Korean breast cancer patients carrying BRCA mutations

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Background: In contrast to *in vitro* studies, most clinical trials testing the radiosensitivity of *BRCA* mutations do not find a correlation between *BRCA* status and enhanced radiosensitivity. These trials include different ethnicities, and there is a lack of clinical data on *BRCA1/2* mutation carriers and radiosensitivity in non-Caucasian patients. The goal of this study was to investigate acute skin toxicity, as a part of radiosensitivity, in breast cancer patients with *BRCA1/2* mutations.
Material and Methods: *BRCA* mutation analysis was performed for 213 patients who underwent breast-conserving therapy using radiotherapy. Skin toxicity was scored according to the radiation therapy oncology group (RTOG) criteria during treatment and during one-month follow-up after radiation therapy.
Results: Forty-six patients had *BRCA1/2* mutations and 57 patients showed higher than grade 2 (RTOG) skin toxicity. In multivariate analysis, significant associations were found between mean breast volume and acute skin toxicity. *BRCA* mutation status, however, failed to show a significant correlation. Some single nucleotide polymorphisms (SNPs) were associated with increased acute skin toxicity.
Conclusions: Our results indicate that carriers of *BRCA1/2* mutations among non-Caucasian breast cancer patients showed no enhancement in radiation sensitivity. Although some *BRCA* SNPs have marginal correlation with skin toxicity, the clinical impact is undetermined. Multiple genetic markers may be correlated with normal tissue responses after radiotherapy. Further studies are needed to identify genetic predispositions to normal tissue responses after radiotherapy.
No conflict of interest.

2026 POSTER

Multicatheter brachytherapy under local anesthesia for accelerated partial breast irradiation

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Background: Accelerated partial breast implantation (APBI) becomes important adjuvant modality for early breast cancer patients. There are several techniques of brachytherapy (BT). Multicatheter interstitial APBI is performed in our department. One of the disadvantages is implantation procedure under anesthesia. Due to age many of women have increased risk of complications during general anesthesia. We decided to perform catheters implantation in local anesthesia to avoid that. This study aimed on quality of local anesthesia during multicatheter implantation procedure.
Material and Methods: 85 consecutive APBI patients filled anonymously the anesthesia quality questionnaire (AQQ). Part one was filled before procedure and part two after it. Third part was given to patient after removing catheters. Questions asked about fear of APBI, former anaesthesia and pain during procedure. Pain Intensity was evaluated in 10 points scale. Patient had usually interstitial catheters implantation on Monday. Fractionation schedule was 8 fractions, twice a day (6 hours gap) for four days. Catheters were removed immediately after last fraction.
Local anesthesia region was chosen directly after preplanning. Oral 7.5 mg midazolam was used. Breast skin after disinfection was anesthetized with 1.5% lignocaine. Only this parts of skin was anesthetized, which were covered with template.
Results: Every AQQ was valid, however there were information lacking in several questionnaires. Median age was 63 years (range 49−80). 11 women had ischemic heart disease (IHD), 38 patients had hypertension and 15 patients had diabetes. Only 4 women had depression, 11 more were neurotic with occasional sedative use. 8 patients had diabetes and hypertension. 7 women had IHD and hypertension. Two patients had IHD, hypertension and diabetes.
Even after usual doctor conversation and signing consent, 59 patients had concerns of APBI. 26 women were afraid of pain during catheter placement. 7 patients was afraid of pain after procedure. 10 patients were afraid of combination of these. 40 patients were anxious of APBI.
Median score on fear scale was 4 points (range 0−10). Median score on pain scale after the catheter implantation was 2 points (range 0−8). 45 women suggested that the most painful procedure was breast skin anesthetization.
70 women gave maximum of 10 points, when asked to evaluate APBI on last day. Median score was 10 points (range 7−10). All of the patients did not regret they chose APBI BT. Moreover they would recommend it to their friends.
In univariate analysis fear of pain strongly correlated with pain during implantation (HR:7.5; p-0.000). Also APBI anxiety was linked to pain during procedure (HR:2.96; p-0.007).
Conclusions: Local anesthesia for multicatheter implantation in APBI patients is good alternative to general anesthesia. Breast cancer patients were content of choosing this option of adjuvant treatment.
No conflict of interest.

2027 POSTER

Lung and heart sparing in breast cancer patients treated in the lateral decubitus position

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Background: The isocentric lateral decubitus position (ILD) is an original radiotherapy technique developed at the Institute Curie for 17 years and thousand patients have been treated using it. We have introduced computed tomography planning for all patients treated in the ILD position. The purpose of this study is to evaluate the doses to two principal organs at risk (OAR): heart and lung.
Materials and Methods: Fifty patients (pts) with left breast cancer treated using 3D ILD have been studied. The patient undergoes a planning CT scan in this position used dedicated device. Using virtual simulation, two isocentric tangential beams-medial and lateral-with matching posterior borders are set-up. Then individual dosimetric planning is realized with Eclipse (Varian) and algoritme photon_AAA. The treatment is performed by photons of 6 or 4 MV. In all patients the breast volume, heart and lung were delineated and evaluated its dose-volume histograms (DVH). We measured the central lung distance (CLD) and maximal heart distance (MHD) in all patients and analysed the results.
Results: Fifty consecutive left side early stage breast cancers were studied, of them: 33 received a total dose of 66 Gy/33 fractions (50 Gy on breast and boost to 16 Gy),16 pts a dose of 41.6 Gy/13 fractions/5 weeks, 1 pt 47.25 Gy. 14% of pts treated have a part of heart in the treatment field; the average value of MHD is of 0.4 cm. 28% of pts treated have their lung in the treatment field. In the 33 pts who received a total dose of 66 Gy: the heart and the lung received respectively a mean dose of 1.71 Gy [1.28;2.69], σ=0.57 and a mean dose of 0.97 Gy [0.57;1.61], σ=0.31. In the 16 pts who received a total dose of 41.6 Gy: the heart and the lung received respectively a mean dose of 0.77 Gy [0.33;1.60], σ=0.28 and a mean dose of 0.71 Gy [0.23;1.90], σ=0.53. The mean dose to the heart covers in average 38% of cardiac volume; the mean dose to the lung in average 30% of left lung volume.
Conclusions: Irradiation of the heart and lungs is extremely low in 3D ILD position and is associated with a limited risk of complications. In many cases the dose received by OAR is released outside the irradiation field so it is important to validate the accuracy of dose calculation model of the TPS in these regions of low dose.
No conflict of interest.

2028 POSTER

Hypofractionated radiotherapy in the conservative treatment of breast cancer

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Background: The scheme of standard radiotherapy for breast cancer treatment involves a high total dose in 25 fractions. However, a decrease in the total dose, together with an increase in the dose per fraction (hypofractionation) is discussed to be at least as safe and effective as standard treatment. The objective of this study is to analyse the results in local control, acute and late toxicity and cosmetic outcome in patients treated with hypofractionated radiation therapy after conservative surgery for breast cancer in our center.
Material and Methods: A retrospective analysis of all women diagnosed with breast cancer and treated with breast-conserving surgery followed by hypofractionated scheme from 2006 to 2011. Total dose on mammary gland: 42.4 Gy to 2.65 Gy/fraction, 1 fraction day, 5 days a week, for a total of 16 sessions with concomitant boost to 7.7 Gy (0.48 Gy/fraction). We included patients treated with chemotherapy, hormonal therapy and trastuzumab. Acute and late toxicities were scored according to the Common Terminology Criteria for adverse Events (CTCAE v4).
Results: We have treated 143 women with hypofractionated scheme. After a median follow up of 30 months, the local recurrence rate was 0%, only 2.2% experienced nodal relapse, one patient developed a contralateral breast cancer and 7.4% had distant metastases. There was no acute toxicity in 28.4% of cases, being the most frequent grade 1 radiodermatitis (61.1%). Regarding late toxicity, this was not observed in 65.6%, being grade 1 fibrosis in the treated area the most common. The aesthetic result was good or excellent in 90% of patients treated. At the end of the study, 88.1% remained alive without disease, 5.2% alive with disease, 3% exitus due to tumour and 3.7% were died due to other causes.
Conclusion: The hypofractionated scheme after conservative surgery in breast cancer provides a good control of the disease without causing excessive toxicity and providing good aesthetic results. Similar results to standard treatment can be obtained with a significant reduction in overall treatment time.
No conflict of interest.

2029 POSTER

Impact of adjuvant systemic chemotherapy on wound healing and cosmetic outcome in 224 consecutive patients treated with accelerated partial breast irradiation (APBI) using interstitial brachytherapy

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Background: Accelerated Partial breast Irradiation (APBI) is being increasingly used as an alternative to whole breast radiation. However there is lack of data regarding timing and impact of systemic chemotherapy on wound healing and cosmetic outcome in this group of women. This study was aimed to evaluate the impact of adjuvant systemic chemotherapy on wound healing and cosmetic outcome in women treated with APBI for early-stage breast cancer.

Materials and Methods: Between August 2000 to December 2011, 224 women diagnosed with early breast cancer were treated with APBI using High Dose Rate (HDR) brachytherapy (post-op or intra -op) using ^{192}Iridium afterloading system. Women with age >40 years, tumours </= 3 cm and clinically negative axillary lymph nodes were considered suitable for the procedure. Two to four plane implants were done based on the volume of excision. Adjuvant systemic chemotherapy was administered as per the standard guidelines. Three weeks gap between radiation and chemotherapy was considered during the treatment. Patients were treated to a dose of 34 Gy in 10 fractions over 1 week with 2 fractions per day.
Results: Median age of presentation was 56 years (Range: 30−79 years). Median pathological T size was 2 cm with IDC being the most common histology (96%). Intraoperative placement of catheters was done in 136 (60%) and postop in 88 (40%). Adjuvant chemotherapy was given in 114 women (50%). Sixty three (56%) received chemotherapy after APBI and 51 (44%) before it. Wound complications were observed in 15 patients (7%). Ten patients in chemotherapy group and 5 patients in no chemotherapy group developed wound complications ($p = 0.20$). Four patients developed ulcer. All these were treated with intraoperative placement of catheters and 2 had inadvertently received chemotherapy within 15 days of completion of brachytherapy. In all these patients ulcer developed during chemotherapy as a radiation recall phenomenon. Six patients required additional antibiotics and 4 patients required secondary suturing. Wound issues resulted in fair to poor cosmetic outcome in 7 (47%) women.
Conclusion: Wound complications in women receiving APBI were within acceptable limits however were marginally higher in those who received adjuvant systemic chemotherapy. The risk was more in women who were treated with intraoperative placement of catheters. Time gap of upto 3 weeks appears important between the two modalities. Wound complications had poorer impact on cosmetic outcome in women treated with APBI.
No conflict of interest.

2030 POSTER

Incidental irradiation of internal mammary nodes in breast cancer: comparison between conventional and tridimensional conformal techniques between two institutions

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Background: The increasing use of tridimensional conformal radiotherapy (3D RT) reveals that in local treatment of breast cancer patients adjacent structures may be occasionally irradiated. This study purposes to evaluate the incidental irradiation of the IMN in patients treated with opposed tangents fields, planned with conventional (2D) or 3D RT, and to compare the results between both techniques.
Materials and Methods: Eighty patients, with no indication of RT of the IMN, were selected for this study: 40 submitted to 2D RT with computed tomography for dosimetric control (public institution), and 40 to 3D RT (private institution). Total prescribed dose was 50 or 50.4 Gy (1.8 or 2 Gy/day). Treatment plans were reviewed and a Clinical Target Volume (CTV) for the IMN was defined according to the Radiation Therapy Oncology Group (RTOG) recommendations. The volumes of IMN irradiated by the tangent fields were analyzed: percentage of the volume that received 45 Gy (V45), dose in 95% of volume (D95), minimum (Dmin), maximum (Dmax) and mean (Dm) doses, volume that received 50% of the dose (V25) and the dose in 50% of the volume (D50).
Results: No difference related to the treatment side (right/left), type of surgery (mastectomy, breast conserving surgery, and mastectomy with immediate reconstruction) and delineated IMN volumes between the two institutions (mean 6.8 versus 5.9cc, respectively for 2D and 3D, $p = 0.411$) were observed. All dosimetric parameters presented higher mean values on the 3D plans ($p < 0.05$), except for Dmin. The median Dmax with 3D was 50.34 Gy, but the mean dose to the IMN was 7.93 Gy with 2D, and 20.64 Gy with 3D technique.
Conclusion: None of the analyzed techniques delivered enough doses to the IMN for subclinical disease control. With 3D technique, however, all the dosimetric analyzed parameters were significantly higher when compared to 2D.
No conflict of interest.

2031 POSTER

Breast cancer recurrence after ROLL lumpectomy − ten year experience

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Background: Very few literatures are available on the long term outcomes after Radioguided Occult Lesion Localisation (ROLL) guided lumpectomy for non palpable invasive breast cancer. We previously published a recurrence of 1.9% with median follow up of 33 months. This is the first observation reporting after a Ten year experience with ROLL.
Materials and Methods: A continuous prospective series of patients undergoing ROLL for non palpable invasive breast cancers is followed with 6 monthly clinical exam and an annual mammography for five years. All patients' clinical records and investigation are checked for diagnosis of recurrence (local/systemic). All patients who had clinical or radiological suspicion of local recurrence underwent clinical or image guided core biopsy or fine needle cytology to prove the recurrence. Similarly, when there is clinical suspicion of systemic recurrence, patients underwent relevant imaging to rule out or to confirm systemic recurrence. Statistical analysis is carried out by using SPSS 14.
Aim: What is the long term outcomes after ROLL for non-palpable invasive breast cancers?
Results: 460 ROLL lumpectomies were performed for invasive breast cancers during Nov 2002–Dec 2012. Median tumour size was 12 mm. Median follow up time is 60 months. Neo-adjuvant therapy was given to 41 pts (8.9%). Presence of tumour (<1 mm) at margins (including superficial and deep margin) was +ve in 113 (24.4%). However, when superficial and deep margins were excluded as it did not affect clinical decision, margin +ve for tumour are 69 (15.4%). Median number of cavity shavings; 2 (0−7). Cavity shavings containing tumour were observed in 38 pts (8.2%). 10 pts (2.2%) developed local recurrence more frequently among patients with tumours having Lympho Vascular Inavasion ($P < 0.003$), ER negative and HER 2 negative ($P < 0.001$) and among those with Cavity shaving involved with tumor ($P < 0.063$). Tumour grade & margin status failed to associate with local recurrence ($p = 0.985$). Biological variables associated with systemic recurrences [23 (4.9%)] were; Lymph node metastases ($p < 0.022$), +ve Cavity shave ($p < 0.001$), +ve LVI ($P < 0.019$) and grade 3 tumours ($p < 0.044$), those needing neo-adjuvant therapy ($p < 0.004$). Margin status, Invasive tumour size, failed to achieve statistical significance.
Conclusions: The local recurrence observed is very low (2.2%) and is affected by biological status of the tumour more than the margin status. Similarly systemic recurrence (4.9%) after ROLL is once again affected by the biological behaviours of the tumour.
No conflict of interest.

2032 POSTER

Pre-operative selection of patients with limited disease of the axilla using ultrasonography of the axilla: Might additional lymph node dissection (ALND) be safely omitted in the future?

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Background: The sentinel lymph node biopsy (SLNB) procedure is the method of choice for the identification and monitoring of regional lymph node metastases in patients with breast cancer. In the case of a positive sentinel node additional lymph node dissection is still warranted for regional control, though 40−60% have no additional axillary disease. Recent studies showed that after breast-conserving surgery, SLNB and adjuvant systemic therapy there is no significant difference between recurrence-free interval and overall survival if there are 2 or less positive axillary nodes.
Purpose: Preoperative identification of patients with limited axillary disease ($\leqslant$2 macrometastases) using ultrasonography (US).
Method: Between January 2007 and August 2011, data from 1102 consecutive primary breast cancer patients who underwent surgery in our hospital were collected into a single database. Patients were selected by clinical tumours smaller than 50 mm (cT1−2), no palpable adenopathy (cN0) and a maximum of 2 SLNs containing macrometastases. The variable of interest was ultrasonography of the axilla. The population was divided into two groups: the group with 2 or fewer positive nodes and the group with more than 2 positive nodes in the axilla after ALND.
Results: After selection, 1060 patients remained of which 102 (9.6%) had more than 2 positive axillary nodes on ALND. Selected by unsuspected US, the chance of having more than 2 positive lymph nodes is substantially lower (4.2%). This is significant on univariate and multivariate analysis. The

chance of more than 2 positive lymph nodes was 12.8 times as big in case of a positive axillary US. When we select this subgroup even further by excluding the patients with extra capsular extension (ECE) on SLN, the chance of more than 2 positive lymph nodes is only 2.6%. Subdivided by clinical tumour size the chances are 0.96% in case of cT1 tumour and 7.0% in case of a cT2 tumour. For pathological T-status the numbers are respectively 0.87% en 5.0%. For pT1−2 this is 2.2%.
Conclusion: The risk of more than 2 positive axillary nodes is relatively small in patients with cT1−2 breast cancer. Ultrasonography of the axilla helps in further identifying patients with a minimal risk of additional axillary disease, putting ALND up for discussion.
No conflict of interest.

2033 POSTER

Axillary dissection vs no axillary surgery in T1N0 breast cancer patients: A randomized clinical trial (INT 09/98)

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Background: Although axillary surgery is still considered as a fundamental part of breast cancer management, it may no longer be necessary either as treatment or as guide to adjuvant treatment. We conducted a single-center randomized trial (INT 09/98) to determine the impact of avoiding axillary surgery in patients with T1N0 breast cancer and planning chemotherapy based on biological factors of the primary tumor on long-term disease control.
Methods: From June 1998 to June 2003 565 T1N0 breast cancer patients, aged 30−65 years, were randomized to quadrantectomy with (QUAD) or without (QU) axillary dissection; 517 patients were finally evaluated. All patients received radiotherapy in the operated breast only. Chemotherapy in the QUAD arm was decided on nodal status, estrogen receptor (ER) status and tumor grade. Chemotherapy in the QU arm was based on ER status, tumor grade, HER2-receptor and laminin-receptor status, defining an unfavorable (QU/Poor Panel(PP) or favorable (QU/Good Panel(GP)) prognostic groups, treated or less with chemotherapy, respectively.
Overall survival (OS) was the primary endpoint. Disease-free survival (DFS), rate and time of axillary relapse in QU arm were the secondary end-points.
This trial is registered with ClinicalTrials.gov.NCT01508546.
Results: After a median follow-up of more than 10 years [127.5 months, interquartile range (IQR)=112.5–141.1], OS was 93.3% (95% CI=89.4–95.8) and 91.5% (95% CI=87.0–94.4) in the QUAD and QU arms, respectively. In the QUAD arm, 10-year DFS was 92.4% (95% CI=88.5–95.1) and 91.3% (95% CI=86.7–94.3) in the QU arm. Estimated adjusted HR of the QUAD vs. QU arms was 1.09 (95% CI=0.56–1.94;p = 0.898) for DFS and 1.09 (95% CI=0.59–2.00;p = 0.783) for OS. These results indicate no statistically significant difference between survival curves in study arms. In the QU arm, 22 of 245(9.0%) patientsQU experienced axillary relapse. Axillary relapse occurred in 16/158(10.1%) of QU/GP and 6/87(6.9%) of QU/PP patients (p = 0.488). The median time of axillary relapse from breast surgery was 30.0 months (IQR=24.2–73.4); 35.8 months (IQR=27.6–82.5) in QU/GP patients and 22.8 (IQR=9.1–28.0) in QU/PP patients (p = 0.033).
Conclusion: T1N0 breast cancer patients did not benefit from immediate axillary surgical staging in terms of DFS and OS. Biological characteristics of the primary tumor appear adequate for guiding adjuvant treatment.
No conflict of interest.

2034 POSTER

The impact of preoperative MRI on the surgical management in invasive breast cancer with a lobular component of any size

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Background: Invasive breast cancer comprises a spectrum of histological changes with purely lobular cancer on one side and purely ductal cancer on the other and many mixed lesions in between, by some denoted as ductolobular cancer. Magnetic resonance imaging has shown to be of added value in the diagnostic work-up of pure invasive lobular cancer (ILC) as it detects additional contralateral and ipsilateral findings in up to 32% of patients. The impact of preoperative MRI on management of patients with such a mixed differentiation is still unclear. Our aim is to determine the impact of preoperative MRI on TNM-classification and surgical management in patients diagnosed with invasive breast cancer and any proportion of lobular component at core needle biopsy.
Material and Methods: All patients diagnosed with breast cancer containing a lobular component between Jan 2008 and Oct 2012 were prospectively offered preoperative MRI. Histological slides were reviewed by a dedicated breast pathologist and the percentage of lobular component was determined. Patients were allocated to either the 1−30%, 31−70% or 71–100% lobular component group. In a multidisciplinary setting comprising experienced breast surgeons and breast radiologists, TNM-classification and surgical policy were determined based on mammography and/or ultrasound only, and for a scenario including additional preoperative MRI.
Results: A total of 109 patients were eligible for this study. Preoperative MRI changed TNM-classification in 43% of patients and altered surgical policy in 38% of patients. The surgical plan changed from breast conserving therapy (BCT) to mastectomy (MST) in 12 (11%) patients, from BCT to neoadjuvant chemotherapy (NEO) in 4 (4%) patients, from MST to NEO in 4 (4%) patients, from NEO to MST in 2 (2%) patients and a wider excision was performed in 8 (7%) patients. In 10 (9%) patients MRI revealed contralateral malignancies necessitating surgery. There was no correlation between the percentage of lobular component and change in TNM-classification or surgical policy (P-value respectively 0.345 and 0.413).
Conclusions: In patients presenting with breast cancer with a lobular component at core needle biopsy, preoperative MRI leads to changes in both TNM-classification as well as surgical policy. This is independent of the size of the lobular component.
No conflict of interest.

2035 POSTER

Quality improvement in surgical breast cancer care: A decrease in positive surgical margins after first breast conserving surgery

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Background: In recent years there has been a growing public interest in quality of breast cancer care. In the Netherlands, hospitals are obliged to report on the percentage of patients with positive margins after first breast conserving surgery (BCS) since 2007. In BCS, a delicate balance exists between the cosmetic result and completeness of the surgery. This indicator may unintentionally lead to the perverse incentive of aiming for the lowest possible positive margin rates by reducing the rate of breast conserving surgeries.
This study describes positive margin rates after BCS since the introduction of this quality indicator in the Netherlands. Furthermore, the occurrence of a shift towards higher mastectomy rates instead of BCS is investigated.
Material and Methods: All early breast cancer patients (T1−2, any N, M0) diagnosed between July 1, 2008, to December 31, 2011 that underwent surgical resection were selected from the Netherlands Cancer Registry (NCR). Type of first surgery was coded as BCS or mastectomy. Margin status was coded as clear, focally positive margins (tumour in a limited area of the inked surface, i.e. on or two foci of tumour, with a maximum of 4 mm), more than focally positive margins or unknown.

Table 1. Surgical margin status after initial BCS for 23,628 breast cancer patients, 2008–2011.

	2008*		2009		2010		2011	
	n	%	n	%	n	%	n	%
Clear margins	2,580	78.4%	5,315	80.1%	5,337	79.7%	5,759	82.1%
Focally positive margins	324	9.8%	641	9.7%	675	10.1%	726	10.3%
More than focally positive margins	321	9.8%	571	8.6%	493	7.3%	471	6.8%
Unknown or inconclusive	67	2.0%	109	1.6%	194	2.9%	55	0.8%

*Data from 2008 includes 6 months (July 1 through December 31).

Results: Of the 38,380 included patients, 62% (23,628 patients) received BCS in 89 hospitals in the Netherlands. The percentage of mastectomies as first surgery slightly decreased over time (39% and 38% in 2008 and 2011 respectively; χ^2 for trend: p = 0.029). The percentage of positive tumour margins significantly decreased over time; 9.8% in 2008 versus 6.8% in 2011 (table 1; X^2 for trend: p = 0.001).

Conclusion: The percentage of patients with positive surgical margins after first BCS for breast cancer decreased between 2008 and 2011. This decrease in positive margins was not accompanied by an increase in mastectomies. The fear for an increase in mastectomies since the introduction of the indicator is therefore not justified.
No conflict of interest.

2036 POSTER

Intra-operative specimen radiography reduces re-excision rates in palpable breast cancers undergoing wide local excision

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Background: Safe breast conserving surgery (BCS) for cancer necessitates clear excision of margins whilst providing reduced morbidity and improved cosmesis. Reported re-excision rates for close or involved margins range from 10−37%. Current guidelines recommend the use of intra-operative specimen imaging (IOSR) for all impalpable breast cancers. This study assesses the use of in theatre specimen imaging to guide BCS for all **palpable** lesions with a view to reducing re-excision rates.
Methods: Retrospective comparison of two randomly selected discrete cohorts (n = 200, 100/cohort) was undertaken for patients undergoing BCS for palpable breast cancers before and after the inauguration of the use of IOSR (Faxitron Bioptics, Tucson, AZ) in our centre. Comparative data analysis included patient demographics, tumour size and characteristics and intra-op and further secondary operative excision rates. Data were analysed using SPSS Statistics 20.
Results: See the table.

	WLE		*p* value
	pre-IOSR	with IOSR	
Age	59.5±12.0	61.5±12.6	0.293
Laterality L : R	53 : 47	47 : 53	
Excision volumes	364 cm^3 (IQ range 148–414)	205 cm^3 (IQ range 92–253)	<0.001
Tumour size	19.3 mm±10.3	22.1±11.2	0.079
Closest excision margin			0.273
Mean	6.8 mm±5.9	6.0 mm±3.7	
Range	0−40 mm	0−20 mm	
Percentage of patients undergoing further intra-operative excision of margins	10%	31%	<0.001
Percentage of patients requiring further re-operative excision of margins following MDT discussion	35% 11/35 histological positive	17 % 12/17 histological positive	0.004

Conclusion: Intra-operative specimen imaging using Faxitron for palpable breast cancer reduces both excision volumes and the need for post-operative further margin re-excision. Reduced morbidity, improved cosmetic outcomes, cost effectiveness and earlier patient access to adjuvant therapies must make this the gold standard in all breast conserving surgery for palpable tumours.
No conflict of interest.

2037 POSTER

Outcomes of immediate perforator flap reconstruction after skin-sparing mastectomy

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Background: Perforator flap reconstruction after skin-sparing mastectomy (SSM) seems to be useful because it is characterized with autologous graft, less invasive than myocutaneus flap and excellent aesthetic result. Immediate reconstruction is also patient-friendly, because it is less expensive, and limits exposure to anesthesia risk. Objective of this study is to clarify surgical complications and oncological outcomes of an immediate perforator flap reconstruction after SSM.
Patients and Methods: From 2004 to 2012, 201 consecutive patients underwent immediate perforator flap reconstruction after SSM for biopsy-proven breast cancer. The mean age of them was 42.3 years (23−64) and mean body mass index was 21.1 (16.0–28.2). Skin sparing mastectomy was performed by breast surgeons and reconstruction was performed by plastic surgeons concurrently or consequently. Nipple-areolar complex (NAC) was resected for cases with apparent tumor invasion, whereas nipple-sparing mastectomy (NSM) was performed for cases without NAC involvement by pre-operative imaging. Frozen section intra-operative pathological diagnosis of margin just below the NAC was routinely performed when performing NSM. We used various kinds of perforator-flaps. Deep inferior epigastric perforator (DIEP) flap, superior gluteal artery perforator flap/inferior gluteal artery perforator flap or posterior median thigh perforator flap were taken from the inferior abdomen, the gluteal region and the thigh, respectively. The blood flow of grafts was monitored intensively with a Doppler ultrasonography after surgery. Patients were followed with 3−6 month intervals during first 5 years and 3−12 month intervals thereafter. The surgical complications and oncological outcomes were reviewed retrospectively.
Results: The mean duration of this procedure was 499 minutes (range 235–857) and the mean amount of bleeding counted 244 ml (range 5–730). Nipple was preserved in 151 cases (75%). Donor sites of free perforator flap were lower abdomen (101 cases, 50%), gluteal region (52 cases, 26%) and thigh (48 cases, 24%). Seven patients developed graft ischemia. The emergent revascularization was performed for all 7 cases and salvaged the grafts in 6 of them, resulted in a loss of graft in 1 case. The median length of stay after surgery was 8 (range 6−37). As to oncological outcome, a total of 8 patients (4%) developed recurrence with the median follow-up time of 2.8 years. Local recurrence was found in 3 of them (1.5%).
Conclusion: The outcome of immediate perforator flap reconstruction after SSM is acceptable as a procedure of oncoplastic surgery. However, it accompanies longer duration of surgical procedure, and requires intensive monitoring and occasional emergent surgery. Thus, this technique should be performed with a team combined with breast- and plastic-surgeons meticulously.
No conflict of interest.

2038 POSTER

Guiding breast conserving surgery in 383 patients with non-palpable breast cancer − comparison of two techniques: Radioactive seed localization versus radioguided occult lesion localization with 99m Technetium colloid

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Background: Radioguided Occult Lesion Localization with 99mTechnetium colloid (ROLL-99mTc) and Radioactive Seed Localization with a radioactive iodine-125 seed (RSL) are both alternatives to wire localization for guiding breast conserving surgery (BCS) of non-palpable breast lesions. The aim of this study was to evaluate and compare the efficacy of ROLL-99mTc and RSL.
Methods: We retrospectively analyzed 383 patients with one or more unifocal non-palpable ductal carcinoma in situ (DCIS) or invasive carcinoma who were treated with BCS at the Netherlands Cancer Institute. In total, 403 non-palpable lesions were diagnosed. The disease was localized either by ROLL-99mTc (N = 275) or by RSL (N = 128). Logistic regression and propensity scores were used to compare positive margins in the RSL and the ROLL-99mTc group after adjusting for clinical variables.
Results: In the RSL group (n = 128), more lesions were DCIS (58.6%) as compared to the ROLL group (n = 275), in which only 32.0% were pure DCIS. Nevertheless, the proportion of focally positive margins (10.9% vs. 9.8%) and extensive positive margins (8.6% vs. 8.7%) was comparable between the RSL and the ROLL-99mTc group (p = 0.225), resulting in the same re-excision rate in both groups (9.4% vs. 10.2%). Patients with positive sentinel node status were more likely to have positive margins than those with negative node status (odds ratio 0.35, 95% CI 0.15 to 0.80). Median specimen weight was significantly lower in the RSL group than in the ROLL-99nTc group (29 vs. 38 g; p < 0.001) as well as median volume (70 vs. 90 cc; p = 0.001), whereas the median tumor size was identical for both groups.
Conclusion: Margin and re-excision rates were comparable for the ROLL-99mTc technique and I-125 seed localization in patients with non-palpable breast lesions. Because of the lower median weight and volume of the resected specimen, we favor RSL over ROLL-99mTc to guide breast-conserving therapy.
No conflict of interest.

2039 POSTER

The incidence of metastases to the sentinel lymph node and other axillary lymph nodes in particular molecular subtypes of breast cancer

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Background: The possibility of determining such groups of breast cancer female patients where the procedure of complete axillary lymph nodes dissection (ALND) could safely be abandoned despite a positive sentinel node is still under investigation. The division of breast cancers into molecular subtypes creates new possibilities of searching for the probability of metastases in consecutive lymph nodes in the case of a positive sentinel lymph node.
Aim: The aim of the study was to assess the number of positive lymph nodes depending on a cancer molecular subtype in female patients operated for breast cancer.
Material and Methods: The study comprised all the female patients operated for breast cancer and diagnosed as having lymph node metastases in COZL oncological surgery department in 2011. The division of tumours into molecular subtypes was performed on the basis of tumour receptor status, and qualifying for luminal subtype A and luminal B HER 2 negative depended on Grading of a tumour. In 2011 in COZL oncological surgery department there were performed 244 sentinel lymph node biopsies (SLNB), and in 52 cases the results were positive. There were conducted 199 prim aryALND connected with wide local excision (WLE) or simple amputation. In a total of 251 cases of female patients operated for breast cancer metastases to the lymph nodes were found either by preoperative diagnostics or SLNB. The examination also included the number of positive lymph nodes in 3 brackets/1; 2−3; 4 or more/.
Results: In the group of patients with 1 positive lymph node/ **121** patients/ luminal A cancers constituted 53.7%, luminal B/ Her2 negative/ ones −19%, luminal B/ Her2 positive/ ones − 8.3%, non-A non-B ones/ 4.9%, basal ones − 4.1%, special subtypes/ 9.9%. In the group with 2 −3 positive lymph nodes/ **50** patients/ luminal A cancers consituted 16%, luminal B/ Her2 negative/ ones − 44%, luminal B /Her2 positive/ ones − 18%, non-A non-B ones/ 10%, basal ones − 8%, special subtypes − 4%. In the group with 4 positive lymph nodes or more/ **76** patients/ luminal cancers A constituted 9.2%, luminal B /Her2 negative/ ones −44.7%, luminal B /Her2 positive/ ones 21%, non-A non-B ones- 10.5%, basal ones- 10.5%, special subtypes − 3.9%.
Conclusions: The division of breast cancers into molecular subtypes alone cannot be a factor determining the presence of metastases in consecutive lymph nodes in the case of positive SLNB results. It is necessary to continue the analysis of the following factors: patient's age, tumour size and its molecular subtype/especially luminal A/ in order to determine a group of patients with positive SLNB results in whom performing of ALND could safely be abandoned.
No conflict of interest.

2040 POSTER

Evaluation of one step nucleic acid amplification (OSNA) molecular assay for intraoperative diagnosis of sentinel lymph node (SLN) metastasis

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Background: In the management of breast cancer, histopathological assessment from a sentinel lymph node biopsy (SLNB) for evidence of metastatic spread is the gold standard for accurate staging, patient prognosis and to determine need for further axillary surgery. This process is currently two-stage, requiring patients with positive SLNB to return for a subsequent axillary clearance, increasing patient risk and reducing effective theatre utilisation.
OSNA is an innovative molecular diagnostic assay that identifies lymph node metastases in breast cancer utilising cytokeratin 19mRNA as a molecular marker. The technique was recently introduced into our institution. With the National Institute for Health and Care Excellence (NICE) due to publish guidelines in July 2013, 'Intra-operative tests for detecting sentinel lymph node metastases in breast cancer' this study aims to assess prospectively the accuracy and usefulness of OSNA for intraoperative detection of SLN metastases in one single centre.
Method: Fifty-five patients with clinically and ultrasonographically negative axillae underwent SLNB via a standard dual agent technique. Following excision, lymph nodes were processed and prepared into multiple slices with alternate sections sent for traditional histopathology and OSNA respectively. 93 SLN in total were compared prospectively utilising both techniques. Further parameters were recorded including length of operation and time taken from removal of node to OSNA report.
Results: 16 of 93 (17%) lymph nodes were positive on OSNA assay, 15 of these nodes demonstrated metastatic disease histologically. There were no metastatic tumour cells identified by the histolopathologist in the slices of the remaining OSNA positive node. An overall concordance rate of 93.75% is reported for OSNA versus histopathology in the identification of macro-metastasis. An increased discordance however, was revealed with respect to micro-metastasis. 7 SLNs had micro-metastasis on OSNA assay whilst only two of the half lymph nodes were reported to show micro-metastasis on histology. The average time for the OSNA assay was 55 minutes.
Conclusions: OSNA is a reliable and rapid diagnostic tool for intraoperative detection of lymph node metastases in patients with breast cancer. It can prevent diagnostic delay or need for second surgery for nodal positivity identified postoperatively. Our institution is now utilising the technique routinely for all SLNB using whole nodes. Current local guidelines preclude further immediate surgery for those patients with OSNA identified single micro-metastasis but a normal second gland. There is still debate regarding patients who have micro-metastases identified in more than one node.
No conflict of interest.

2041 POSTER

Detection of breast cancer using near-infrared fluorescence imaging and methylene blue

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Background: Despite recent developments in preoperative breast cancer imaging, intraoperative localization of the tumor can be challenging. As a result, irradical resections during breast-conserving surgery are still a major problem.
With Technetium(^{99m}Tc)-sestamibi (MIBI), a pharmaceutical agent used in nuclear medicine, preoperative identification of breast cancer is possible in 84−94% of patients.
Based on chemical structure, we hypothesized that Methylene Blue (MB) might have a comparable biodistribution as the nuclear tracer used for a MIBI scan. Moreover, MB in low dosage can be used as a fluorescent tracer during near-infrared fluorescence (NIRF) imaging. The aim of this study was to determine feasibility of MB as fluorescent tracer for the identification of breast cancer with NIRF imaging.
Methods: Twenty-four patients with breast cancer, all planned for surgical resection, were included. N = 12 patients per group were administered 1.0 mg/kg MB intravenously either immediately before or 3−4 h before surgery The mini-FLARE imaging system was used to identify the fluorescent signal during surgery and on post-resected specimens transferred to the pathology department. Fluorescence microscopy images were obtained with the Odyssey Infrared Imaging System.
Results: 20/24 (83%) of breast tumors (carcinoma (N = 21) and ductal carcinoma in situ (N = 3)) were identified in the resection specimen with NIRF. Overall tumor-to-background ratio (TBR) was 2.4±0.8. There was no significant difference between TBR and background signal between administration groups ($P = 0.50$ en $P = 0.23$). Four resections were irradical (17%), and in one of these cases, tumor tissue was identified intraoperatively in the wound bed using NIRF imaging. Direct re-resection was performed, after which the tumor was radically removed. No fluorescent tumor signal was seen in the second irradical case, and in the third case, no intraoperative fluorescent images were available. In the fourth irradical case, clear fluorescent spots were identified in the wound bed, but these were characterized as benign on visual inspection. Therefore, no addition resection was performed. During histopathological assessment, the resection was found to be irradical at this margin.
Histological validation with fluorescence microscopy showed a clear overlay between fluorescent signal and tumor tissue. No adverse reactions associated with the use of MB or fluorescent imaging were observed.
Conclusion: This feasibility study shows that the identification of breast cancer with NIRF imaging and MB was possible in 83% of tumors. This is in agreement with the sensitivity of a MIBI scan for breast cancer of 84−94%. In 2/4 (50%) of patients, breast cancer tissue identified in the wound bed during surgery using NIRF would have changed patient management. Intraoperative NIRF imaging with MB has thereby the potency to increase the number of radical resections in breast cancer patients.
No conflict of interest.

2042 POSTER

Is there a role for microdochectomy in the treatment of nipple discharge and the detection of breast cancer?

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Background: Nipple discharge is a recognised symptom of breast cancer, although most malignant cases present with a mass. The aim of this study was to determine whether microdochectomy is a valid procedure in the treatment of nipple discharge and the detection of breast cancer.
Method and Materials: Between January 2002 and December 2012, 49 microdochectomies were carried out on 47 patients by a single breast surgeon at a breast unit. The indication for 48 of these procedures was persistent nipple discharge, defined as greater than 3 months duration. Nipple discharge was blood stained in 32 patients. A retrospective study was conducted, using cytology, histological records and operative notes, to investigate the effectiveness of microdochectomy as a treatment for nipple discharge and the detection of breast cancer.
Results: Following microdochectomy, 45 patients (96%) did not have recurring nipple discharge. Histological findings showed 17% (7/49 cases) were malignant. All 7 patients presented with either frank blood stained discharge or discharge which was positive for blood on dipstick. All patients had benign cytology and 5 of the 7 cases had normal radiological imaging. All 7 cancers were ductal carcinoma in situ (DCIS) which were managed with wide local excision of the tumour. Three patients went on to have total mastectomies.
Conclusion: This audit found that microdochectomy is a valid procedure for nipple discharge with 96% of patients experiencing symptomatic relief. This procedure found 17% of patients with nipple discharge (all blood stained discharge) had breast cancer. This reflects the incidence previously reported in recent literature. These patients had no other symptoms of breast cancer and would otherwise have been missed or presented at a later stage. We conclude that since negative imaging does not exclude malignancy, microdochectomy is an effective procedure in the early detection of breast cancer.
No conflict of interest.

2043 POSTER

The anatomy of intercostobrachial nerve in nerve-sparing axillary lymph node dissection

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Background: The intercostobrachial nerve (ICBN) is the lateral cutaneous branch of the second intercostal nerve (T2). From its origin, it crosses the axilla and supplies sensory fibers to the medial aspect of the upper arm, axillary skin, and upper lateral breast. Previous studies have shown that preservation of the ICBN during axillary lymph node dissection (nerve-sparing ALND) produces minimal postoperative alterations in sensitivity significantly improving quality of life of operated patients.
Material and Methods: The purpose of this study was to evaluate the anatomical variants of the ICBN in 115 patients who underwent level-2 nerve-sparing ALND for operable breast cancer at our institution in the period of 2005–2010 years. The mean age of the patients was 47.8±12 years.
Results: We encountered 3 main types of anatomical variants of the ICBN (according to Cunnick classification, 2001). Type I (nerve arises from T2 alone and does not give off any branches) accounted for 76/110 (69.1%) of the cases. Type II (nerve arises from T2 alone and divides into a large main trunk and a much smaller branch) and type III (nerve arises from T2 alone and divides equally into two branches) occurred in 22/110 (20%) and 8/110 (7.3%) cases, correspondingly. The incidence of 3 other types (IV, V, VI) was very rare (3.6%).
Conclusion: If an attempt at ICBN preservation is the standard practice for the majority of patients, it will be necessary to understand the anatomy and anatomical variants of this nerve to prevent severe complications of nerve damage.
No conflict of interest.

2045 POSTER

Closing the stable door after the horse has bolted: Sentinel lymph node biopsy in breast cancer; before or after neodjuvant chemotherapy?

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Background: Axillary lymph node status is the most significant prognostic factor in breast cancer patients. Assessment and management of axillary lymph nodes is still an area of debate in breast cancer. Sentinel lymph node biopsy (SLNB) is now a standard tool to evaluate nodal status in clinically and radiologically node-negative cancer patients. Neoadjuvant chemotherapy is increasingly being offered in breast cancer. The timing of sentinel lymph node biopsy in neoadjuvant chemotherapy setting is debatable due to possible impact of chemotherapy on the accuracy of positive lymph node detection. Inaccurate assessment of sentinel lymph node may lead to axillary disease mismanagement.
Material and Methods: Literature review was undertaken using the following keywords: sentinel lymph node biopsy, breast cancer, Neoadjuvant chemotherapy, and preoperative chemotherapy on PubMed, Medscape, Cochrane library and other online resources.
Results: All articles were collected including 19 prospective studies, 9 retrospective studies and 2 further reviews. Four studies demonstrated high accuracy of detection of metastatic disease in sentinel lymph nodes prior to Neoadjuvant chemotherapy with a false negative rate of 0 to 1%. Thirteen studies showed that both timings for sentinel lymph node biopsy of breast cancer patients with neoadjuvant chemotherapy were feasible and accurate with a false negative rate of 0 to 22%. However, 3 of these studies recommended further evaluation of sentinel lymph node biopsy after neoadjuvant chemotherapy. Fourteen studies have clearly advocated performing sentinel lymph node biopsy prior to initiation of neoadjuvant chemotherapy due to unacceptably high false negative rate in the post chemotherapy patients.
Conclusion: It is recommended that sentinel lymph node biopsy should be performed prior to Neoadjuvant chemotherapy as it is associated with significantly lower rates of false negative results and accurately delineates the axilla.
No conflict of interest.

2046 POSTER

Local excision alone for patients with small size ductal carcinoma-in-situ of the breast: A Korean single institutional experience

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Background: To determine the risk of local recurrence in Korean patients with small size ($\leqslant$1 cm) ductal carcinoma in situ (DCIS) after local excision alone without radiotherapy.
Material and Methods: From December 1999 to December 2009, 498 patients with DCIS received breast-conserving surgery at Samsung Medical Center. Among the patients, 107 patients who had DCIS measuring $\leqslant$1 cm with microscopic margin widths of $\geqslant$0.3 cm were treated with excision alone per institutional protocol. The medical records of the patients were retrospectively reviewed.
Results: Median age of the patients was 46 years (range, 23−80). Tamoxifen was used in 89% of the patients. The 92% of the patients had low- or intermediate grade tumor, and the 77% of women had resection margin of $\geqslant$1.0 cm. With a median follow-up time of 58 months, 5 patients developed local recurrence. Three patients experienced recurrence with invasive disease and 2 patients had recurrence of DCIS. The rate of recurrence at 5-year and 10-year were 6.1% and 10.4%, respectively. Patients with resection margin of <1.0 cm had significantly higher recurrence rate than the patients with resection margin of $\geqslant$1.0 cm (23.1% vs. 1.5% at 5-year, $p = 0.02$).
Conclusions: The recurrence in the patients who had small size DCIS with resection margin of $\geqslant$1.0 cm was acceptably low following excision alone. For the patients with resection margin of <1.0 cm, the risk of recurrence was substantial when treated with excision alone, suggesting that radiotherapy is necessary in these patients.
No conflict of interest.

2047 POSTER

The impact of preoperative real-time virtual sonography (RVS) in the surgical management of breast cancer: A single-institution review

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Background: Real-time virtual sonography (RVS) is a newly developed modality which enables us to synchronize sonographic images and MRI-MPR images of the same section in real time. The aim of this study was to evaluate the impact of preoperative RVS in the surgical management of primary breast cancer.

Material and Methods: We reviewed 88 breast cancer patients who were identified as candidates for breast-conserving surgery (BCS) on the basis of conventional assessment, and underwent radical surgery at Aichi Medical University between January 2011 and December 2012. All of them preoperatively underwent an ordinary bilateral breast MRI in a prone position using a double-breast coil, unless contraindications were present. Of the breast in which the additional MRI lesion was detected, we performed second-look sonography (US). When we were not able to detect the additional MRI lesion by second-look US without using RVS, we additionally performed a unilateral MRI with the patient in a supine position using a flexible body surface coil and second-look US with RVS which enables the synchronization with supine MR images. The additional MRI lesions that were detectable by second-look US or RVS, if necessary, were confirmed preoperative pathological diagnosis by image-guided needle biopsy. Finally, from pathological examination of the resected specimens, we verified the accuracy of preoperative assessment of tumor extent by the combined use of conventional imaging modality, MRI and RVS.
Results: Out of a total of 85 women; 46 additional ipsilateral MRI lesions were detected in 43 breasts. With conventional second-look US, the detection rate for the additional ipsilateral MRI lesions was 43% (20/46), while the rate went up to 91% (42/46) when using RVS. Of these 46, 38 lesions in the 37 breasts were suspected of malignancy from second-look US/RVS findings and (or) preoperative pathological examination and we made changes to the extent of resection (BCS with wider margins than anticipated: Mastectomy = 17: 20). In 38 of a total of 43 breasts in which the additional ipsilateral MRI lesions were detected (88%), the addition of second-look US/RVS assessment favorably affected the determination of the extent of resection. Although the rate of positive margins after BCS (the presence of tumor cells on the edge of the resection) was still as high as 14% (9/67), incomplete resection of invasive disease was only 2% (1/67). As the additional contralateral MRI lesions, only one lesion was preoperatively diagnosed as malignant. We also performed an additional contralateral breast surgery.
Conclusions: Our results suggest that using preoperative MRI and RVS in combination with conventional imaging modalities can determine the extent of resection more precisely and reduce the rate of incomplete resection of invasive diseases after BCS.
No conflict of interest.

2048 POSTER

Using both a 125I seed and a Tc-99 nanocolloid source in nonpalpable breast-conserving surgery: Interference or not?

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Background: The challenge of nowadays widely performed breast-conserving surgery is to achieve tumor-free margins while excising no more breast tissue than necessary. This issue especially concerns non-palpable breast lesions. Radioactive seed localization (RSL) is a new localisation method. A ^{125}I seed is placed in the centre of the lesion and the gamma probe using the 125I setting guides the local excision. An intratumoral injection of ^{99m}Tc-nanocolloid is needed to perform the sentinel node procedure. The wavelengths of the radiopharmaceutical and the I-125 seed may overlap.
The purpose of the present study was to investigate any interference when a ^{125}I seed and an injection of ^{99m}Tc-nanocolloid are combined.
Material and Methods: Between the 14th of February and the 27th of June 2012 consecutive patients with a nonpalpable breast lesion were included. An iodine-125-radiolabelled seed and technetium-99m-nanocolloid were inserted intratumorally using mostly ultrasound guidance. Respectively the 125I setting and 99mTc setting of the gamma-probe guided the wide local excision and the sentinel node procedure. Maximum counts were measured at the tumor site and two centimetres away from the site.
Results: In the 25 included patients the I-125 seed was placed 26 days before surgery. The average strength of this source was 5.5 MBq on the day of insertion and 4.0 MBq on the day of surgery. An average amount of 115 MBq technetium-99m-nanocolloid was injected the day before surgery. The average counts of the ^{125}I seed at the tumor site were almost 4 times higher than the Tc-99 nanocolloid source. The counts depicted 20 mm away from the tumor site were comparable. The average residual counts were 3 times less for the ^{125}I seed. The sources could be well distinguished in 92% of the patients.
Conclusions: The ^{125}I seed and Tc-99 nanocolloid can be used in one procedure without interference in radiation energy. Nonpalpable breast lesions can be safely excised based on the ^{125}I seed in an area of radioactivity created by the Tch injection. Moreover, the ^{125}I seed acts as a point source and has no tendency to scatter its surrounding. The usage of the ^{125}I seed is a next step within fine-tuning breast-conserving surgery that should lead to further investigation.
No conflict of interest.

2049 POSTER

The clinical relevance of axillary reverse mapping (ARM) − a multicenter randomized controlled trial

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Background: Axillary lymph node dissection (ALND) has potential negative procedural related side effects including upper extremity lymphedema. Axillary reverse mapping (ARM) is a recently described technique which enables discrimination of the lymphatic drainage of the breast from the upper extremity in the axillary lymph node basin. If upper extremity lymphedema is caused by cutting axillary lymphatic's, then being able to see and identify them would allow them to be preserved. In a feasibility study on ARM we found a high visualization rate using blue dye only (86.0–94.0%). Further we found that sentinel lymph node patients (SLN?-group, N = 43), indicated for a complementary (c)ALND did not have metastases in the arm nodes. Clinical positive lymph node patients (CP?-group, N = 50) had arm-metastases in 22% (P = 0.001). In the latter group arm-metastases, in patients treated with neo-adjuvant chemotherapy (NAC) was 24.6 vs 44.4% for patients who did not (P = 0.046). Because the cohort of patients treated with NAC is limited, these results need to be confirmed in a larger cohort.
In a multicenter randomized controlled trial we will investigate the clinical relevance of ARM expressed by the occurrence of postoperative complications. To minimize the risk of overlooking arm-node metastases, we will only include patients with an indication for a cALND based on a tumour-positive sentinel lymph node. Patients with an indication for an ALND based on a clinical positive axilla will be included in a registration study. Subgroup analysis of patients treated with NAC vs primary surgery will be performed.
Methods and Design: Patients diagnosed with invasive breast cancer with axillary metastasis and an indication for a cALND based on a positive SLN will be randomized between an ARM-ALND (in which arm-nodes and lymphatic's will be left in situ) and a standard ALND (at least level I−II). The primary outcome is the presence of breast cancer related lymphedema. The secondary outcome measurements include other postoperative complications (pain, paresthesia, numbness and loss of shoulder mobility), quality of live and axillary recurrence ratio.
The postoperative outcome will be measured after 6, 12 and 24 months. De quality of life and local recurrence rate will be documented. Lymphedema will be measured with the water displacement method and the circumference method. Paresthesia and numbness will be documented with the aid of a standardized questionnaire developed for breast cancer patients. Pain will be measured through a VAS-score and the shoulder function of the affected upper extremity will be compared with the not affected upper extremity.
Discussion: The study is funded by Pink Ribbon, a breast cancer foundation of the Netherlands. Recently obtained approval from the medical ethical committee. At the moment six breast cancer centers in the Netherlands will participate. The study will finish as soon as 280 patients are included and is expected to finish by January 2016.
No conflict of interest.

2050 POSTER

The effect of gentamicin-collagen sponges on the incidence of seroma and surgical site infections following mastectomy

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Background: Seroma is the most frequent reported complication following breast cancer surgery, urging the search for preventive measures. Clinically significant seroma (CSS) is associated with secondary problems like pain and discomfort. Repeated aspirations are often necessary resulting in a higher risk of surgical site infections (SSI). Gentamicin-collagen (GC) sponges are hypothesized to lower the CSS and SSI incidence.
Method: A retrospective analysis was performed. Two consecutive cohorts of patients who underwent a mastectomy (ME) with or without an axillary lymph node dissection (ALND) were compared. One cohort received GC sponges, the other cohort was treated conventionally. Endpoints were the incidence of CSS and SSI, the mean number of aspirations and the mean aspirated volume.
Results: GC sponges lowered the CSS incidence from 73.7% to 38.5% (p = 0.002). The mean number of aspirations, the mean aspirated volume

and the SSI incidence were not affected. SSI incidence was 15.8% in the conventional cohort compared to 7.7% in the GC cohort (p = 0.227).
Conclusion: Application of GC sponges significantly lowers the CSS incidence compared to the conventional cohort, the SSI incidence was not influenced.
No conflict of interest.

2051 POSTER

Targeted intraoperative radiotherapy using low-kilovoltage X-rays for early breast carcinoma: single centre case series with 5-year follow-up

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Background: Intraoperative radiotherapy (IORT) delivered immediately after the removal of a tumour is increasingly used in breast conserving therapy (BCT) of patients with early breast carcinoma. The aim of the study is to analyze the results of BCT in these patients who undergo IORT using low energy X photons.
Materials and Methods: Eighty five females with early invasive breast carcinoma, who had IORT during breast conserving surgery between December 2005 and March 2008 were included in the study. The follow-up time was at least 54 months (from 54 to 80; median was 63; mean 63.7 months). For the IORT, INTRABEAM® PRS 500 system (Carl Zeiss Meditec AG, Jena, Germany) was used, which generates low energy (⩽50kV) X-rays. 20 Gy dose was applied to the surface of the tumour bed. Two groups of patients were investigated: 1) IORT group (n = 19), where it was the only form of radiation therapy; 2) IORT plus EBRT (external beam radiotherapy) group (n = 61), where the whole breast irradiation with 50 Gy was delivered additionally. The analysis focused on early (RTOG/EORTC scale) and late (LENT-SOMA scale) toxicity, long-term outcomes, and aesthetic effect.
Results: Early complications occurred in 20% of patients, but there were no serious complications that would prolong hospitalisation. The most frequent early complications were: prolonged wound healing (20%), inflammation of the tumour bed (14.1%), and breast inflammation (7.1%). Early radiation toxicity was observed in 15.3% of patients. The most frequent (11.3%) late complication was grade 2 fibrosis limited to the treated quadrant, which were reasons for diagnostic difficulties in the follow-up period. In over 10% of patients the fibrosis was a reason for subsequent surgical re-intervention. The intensity of fibrosis decreased with the time from surgery. No grade 3 or 4 fibrosis was detected in a 48-month of follow-up. Fluid collections (seroma) were most frequently (37.7%) observed. In the IORT group, local recurrence was detected in one patient 40 months after the treatment. There were no local recurrences in the IORT plus EBRT group. Five-year overall and disease-specific survival was 100% in the IORT group, whereas 95.1% and 96.7% in the IORT plus EBRT group, respectively. Excellent and good aesthetic outcome was achieved in about 90% of patients.
Conclusions: The IORT using INTRABEAM® PRS 500 system with low energy 50 kV X-ray irradiation, combined with breast conserving surgery in early breast carcinoma, is a well-tolerated and safe method, with a low complication rate. It provides good local control in 5-year follow-up. This is an effective procedure that provides high survival rate and provides fine aesthetic effect.
No conflict of interest.

2052 POSTER

Survival outcomes of breast conserving therapy via reduction mammoplasty in breast cancer patients

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Background: Reduction mammoplasty (RM), which has long been used for the treatment of macromastia, has recently become a preferred technique in the surgical treatment of breast cancer patients with macromastia. There is limited evidence in the literature on the oncologic safety and aesthetic outcome of the oncoplastic procedures. There is a small amount of data on its impact on local recurrences, distant metastasis, and overall survival. In the present study, we have reported the late results of the 117 breast cancer patients with macromastia treated with this technique.
Patients and Methods: 117 breast cancer patients with macromastia who underwent BCT via RM between 2003 and 2011 at Ankara Oncology Hospital were enrolled in the study. The patients who underwent with lower or upper pediculated flaps as a reduction technique are included. All of the patients were stage I, II and IIIA. Age, histopathological type, tumor size, local recurrence, distant metastasis, weight of the reduction mammoplasty specimens were analyzed.
Results: The median follow-up time was 31 months. Median age was 52.5 years. Median weight of the reduction mammoplasty specimen for the cancerous side was 950±20 g, for the other side was 960± 32g. During follow-up one loco-regional recurrence was noted. Seventeen patients developed distant metastases. The 5-year disease free survival (DFS) rate was 69% and the overall survival (OAS) rate was 79%. In stage I 5-year disease free survival rate was 100 % and the overall survival rate was 100%. In stage II 5-year disease free survival rate was 60 % and the overall survival rate was 78%. In stage III 5-year disease free survival rate was 24 % and the overall survival rate was 31%.
Conclusion: Reduction mammoplasty provides techniques to achieve good esthetic results while also providing possibility for wide excision margins. Few studies report on long-term oncological results of oncoplastic surgery, our findings indicate that BCS via RM are as effective and safe as standard surgical procedures in breast cancer patients with macromastia.
No conflict of interest.

2053 POSTER

Application of artificial neuronal networks for predicting presence of non-sentinel lymph node metastases in breast cancer patients with positive sentinel lymph node biopsies

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Background: We should expect involvement of other axillary lymph nodes in about 40% of breast cancer patients with metastatic lesions diagnosed in sentinel lymph node biopsy (SLNB). The goal of this work is to present a new model of predicting presence of metastatic lesions in non-sentinel lymph nodes (nSLNs).
Material and Methods: Among 1583 patients with non-advanced breast cancer (cN0) subjected to SLNB between 2004 and 2012 we found metastatic lesions in sentinel lymph nodes excised from 348 patients (22%). Accessory ALND was performed in the majority of cases (94%). Involvement of nSLNs was identified in 32.1% of patients following ALND. Among patients with SLN metastases we examined the correlation between nSLN involvement and selected epidemiological data as well as primary tumor features and details of diagnostic and therapeutic management. Artificial neural networks were used to create a nomogram.
In the analyzed subjects we also assessed the predictive value of other prognostic systems (MSKCC, Tenon and Stanford nomograms).
Results: There were 347 women and 1 man included in the study group with median patient age of 55.2±9.9 years (from 23 to 80 years). Mean size of the excised primary lesions was 21.7±10.7 mm (4−70 mm). A mean of 2.8±1.6 lymph nodes (1−13) were excised during SLNB, with median number of metastatic SLNs amounting to 1.4±0.7 (1−6 nodes).
We made surgical treatment more radical by performing ALND in 94.0% of patients with SLN metastases (327/348). We identified nSLN lesions in 32.1% of patients (105/327). Mean patient follow-up time was 25.1 months (3−66).
Multidimensional analysis of the evaluated factors was performed using an artificial neural network with MLP 40−5−2 architecture. It included patients with a set of necessary clinical data (237 patients). Taking into consideration the presence of SLN capsule infiltration, vascular embolisms, palpability and multifocal nature of the tumor, involvement of the other breast, HER2 status, clinical staging, familial occurrence of breast cancer, hormonal therapy, presence of *comedo* component, tumor location, histological and molecular type of the tumor and Ki-67 value, we obtained AUC coefficient equal to 0.87. Sensitivity of the test amounted to 69%, specificity to 86% and accuracy − 80%.
In case of MSKCC nomogram the calculated AUC value was 0.71, for Stanford nomogram − 0.68, for the Tenon model − 0.67.
Conclusions: In the analyzed group of patients, only the MSKCC nomogram and the new model for prediction of nSLN involvement exhibited AUC values exceeding the expected level of 0.70.
During creation of our test, unlike previous nomograms, for the first time we used variables such as biological tumor subtype and Ki-67 index value.
No conflict of interest.

2054 POSTER

Unexpected ductal carcinoma in-situ is associated with a higher re-operation rate following breast conserving surgery

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Introduction: It has recently been reported that the reoperation rate after breast conserving surgery is surprisingly high at 20% and higher when in-situ disease is present (29.5% v 18%). This was reported on postoperative histology. We examined how often the postoperative histology was at variance to the preoperative core biopsy and analysed the reoperation rate by the core biopsy.
Methods: We analysed pre-operative core biopsy, post-operative histological reports and reoperation rates on a series of 174 patients undergoing breast conserving surgery, whose pre-operative core biopsy found invasive ductal carcinoma only.
Results: Out of 174 patients, 100 (57%) had ductal carcinoma in situ as well as invasive carcinoma reported on the post-histopathology, that had not been identified pre-operatively. This was associated with a subsequent higher reoperation rate of 19% compared with 8% ($p < 0.05$ Chi-square).
Conclusions: Reoperation following breast conserving surgery was higher when in-situ disease was unexpectedly identified postoperatively. Discussion with breast histopathologists reveals that not all would report the presence of in-situ disease in a core biopsy containing mainly invasive carcinoma. We recommend a standard proforma for preoperative core biopsy reports to include both invasive and in-situ components.
No conflict of interest.

2055 POSTER

A portable gamma camera for intraoperative real time imaging of sentinel lymph nodes in early breast cancer

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Background: Access to nuclear medicine department for sentinel node imaging remains an issue in number of hospitals in the UK and many parts of the world. Sentinella® is a portable imaging camera used intra-operatively to produce real time visual localisation of sentinel lymph nodes.
Material and Methods: Sentinella® was tested in a controlled laboratory environment at our centre and we report our experience on the first use of this technology from UK. Moreover, preoperative scintigrams of the axilla were obtained in 144 patients undergoing sentinel node biopsy using conventional gamma camera. Sentinella® scans were done intra-operatively to correlate with the pre-operative scintigram and to determine presence of any residual hot node after the axilla was deemed to be clear based on the silence of the hand held gamma probe.
Results: Sentinella® detected significantly more nodes compared with CGC ($p < 0.0001$). Sentinella® picked up extra nodes in 5/144 cases after the axilla was found silent using hand held gamma probe. In 2/144 cases, extra nodes detected by Sentinella® confirmed presence of tumour cells that led to a complete axillary clearance.
Conclusions: Sentinella® is a reliable technique for intra-operative localisation of radioactive nodes. It provides increased nodal visualisation rates compared to static scintigram imaging and proves to be an important tool for harvesting all hot sentinel nodes. This portable gamma camera can definitely replace the use of conventional lymphoscintigrams saving time and money both for patients and the health system.
No conflict of interest.

2056 POSTER

Comparison of FNA, touch print, and crush print with permanent pathology in the diagnosis of breast lumps in patients in Shohada Hospital of Khorramabad

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Introduction: Breast mass is a common disease and one of the most common complaints of patients in clinics of breast surgery. Breast mass is one of the most important symptoms of cancer. In addition to the methods of imaging and clinical examinations, fine needle aspiration (FNA) preoperatively along with Touch Print, Crush Print, and Frozen Section intraoperatively are applied to reach the diagnosis. In this study, in addition to the epidemiologic and clinical characteristics of the disease, the results of Crush Print and Touch Print methods intraoperatively were compared with permanent pathology.
Materials and Methods: This cross-sectional, epidemiological, analytical study was conducted on 107 patients with breast masses, who had been referred to Shohada Hospital of Khorramabad in 2012. The epidemiologic and clinical features of the patients were collected using a questionnaire. FNA was performed preoperatively, and Touch Print and Crush Print were prepared intraoperatively and sent to the Pathology Ward. The results were compared with permanent pathology. For all the methods, the diagnostic values of sensitivity, specificity, positive predictive value, negative predictive value, false positive percentage, and false negative percentage were calculated.
Results: The comparison between Touch Print and Crush Print with pathological diagnosis in detecting breast cancer showed the sensitivity, specificity, positive predictive value, negative predictive value, false positive percentage, and false negative percentage to be 97/8%, 100%, 98/4%, 0%,2/2% The comparison between the diagnostic values of FNA with pathological diagnosis in the diagnosis of breast cancer showed the rates to be 80.4%, 98%, 97.3%, 87.7%, 2%, and 19.6% respectively.
Conclusion: Considering the sensitivity, specificity, and positive predictive values of Touch Print and Crush Print methods in detecting breast cancer, we recommend the use of these easy and quick methods for these patients.
No conflict of interest.

2057 POSTER

Management of nipple discharge: should we operate when advanced digital mammography fails to detect cancer?

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Background: There are no clear guidelines for the management of nipple discharge when triple assessment indicates benign features. The aim is to assess the outcome of microdochectomy and total duct excision as a management of nipple discharge.
Material and Methods: Patients who underwent a total duct excision or microdochectomy between 2008 and 2012 in a single centre were identified. Patient demographics, outcomes of triple assessment and final histology, including the need for further surgery were analysed, and the Fisher's exact test used.
Results: Of the total 81 patients, 4% ($n = 3$) were male and the median age at presentation was 51 years. Total duct excision was performed in 86% of patients and microdochectomy in 14%. On final histology, 12% ($n = 9$) were diagnosed with malignant disease. The rate of malignancy in women over the age of 50 was 20% compared to 0% in those younger ($p < 0.01$). A malignancy rate of 38% was observed in women over 70. Of the 3 male patients 1 had ductal carcinoma in situ (DCIS), 1 developed invasive ductal carcinoma at 17 months and the other had a papilloma with associated atypical ductal hyperplasia. Papillomas were found to be the cause of symptoms in 24% of cases. Blood stained discharge was the most common presentation in patients treated surgically (43%) and also in those found to have malignancy (90%). In patients with malignant disease, benign features were identified in 90% on clinical examination, 50% on radiological examination; and core biopsies were undertaken in 60%. Of the 10 confirmed cases of malignancy, triple assessment only identified 2 cases as suspicious, and 1 case as malignant.
Conclusions: In the era of advanced digital mammography, a malignancy rate of 12% indicates the need to continue to offer surgical excision for patients with persistent symptoms or atypical history, especially women over 70 and men of any age. Young women under 50 can be managed conservatively with close follow up.
No conflict of interest.

2058 POSTER

Oncoplastic surgery of breast cancer in developing countries

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Background: Breast cancer is the most common malignant tumor in women. Due to trauma and deformity occurring after mastectomy oncoplastic surgical approach has become routine and necessary. Primary breast reconstruction is regular procedure on Institute for Oncology and Radiology of Serbia in Belgrade. Result is an adequate oncological surgery with improved quality of life, aesthetics and psychosocial rehabilitation. Because of limited funds expander prosthesis are not implanted.

Materials and Methods: On our clinic for oncological surgery 76 breast reconstructions were performed in year 2012. Primary reconstruction was performed on 66 patients (86.8%). Secondary reconstruction was performed on 10 patients (13.1%).
Results: Primary subcutaneous mastectomy with axillary node dissection and frozen section examination of retromamilar cone with implantation of subpectoral endoprothesis was performed on 55 patients(83.3%). At the same time, on 4 patients (6.06%) augumentation of contralateral breast was done because of simetralisation.
In 6 patients (9.09%) retromamilar cone was positive on malignancy so excision of areola and mamila was performed. In one patient endoprothesis was placed subcutaneously because of defect reconstruction due to DCIS resection.
Secondary reconstruction was performed on 10 patients, on 4 because od prosthesis perforation (described by Ultra Sound or NMR) and in 6 patients because of skin necrosis due to radiotherapy.
Conclusion: Oncoplastic approach to breast surgery is continuously evolving. Given the psychosocial trauma that is more or less common in all patients in addition to appropriate surgical intervention adequate multidisciplinary team is necessary consists by medical oncologist, radiotherapist, physiotherapist, psychologist etc. Survival rates are almost the same but effect in term of life quality are significantly better.
No conflict of interest.

2059 POSTER

Evaluation of the inferior pedicle therapeutic mammoplasty as a primary procedure for upper quadrant breast cancer

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Background: The treatment of breast cancer in large breast patients represents a great challenge to both surgeons and radiation oncologist. The aim of this study is to evaluate the outcome of inferior pedicle therapeutic mammoplasty in patients with upper quadrant early breast cancer and have large breast.
Materials and Methods: Thirty-five patients with early breast cancer and have macromastia were included in this study. Simultaneous bilateral inferior pedicle therapeutic mammoplasty was performed.
Results: The age of the patients ranged from 36 to 61 (median 46) years and tumour size ranged from 1 to 3.5 cm. the weight of the tissue removed ranged from 350gm to 780gm and the tumour safety margins ranged from 3 to 8 cm. Wound dehiscence was the commonest post operative complications and affect 6 patients (17.6%). the cosmetic outcome were excellent in 22 patients (64.5%), 9 patients (26.5%) showed good results, two patients (6%) were satisfactory and one patient (3%) showed poor result. The follow up period ranged from 6 to 42 months with one case (3%) of systemic metastasis.
Conclusion: Inferior pedicle therapeutic reduction mammoplasty for upper quadrant early breast cancer in large breasted women is a surgically and oncologically safe procedure and carries a satisfactory esthetic outcome.
No conflict of interest.

2060 POSTER

Immediate breast reconstruction of segmentectomy defects using extended lattisimus dorsi flap via single axillary incision

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Background: Aim of this study is to describe the technique of extended autologous latissimus dorsi flap to reconstruct segmentectomy defects via single axillary incision and to assess the outcomes of this procedure.
Methods: Between December 2008 and December 2012, 88 patients with early breast carcinoma, underwent extended latissimus dorsi flap for reconstruction of segmentectomy defects (reaching about 20−30% of breast volume). Measured outcomes included: surgical complications, cosmetic outcome, and functional disability.
Results: Acceptable results were noticed with this technique as regard: postoperative complications (4 patients) with no further surgical intervention, sensory loss (nipple-areola complex; 4 patients, quadrant; 18 patients), restricted activities in 4 patients. Considering aesthetic evaluation, very much acceptable results were noticed as regard panel assessment and patient satisfaction.
Conclusion: This technique is associated with few adverse surgical and physical sequalae, without compromising cosmetic outcome, representing good alternative to mastectomy (if similar), avoiding additional scars and use of prosthesis.
No conflict of interest.

2061 POSTER

Periareolar single-port surgery of skin-sparing mastectomy by video-assisted breast surgery (VABS) is better aesthetic and lower invasive

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Background: Early-stage breast cancer, such as DCIS, may force to complete removal of the mammary gland because of its wide spread in the breast. For such cases, skin-sparing mastectomy (SSM) should be recommended. However, the conventional oncoplastic surgery leaves some ugly scars on the breast due to large skin incisions. By applying the endoscopic video-assisted breast surgery (VABS), we can provide more aesthetic surgery with single periareolar port approach, leaving only a small and inconspicuous scar on the breast.
Methods: VABS of SSM consists of periareolar skin incision, dissection of whole mammary gland, sentinel node (SN) biopsy, and axillary node (AN) dissection. After SSM, the breast reconstruction was performed by the delayed or simultaneous method. We use the implant for simultaneous reconstruction. SN biopsy was performed endoscopically with only 1 cm incision in the axilla which was marked with 3D-CT lymphography prior to surgery. For SSM, we made a skin incision of 2.5−3.5 cm incision at the foot-side edge of the areola, to preserve blood flow around the areola. We cut across the gland near the nipple and quickly checked the transected stump by fast frozen section. Subcutaneous detachment was applied to the entire gland. Back of the gland was peeled just above the pectoralis major muscle fascia. The liberated gland was removed through the port with a plastic bag.
Results: We performed VABS on 300 patients since 2001, and SSM on 30 patients. Tumor size is 1.6 cm on average. Age is 57.2 years. 23 nipples were preserved. 17 cases were DCIS. 4 were invasive lobular carcinoma. 9 were invasive ductal carcinoma. 2 cases had SN metastasis. One case had AN metastasis. Between VABS and the conventional surgery, there was no difference in the amount of blood loss and operation time. Postoperative aesthetics was particularly good after simultaneous reconstruction. They had less sensory disturbance and high satisfaction. After 38 months, there have been no distant metastases, no postoperative deaths, and one local recurrence).
Conclusions: VABS SSM with periareolar skin incision approach makes better aesthetic results.
No conflict of interest.

2062 POSTER

Baseline results of the EORTC 10041/MINDACT TRIAL (Microarray In Node 0−3 positive Disease may Avoid ChemoTherapy)

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Background: The EORTC 10041-MINDACT TRIAL investigates whether the 70-gene profile (MammaPrint®, MP) selects the right patients for adjuvant chemotherapy (CT) as compared to standard clinical pathological (CP) criteria.
Methods: Pts consented to MP prior to surgery with results reported as MP genomic high (Gh) or low (Gl) risk. Conditional on nodal status, successful gene testing and other eligibility criteria, pts were then enrolled into the trial. CP prognostic risk was assessed through a modified version of Adjuvant! Online (CP low risk (Cl) is >88% 10-years breast cancer specific survival for ER+ disease and >92% for ER negative). Genomic (G) and clinical (C) high risk pts were proposed adjuvant CT and were randomized between a non-anthracycline vs. a taxane-based CT regimen. G-low and C-low risk patients were not proposed for adjuvant CT and could be randomized between Tamoxifen 2 years, followed by Letrozole 5 years vs. Letrozole

7 years. Discordant patients, either G-low/C-high (Gl/Ch) or G-high/C-low (Gh/Cl) were randomized by MP risk or CP risk for CT decision.
Results: From March 2007 to July 2011, 11289 patients were screened in 112 sites over 9 countries, of which 6694 (59%) were enrolled. In the final stages, accrual averaged 385 per month.
Main reasons for non-enrollment after screening were: inadequate/absent sample (13%), patient/investigator decision (19%), genomic testing infeasible (27%, mostly <30% tumor cells), too high LN involvement (16%). After data cleaning the 4 risk groups were Gl/Cl 2743 patients (41%), Gh/Cl 592 (9%), Gl/Ch 1550 (23%) and Gh/Ch 1807 (27%). Using the two risk assessment methods for CT decision, there was 14% decrease in CT assignment when using MP.
Clinical parameters show a relatively favorable population (72% tumor size $\leqslant$2 cm, 67% >50 yrs old), though not uncommon for present-day breast cancer.
Interestingly, CP parameters are only partially reflected in MP assessment: Gl vs. Gh: LN- 79% vs 80%, tumor size $\leqslant$2 cm 76% vs 64%, grade 1 31% vs 5%, ER and/or PgR+ 99% vs 69%, HER2 neg 95% vs 83%.
When comparing CT policies, MP vs. CP would lead to following CT modifications: −5% in N0, −51% in N+, −17% in ER+, +2% in ER-. Actual CT administration data are still in collection.
Conclusions: 1) The logistically complex MINDACT trial turned out to be feasible across several countries 2) 31% of tumors showed discordant MP/CP risk assessment (Gh/Cl or Gl/Ch) 3) as intended, MP stratification only partly overlaps with CP risk (e.g. nodal status (0 vs 1−3) was not correlated with MP risk, r = 0.01).
Conflict of interest: *Ownership: L Van 't Veer is co-founder, stockholder, employee of Agendia NV*

2063 POSTER

Trastuzumab-based adjuvant chemotherapy for breast cancer: Early myocardial dysfunction detected by "speckle tracking echocardiography" (STE)

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Background: Trastuzumab (TZB), an anti HER-2 receptor monoclonal antibody, was shown to be effective in breast cancer patients over-expressing HER-2 in the neo-adjuvant, adjuvant and metastatic setting. Careful cardiac monitoring is required when administered in combination with anthracyclines (ANT) which can increase its toxicity. Myocardial deformation indexes associated with STE myocardial imaging were shown to be very sensitive in identifying left ventricular (LV) dysfunction.
Patients and Methods: A phase IV, prospective, non-randomized study was designed to assess by STE technique the amount, timing and type of TZB-induced pre-clinical cardiac dysfunction when administered after epirubicin (EPI) in patients with HER-2 positive breast cancer. The schedule of TZB treatment was 6 mg/kg q3w for 1 year following EPI. Inclusion criteria: 18−70 yrs, histologically confirmed HER-2 positive breast cancer, LVEF $\geqslant$55%; ECOG PS score 0−2, no history of cardiac disease. ECOG PS score, conventional echocardiography and 2D STE parameters (circumferential and longitudinal S and SR, LV torsion), circulating levels of proinflammatory cytokines (IL-6 and TNF-α), reactive oxygen species (ROS) were assessed at baseline, after EPI treatment and one week after each TZB administration up to the 8th TZB administration.
Results: Thirty-eight patients (mean $\pm$ SD age 51$\pm$10 yrs) were enrolled from May 2012. A significant reduction in SR longitudinal peak (0.71$\pm$0.16 s-1 vs 0.81$\pm$0.14 s-1; $p < 0.05$) and a significant increase in circumferential function (1.03$\pm$0.31 s-1 vs 0.71$\pm$0.13 s-1; $p < 0.01$) were observed after EPI treatment. From the third TZB dose a marked reduction in circumferential function (0.69$\pm$0.18 s-1 vs 1.03$\pm$0.31 s-1; $p < 0.01$) and LV rotation (15.26$\pm$5.38 vs 22.88$\pm$6.41; $p < 0.001$) and no further reduction in longitudinal function were detected. A slight but significant reduction of the LVEF occurred soon after the fourth dose of TZB. ROS increased significantly after EPI treatment but did not change thereafter, while IL-6 and TNF-α were in the normal range throughout the treatment.
Conclusions: We showed that after treatment with EPI longitudinal function was impaired while a compensatory increase in LV circumferential function and LV torsion was observed. TZB treatment had a negative impact on mid and sub-epicardial fibres function, responsible mainly for circumferential function and left ventricle torsion. These effects could be attributed to the higher toxicity of TZB on hyperactive myocardial fibres after EPI treatment. The study is in progress and longer follow-up will show if this mid and sub-epicardial myocardial impairment persists over time and eventually results in an overt clinical cardiac dysfunction.
No conflict of interest.

2064 POSTER

Protein expression profiling in patients with large residual breast cancer (>1 cm) following primary systemic chemotherapy

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Background: Primary systemic chemotherapy (PSC) is a common approach for Early Breast Cancer (EBC). Persistence of large residual tumor following PSC is the strongest predictor of tumor relapse. Identification of molecular markers in the residual tumor may predict relapse risk and identify molecular targets.
Material and Methods: Patients with EBC and PST treated from 1996 to 2010 in two institutions were analyzed. Mayor inclusion criteria: (i) Histologically confirmed Stage II − III BC, (ii) anthracycline and/or taxane based PSC, (iii) residual breast tumor larger than 1 cm and >10% viable tumor cells, (iv) preserved tumor, and (v) signed consent form. A tissue matrix-array was generated with Immunohistochemistry analysis of 29 potential molecular markers associated to phenotype, apoptosis, signaling, deregulation, metastasis, transcription and adhesion. A histo-Score (0–300) was used for cytoplasmatic (cyt)/nuclear (nuc) markers, and a classic (0 to 3) for membrane cell markers. The analysis was done for distant disease-free survival (DDFS).
Results: A total of 256 patients were included. With a median follow-up of 53 months, 80 metastatic events (32%) were reported with a 5 years DDFS of 71%. Univariate analysis identified several predictors of DDFS: ER (p 0.005), Ki67 (0.0002), Cyt-HER4 (<0.04), Bcl2 (<0.05), BP1 (0.02), nuc-Ciclin D1 (0.02), nuc-PTEN (0.02); Cyt-p65 (0.03) and nuc-p65 (0.03). A multivariate model (stepwise method) for DDFS obtains a molecular signature with 6 markers of poor prognosis: ER [= 0], cyt-p65 [<85], cyt-HER4 [>75], cyt-PTEN [= 0], BCL2 [<78] and Ki67 [>20]. The 5-year DDFS for 0−1, 2−3 or $\geqslant$4 conditions were 84.8%, 70.7% and 34.2% ($p < 0.00001$).

Number of conditions satisfied	Progression-free survival time Cox Regression Model		
	HR	95% CI	p-value
0 or 1	1	–	–
2 or 3	2.15	(1.2−3.9)	0.01
4, 5 or 6	5.73	(3.0–11.1)	<0.00001

An analysis stratifying by ER-status identifies dissimilar markers. ER negative [=0]: cyt-HER4 (p 0.01), nuc-P65 (0.01), BP1 (0.001) cyt-65 (0.02) and cyt-ECad (0.04). For ER-positive [>0]: nuc-CiclinD1 (p 0.02), Ki67 (0.02), nuc-Survivin (0.02) and cyt-pAKT (0.03).
Conclusions: A molecular signature in the residual tumor following PSC for EBC identifies patients with low, moderate or high risk of distant progression. ER expression is a determinant prognostic factor differentiating two populations with specific markers. A validation study is ongoing.
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No conflict of interest.

2065 POSTER

Changes in breast cancer subtype between primary tumor and residual disease after neoadjuvant systemic chemotherapy (NSC)

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Background: Breast cancer treatment and prognosis is determined by tumor subtype. Tumor heterogeneity and lack of stability in ER, PR and HER2 has been described between primary tumor and metastatic disease. We evaluate the changes in tumor subtype between primary tumor and residual disease after treatment with NSC and its association with outcome.
Methods: A total of 398 women with known biomarker status in the primary tumor and in the residual disease after NSC were identified between 1992–2012. For each biomarker we evaluated stability and changes from positive to negative or negative to positive. Descriptive statistics were used;

Kaplan–Meier method was used to estimate the 5-year OS and RFS by receptor status change. Cox proportional models were fit to determine the association of receptor status changes with outcomes after adjustment for important patient and disease characteristics.
Results: From the 398 patients included, 162 (40.7%) experienced a change in at least one breast cancer biomarker between the primary tumor and the residual disease. Twenty-nine (40.2%) of the 72 patients with HER2+ primary tumors, changed to HER2−; and of the 320 HER2− tumors, 11 (3.4%) changed to HER2+. Among the 35 trastuzumab-treated patients, 16 (45.7%) of them changed to HER2-. Twenty-three (10.9%) of 211 ER+ tumors changed to ER−; and among 187 ER− tumors, 39 (20.8%) changed to ER+. Fifty-seven (35.2%) of 162 PR+ tumors changed to PR-; and 28 (11.9%) of 235 PR- primary tumors changed to PR+. With a median follow-up of 40 months, the 5-year OS of patients with and without any biomarker status change was 75% and 63% respectively ($p = 0.07$). The 5-year PFS was 63% and 48% for patients with and without biomarker status change ($p = 0.003$). In the multivariable model, a change in any of the tumor biomarkers was associated with improved RFS (HR 0.63, 95% CI 0.44−0.9) but had no statistical impact in OS (HR 0.79; 95% CI 0.53–1.18).
Conclusions: Changes in ER, PR and HER2 between the primary tumor and the residual disease are common. Lack of stability in tumor biomarkers can be associated with issues associated with the test itself, tumor heterogeneity, clonal selection and differential treatment response. In this retrospective study, a change in biomarker status was associated with improved RFS. Further prospective studies are needed to confirm our findings in larger cohorts and to determine the impact that changes in therapy have in the outcome of this group of patients.
No conflict of interest.

2066 POSTER

Outcome of 561 non-metastatic triple negative breast cancer patients: Multi-center experience from Turkey

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Triple negative breast cancers account for 15% of all breast carcinomas. Triple negative cancers presenting as an early stage breast cancer is associated with high recurrence and early distant metastasis risk than hormone receptor positive and human epidermal growth factor receptor (HER-2) positive breast cancers. In the presenting study basic clinico-pathologic characteristics, prognostic factors and recurrence patterns of the triple negative breast cancers were evaluated retrospectively. Between 2000 and 2010 medical records of 561 non-metastatic triple negative breast cancer patients admitted to 8 different cancer centers in Turkey were evaluated retrospectively.
Frequency of triple negative breast cancer was 12% in our study. All patients were women whose median age was 48. Three hundred and eleven (55.4%) of the patients were premenopausal. Majority of patients had early stage breast cancer at the time of diagnosis (16.8% stage I, 48.1% stage II, 35.1% stage III). Invasive ductal carcinoma was the most frequent histology (84.1%). Frequency of grade II and grade III was 27.1% and 48.5%, respectively. As an adjuvant therapy, 94.3% and 41.2% of women received chemotherapy and radiotherapy, respectively.
Median follow up period was 28 (range: 3–290) months. During follow up period 134 (23.8%) patients were diagnosed as recurrent disease. Recurrence sites were mostly bone and soft tissue. Factors affecting disease free survival (DFS) and overall survival (OS) were age (both $p < 0.001$), lymph node involvement (both $p < 0.001$), lymphovascular invasion (LVI) ($p < 0.001$ and $p = 0.004$) and the stage of the tumour (both $p < 0.001$) and adjuvant administration of antracycline based chemotherapy (both <0.001) and the type of surgery (NS for DFS but $p = 0.05$ for OS). In our study group, 3-year DFS and OS were 72.0% and 93.0% respectively. Age, lymph node involvement, LVI, stage, and adjuvant chemotherapy choice were determined prognostic factors in our study. Prevalent recurrence sites were bone, soft tissue and the lung. Further adjuvant prospective randomised trials are needed to confirm prognostic and predictive factors in this quite unique patient population.
No conflict of interest.

2067 POSTER

A prospective, randomized, multicenter, comparative and open-label study on hepatotoxicity of anastrozole compared with tamoxifen in adjuvant therapy in postmenopausal women with hormone receptor+ early breast cancer

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Background: Tamoxifen and aromatase inhibitors are widely used in adjuvant therapy for breast cancer patients, but their hepatotoxicity has not been fully investigated. This study (NCT00537771) was the first study to compare the liver safety of tamoxifen and anastrozole.
Materials and Methods: 353 Chinese postmenopausal women with Hormone Receptor positive early breast cancer, after completion of primary therapy (surgery±radiotherapy±chemotherapy), were randomised 1:1 to anastrozole (1 mg P.O daily) or tamoxifen (20 mg P.O daily). Patients were followed for fatty liver disease, abnormal liver function and treatment failure until 3 years after randomization. The primary endpoint fatty liver disease is defined as a liver-spleen ratio of less than 0.9 on hepatic CT scan. Hepatotoxicity was analyzed in ITT (all randomized subjects) set and safety was analyzed in Safety set (all subjects who took at least one dose of the study medication).
Results: Demographic and other baseline characteristics were well balanced in two groups. Patients in anastrozole group developed less fatty liver disease in years 1, 2 and 3. The cumulative incidence of fatty liver disease after 3 years in anastrozole group was statistically significantly lower than tamoxifen group (14.6% vs. 41.1%, $p < 0.0001$; RR = 0.30, 95% CI: 0.21, 0.45) in ITT population. The cumulative incidence of abnormal liver function after 3 years' treatment showed no significant difference between tamoxifen group and anastrozole group (24.6% vs. 24.7%, $p = 0.6186$). Tamoxifen group had higher treatment failure rate than anastrozole group in 1, 2 or and 3 years. The median time to treatment failure for tamoxifen group was 15.1 months (454 days) and 37.1 months (1112 days) for anastrozole group (HR = 0.27, 95% CI: 0.20, 0.37, log-rank $p < 0.0001$). The most commonly reported adverse events were 'reproductive system disorders' in tamoxifen group (17.1%) and 'musculoskeletal disorders' in anastrozole group (14.6%).
Conclusion: The results from this study indicate that postmenopausal women receiving adjuvant anastrozole showed less fatty liver disease and therefore had a favourable hepatic safety profile than those receiving tamoxifen for hormone receptor positive early breast cancer.
No conflict of interest.

2068 POSTER

A prospective multi-centre study of the impact of Oncotype DX® on adjuvant treatment decisions in patients in the UK with estrogen receptor positive early breast cancer

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Background: The proportion of patients (pts) with estrogen receptor positive (ER+) early breast cancer that benefit from adjuvant chemotherapy (CT) is modest. Onco*type* DX®, a validated multigene assay, provides prognostic and predictive information beyond traditionally used parameters. The test can help in making more informed treatment decisions. It is not routinely used in the UK.
Materials and Methods: 147 patients with ER+, HER2 negative early breast cancer, recommended to discuss adjuvant CT by the multi-disciplinary teams in 3 NHS hospitals were offered Onco*type* DX. Pts with any T stage, N0 and, if >50 yrs old also N1 (1−3 + nodes) disease were eligible. Questionnaires were independently completed by patients and the same oncologist at two consultations, before and after receiving the Onco*type* DX Recurrence Score result. Data from a preliminary analysis, on the first 85 evaluable patients, seen by 10 oncologists, was available at

the time of abstract submission. The final data from 147 pts included in the study will be presented at the meeting.
Results: Median age 56 years (range 31 −74 years). Tumour characteristics: T1 58%, T2 42%. Grade 1 7%, Grade 2 64%, Grade 3 29%. VI+ 20%. N0 68%, N1(mic) 9%, N1 21%, Nx 2%. Mean Recurrence Score = 18: 51% low (<18), 42% intermediate (18−30), 7% high (>31). Oncologists treatment recommendation changed in 36 pts (29 CT to no CT, 7 no CT to CT) Overall, oncologists recommended CT in 55% of pts pre Onco*type* DX and 28% post Onco*type* DX. For 25 pts the Recurrence Score result clearly changed their initial decision; 11 to CT, 14 to no CT. Patient confidence in their decision increased post Onco*type* DX. For 66 pts, after the second consultation, there was concordance between oncologists and pts about treatment (19pts CT; 47pts no CT). For the other 19 pts, 8 chose CT when the oncologist advised there was only likely to be a small benefit, 4pts declined CT despite it being recommended, 1pt decided against CT before the Recurrence Score was available and for 6 pts there was no clear decision documented.
Conclusions: This prospective study confirms the uncertainty pts and oncologists have about adjuvant CT in ER+ early breast cancer. Using Onco*type* DX® was associated with a significant change in treatment decisions and an overall reduction in chemotherapy being recommended. Use of the test was associated with increased patient confidence in their treatment decision.The data are consistent with those presented from Wales, Germany, Spain and the US.
Conflict of interest: *Advisory board: Genomic Health*

2069 POSTER

Preliminary results of the TEAMIIA trial: Efficacy of six months neoadjuvant exemestane therapy in postmenopausal hormone receptor-positive breast cancer patients − a Dutch Breast Cancer Trialists' Group study

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Background: Neoadjuvant treatment is playing an increasing role in the clinical management of breast cancer (BC). Several studies have shown that estrogen receptor-positive (ER+) BC patients are less sensitive to neoadjuvant chemotherapy than ER-negative patients, and may be best treated with neoadjuvant hormonal therapy (NHT) instead. There is currently no consensus on the optimal duration of NHT. Here we present an overview of the preliminary outcomes of the TEAMIIA trial, a multicenter, prospective, phase II trial investigating the efficacy of six months of neoadjuvant exemestane in postmenopausal, strong estrogen receptor-positive (ER+, >50%) BC patients.
Methods: Primary endpoint was clinical response at 3 and 6 months as measured by palpation. Secondary endpoint was radiological response as measured by Ultrasound/MRI and/or mammography. Paired samples T-tests (95%confidence interval (CI)) were used to compare mean changes in tumor size (in mm) between baseline and 3 months, and between 3 and 6 months after randomization. We also evaluated conversion rates from mastectomy to breast conserving surgery (BCS).
Results: 107 patients (stage T2-T4ac) were included in the study (median 72 years (53−88)). Clinical and radiological response data were available for 64 patients at 3 months, and for 34 and 40 patients at 6 months respectively. Overall response rate (partial response + complete response) at 3 months was 48.4% and increased to 67.5% at 6 months. Mean tumor size at the start of treatment was 48.6 mm (SD 81.8), and decreased to 29.3 mm (standard deviation (SD) 12.5) and 24.9 mm (SD 14.3) at 3 and 6 months respectively ($p = 0.001$ at month 3 and 6). Mean decrease in tumor size was 26.6% (SD 24.5) between 0 and 3 months and 9.3% (SD 21.8) between 3 and 6 months ($p = 0.006$). Out of 35 patients (32.7%) who were not eligible for BCS at baseline, 14 (25.5%) underwent BCS after 6 months of NHT, which translates to a conversion rate of 40%.
Conclusion: This study shows that neoadjuvant exemestane therapy is effective in strong ER+ breast cancer patients and persisted after 6 months of treatment. BCS rates also improved following 6 months of NHT.
No conflict of interest.

2070 POSTER

Fertility counseling in young women with breast cancer: A cross-sectional study

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Background: Adjuvant chemotherapy in young patients with breast cancer can cause permanent infertility. Loss of fertility after breast cancer treatment negatively impacts quality of life in young patients. It is therefore important to counsel patients before treatment and to provide the opportunity for fertility preservation. This cross-sectional study investigated the association of fertility counseling and quality of life in young women with breast cancer.
Material and Methods: Sixty-five women who were diagnosed with early stage breast cancer between the ages of 18 and 42 years completed several quality of life questionnaires. Participants were asked if they received counseling by a fertility specialist and if they underwent fertility preservation treatment. The following validated questionnaires were used: Functional Assessment of Cancer Therapy for Patients with Endocrine Symptoms (FACT-ES) and the Hospital Anxiety and Depression Scale (HADS).
Results: Mean age of the women at diagnosis was 34.4 years (range 26−42 years, SD $\pm$ 4.4). Twenty-five patients (38.0%) received only basic information about fertility before chemotherapy by their treating oncologist, while 22 women (33.8%) received intensive counseling by a on this topic specialized medical oncologist and fertility specialist. Ten women with intensive counseling (15.4%) underwent fertility preservation prior to breast cancer treatment. Both patients with fertility counseling by their oncologist or by a dedicated specialized oncologist and fertility specialist scored significantly higher compared to patients without counseling on social well-being ($p = 0.001$), physical well-being ($P = 0.04$) and functional well-being ($p = 0.02$). Fertility preservation in women was significantly related to a wish to have more children ($p = 0.05$) and to fertility counseling ($P = 0.03$).
Conclusion: Fertility counseling prior to breast cancer treatment has a positive influence on quality of life in young women with breast cancer. We recommend to refer women with a wish to have more children to a dedicated medical oncologist and fertility specialist for intensive counseling. In women without a wish to have children, basic information provided by an oncologist is sufficient.
No conflict of interest.

2071 POSTER

Impact of metformin in luminal subtype breast cancer

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Background: Recent observation have shown that metformin use decrease both breast cancer and mortality. Metformin use is also associated with response of neoadjuvant treatment. In the current study, we explored the association between metformin use and survival outcomes in patients with diabetes and non diabetes.
Patients and Method: We analysed the data from Asan medical center breast cancer database from 1997 to 2007.
Total 9916 patients were analysed in this study. Patients were categorized by diabetes status and metformin use. The Kaplan–Meier product method was used to calculate Disease free survival (DFS), cancer specific survival (CCS) and overall survival (OS).
Results: This study cohort was comprised of 8274 non diabetic patients, 251 diabetic patients with metformin, and 250 patients diabetic patients not receiving metformin. At a median 65 months follow up, non diabetic patients group showed better DFS, CSS, OS than diabetic patients ($p < 0.05$). For diabetic patients, metformin group showed better survival than non metformin group ($p < 0.05$). but for subgroup analysis according to the intrinsic subtype, this survival difference was shown only luminal subtypes.
Conclusion: Metformin use impact survival outcomes in diabetic patients especially luminal subtypes.
No conflict of interest.

2072 POSTER

Accuracy of treatment response assessment modalities after neoadjuvant therapy: A Dutch Breast Cancer Trialists' Group (BOOG) substudy

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Background: Studies suggest that MRI is an accurate means of assessing residual tumor size after neoadjuvant chemotherapy (NAC) and neoadjuvant hormonal therapy (NHT). However, little comparative data is known comparing response evaluation using MRI, clinical examination (palpation), and/ or ultrasound with histopathologic response following taxane-based NAC of patients with stage II/III HER2-negative breast cancer treated in a prospective phase III trial.
Methods: From July 2010 to April 2012, 250 patients from 26 participating sites received NAC (6 courses docetaxel, doxorubicin and cyclophosphamide) with or without zoledronic acid. Clinical response (MRI, palpation, and ultrasound measurements) were performed at baseline, after 3 cycles, and post-NAC. Clinical and pathological responses were recorded. Accuracy measures ((true-positives+true negatives)/total cases) were calculated and clinically and pathologically assessed tumor sizes were correlated using Spearman correlation coefficients. Tumor size over- and underestimation were quantified.
Results: The accuracy of MRI (n = 208), palpation (n = 77) and ultrasound (n = 33) for determining pathological response was 75%, 58% and 78% respectively. The correlation coefficient for the comparison between MRI and pathological measurements was 0.44 ($p<0.001$). Correlation coefficients were different for ER-negative ($r = 0.76$, $p < 0.001$) and ER-positive ($r = 0.42$, $p < 0.001$) breast tumors. MRI under- or overestimated the tumor size in 14% and 61% of the patients. In cases of substantial tumor size underestimation (>2 cm) with MRI, surgical margins tended to be tumor positive more often than when tumor size was well- or overestimated (37% vs. 15%, $p=0.06$).
Conclusions: In this relative large HER2-negative breast cancer population, MRI was more accurate than palpation in assessing tumor response. However, MRI measurements correlated only moderately with tumor size on the surgical specimen. MRI predicted residual tumor size more reliably in ER-negative than ER-positive tumors. Therefore, post-NAC MRI should be interpreted carefully in the context of response monitoring with tumor characteristics taken into account.
No conflict of interest.

2073 POSTER

Difference between brand and generic docetaxel in breast cancer treatment

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Background: Docetaxel has emerged as a good option for treatment of breast carcinoma in combination with anthracyclines in both adjuvant and metastatic setting. Recently, several generic formulations were introduced and used in practice.
Objective: The objective of this study was to compare both brand and generic docetaxel in term of toxicity in adjuvant setting and efficacy in metastatic setting.
Material and Methods: The study was performed at Al Bairouni University Hospital in Damascus (SYRIA). In 2011 the brand docetaxel was offered to all patients diagnosed with breast cancer while the generic one was employed to treat breast cancer patients in 2012. In adjuvant setting, the study aimed at comparing toxicity profile between the two formulations while both toxicity and efficacy were evaluated in metastatic setting. Patients included in the study were 1820 patients in 2011 versus 1526 patients in 2012.
Results and discussion: Among the 1820 patients evaluated in 2011, 913 patients presented with metastatic disease either chemonaive or after progression on another line while 710 out of 1526 were metastatic in 2012. Most toxicities were mucosal ulceration, skin burns and cellulitis with different degrees observed in 413 out of 1820 patients in brand arm versus 1224 out of 1526 in the generic arm (P.value 0.039) which favors the brand docetaxel. In term of response, a complete response was reached in 684/913 in brand versus 393/710 in generic arm (P.value 0.14).
Conclusions: Brand docetaxel was shown to be a good option to treat breast cancer in both adjuvant and metastatic setting in the light of good efficacy and toxicity profile. In the other hand, generic docetaxel showed an acceptable efficacy in metastatic setting, however, its toxicity profile does not put it at the top options. It was also noticed that there was an inverse proportion between adverse events and response to treatment in the generic arm, the thing that could be attributed to dose reduction to cope with high grades toxicity.
No conflict of interest.

	Patients	Metastatic disease	Complete response	P value
Brand arm	1280	913	684	0.14
Generic arm	1526	710	393	

2074 POSTER

Evaluation of Ki67 as a potential predictive marker for adjuvant chemotherapy in estrogen receptor-positive and human epidermal growth factor receptor 2-negative breast cancer patients without nodal metastases

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Background: Immunohistochemical (IHC) staining for Ki67 has previously been shown to be a potential prognostic and predictive marker for breast cancer. At the St. Gallen Consensus Meeting, it was determined that the Ki67 labeling index is particularly important for distinguishing between 'Luminal A' and 'Luminal B (human epidermal growth factor receptor 2 [HER2] negative)' subtypes and is a predictive marker for chemotherapeutic efficacy. However, evidence on the Ki67 index being a predictive marker for adjuvant chemotherapy is limited. This study aimed to assess the predictive value of Ki67 in breast cancer patients without lymph node metastases.
Methods: We retrospectively identified 1726 patients in the Tokai University breast cancer database for whom IHC Ki67 data were available between January 2002 and December 2010. Of these, 219 were excluded because of distant metastases (n = 38), a diagnosis of ductal carcinoma in situ (n = 181), or the presence of lymph node metastases (n = 883). Thus, data for 624 patients were evaluated. The Ki67 index was defined as low if <10% of cells stained positive for this marker and high if $\geqslant$10% of cells stained positive. To assess Ki67 levels and survival outcomes, survival curves were calculated using the Kaplan–Meier method and compared using the log-rank test and Cox regression model.
Results: We identified 624 patients with estrogen receptor (ER)-positive, HER2-negative breast cancer and no lymph node metastasis. Of these patients, 27 relapsed and 10 died of breast cancer. Patients with a high Ki67 index (n = 155) had significantly poorer relapse-free survival (RFS) (hazard ratio [HR], 2.335; 95% confidence interval [CI], 1.092–4.990; P = 0.029) and tended to have poorer overall survival (OS) (HR, 3.470; 95% CI, 0.930–12.938; P = 0.064) than patients with a low Ki67 index (n = 468). Adjuvant chemotherapy did not prolong RFS in patients with either a high (HR, 0.966; 95% CI, 0.311–3.004; P = 0.953) or low (HR, 1.131; 95% CI, 0.360–3.555; P = 0.834) Ki67 index.
Conclusion: Our results suggest that Ki67 is a prognostic marker for patients with ER-positive, HER2-negative breast tumors with no lymph node metastases. However, Ki67 is not a predictive marker for the outcome of adjuvant chemotherapy in these patients.
No conflict of interest.

2075 POSTER

Multicenter phase II study of weekly paclitaxel followed by doxorubicin plus paclitaxel as neoadjuvant chemotherapy for triple negative breast cancer (SBCCSG#12, Saitama Breast Cancer Clinical Study Group, Japan)

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Background: Neoadjuvant studies suggest that chemotherapy is effective in triple-negative breast cancer (TNBC). Pathological complete response (pCR), demonstrate an excellent survival in this subtype. In contrast, the outcome of patients who still have residual disease after treatment is relatively poor. These observations suggest that there is a subgroup of TNBC whose tumors are extremely sensitive to chemotherapy. However,

there is no preferred standard regimen of chemotherapy for TNBC, and treatment might be selected as it is for other cancer subtypes. Loesch et al demonstrated that in adjuvant setting, doxorubicin plus paclitaxel followed by weekly paclitaxel (AP-P) is equally effective and tolerable option compare to doxorubicin plus cyclophosphamide followed by weekly paclitaxel (AC-P). In subgroup analysis, TNBC approached significance ($p = 0.07$) that favored AP-P (JCO 28, 2010). Alphonse et al demonstrated that paclitaxel decrease the interstitial fluid pressure and improve oxygenation in breast cancers in patients. Based on this result, to maximize the tumor response, paclitaxel might be administered before doxorubicin in neoadjuvant setting (JCO 23, 2005).
Methods: Patients who were locally confirmed TNBC, tumor size>2 cm and/or with axillary lymphnodes metastases, ECOG PS 0−1 and age over 20 were enrolled in Saitama, Japan. Neoadjuvant chemotherapy was performed as follows: weekly paclitaxel 80 mg/m^2 x 12 followed by doxorubicin 50 mg/m^2 plus paclitaxel 150 mg/m^2 q3W (P-AP). Primary endpoint was pCR (ypT0/is ypN-/+) rate. Secondary endpoints were objective response rate (ORR), breast conserving rate (BCR) and safety.
Results: Sixty-three patients were recruited between July 2008 and August 2011. pCR rate was 30%. BCR and ORR were 60% and 46.8%, respectively. Predominant G3/4 toxicities were neutropenia (24.1%), febrile neutropenia (13.8%) and neuropathy (8.6%).
Conclusions: Sequential P-AP as neoadjuvant treatment for operable TNBC is effective but modest. (UMIN1205)
No conflict of interest.

2076 POSTER

Risk estimations and treatment decisions in early stage breast cancer; agreement among oncologists and the impact of the 70-gene signature

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Background: Estimating the risk of recurrence and related adjuvant systemic treatment (AST) decisions for patients with early stage breast cancer remains challenging, even with the aid of guidelines using clinico-pathological factors. Gene expression classifiers, like the 70-gene signature, have been added to clinical guidelines to improve accuracy and refine risk estimations. This survey evaluated the impact of adding the 70-gene signature on clinicians' risk estimation and AST decisions.
Patients and Methods: In two written questionnaires, 12 medical oncologists assessed 37 breast cancer cases and estimated the risk of recurrence (high versus low) and gave a recommendation for AST (none, endocrine therapy, chemotherapy, trastuzumab, or a combination). The first questionnaire solely presented the clinico-pathological factors age, tumor size, grade, mitose-index, estrogen- and progesterone receptor status, HER2 receptor status, type of surgery, given radiotherapy and the result of the sentinel node biopsy. The second questionnaire in addition disclosed the 70-gene signature result.
Results: The level of agreement among the oncologists in risk estimation (κ=0.55) and AST recommendation (κ=0.57) was moderate. Adding the 70-gene signature result significantly increased the level of agreement to substantial. Risk estimation changed from high risk to low risk in 8% of the cases and 11% less chemotherapy was recommended.
Conclusion: Oncologists' risk estimations and recommendations of AST vary greatly. Our results underline the need for a better standardization in clinical decision-making. Integration of the 70-gene signature may aid to provide each patient with individualized, but more standardized treatment.
No conflict of interest.

2077 POSTER

Monitoring and management of cardiac toxicity in breast cancer patients treated with adjuvant trastuzumab, Northern Ireland Cancer Centre experience

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Background: The incidence of invasive HER2+ breast cancer is 18−20%. These patients (pts) are mostly offered adjuvant trastuzumab therapy which carries a 0.7−7% risk of cardiac toxicity (CT), predominantly declining left ventricular ejection fraction (LVEF). Current practice in Northern Ireland for delivery of adjuvant trastuzumab is based on the HERA trial protocol. We base monitoring and management of trastuzumab-related CT on the updated UK NCRI guidelines which suggest that with early detection and management of declining LVEF, utilising appropriate breaks in therapy and addition of cardioprotective therapies such as Angiotensin Converting Enzyme (ACE) inhibitor drugs, these pts may safely continue trastuzumab treatment. We conducted an audit of institutional practice of cardiac monitoring and management of CT in pts treated with adjuvant trastuzumab.
Methods: A retrospective case note review of 77 consecutive pts treated with adjuvant trastuzumab for invasive breast cancer between December 2010 and December 2011 was performed. We analysed the incidence of adverse cardiac events, their relationship with known cardiac risk factors and the percentage of pts with declining LVEF who were able to complete trastuzumab treatment with the addition of an angiotensin converting enzyme inhibitor (ACEI).
Results: Amongst pts analysed, 13 (16.8%) experienced CT. The incidence of cardiac risk factors was 38% in both those who experienced CT and those who did not. The median age of all pts was 52 (range 31−75), and that of those experiencing CT was 55 (range 31−72). All except one pt experiencing CT received anthracycline-based chemotherapy. One pt (1.3%) had a symptomatic decline in LVEF and 3 (3.9%) had a decrease in LVEF $\leqslant$40%. 9 pts were able to continue and complete treatment with introduction of ACEI, 6 weekly echocardiographic monitoring and referral to cardiology. Of the 4 pts who initially discontinued trastuzumab, 1 was able to restart and complete treatment following an improvement in LVEF with ACEI.
Conclusion: Our management of trastuzumab-related CT was compliant with NCRI guidelines. Our data suggest the rate of trastuzumab-related CT in clinical practice is higher than that reported in most clinical trials. However, treatment with an ACEI allowed the majority of pts who experienced CT to recover LV function and safely complete trastuzumab treatment.
No conflict of interest.

2078 POSTER

Metabolic and anthropometric changes in early breast cancer patients receiving adjuvant therapy

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Background: Weight gain and metabolic changes are common during the first year after breast cancer diagnosis. In this study, we examined clinical factors associated with body size at diagnosis and weight gain during the subsequent year.
Material and Methods: An inception cohort of 465 women with newly diagnosed early breast cancer (EBC) underwent anthropometric [BMI (kg/m^2), weight (kg), waist and hip circumferences (cm), waist-to-hip ratio] and metabolic [insulin level (mU/ml), glucose level (mg/dl), H1Ac (%), total cholesterol level (mg/dl), HDL cholesterol level (mg/dl), LDL cholesterol level (mg/dl), triglycerides level (mg/dl), HOMA score] parameters measurements at baseline and 1 year post diagnosis. Information on tumor- and adjuvant treatment-related variables was collected. All women received adjuvant therapy.
Results: Fifty-seven % of women were postmenopausal, 37% were premenopausal and 7% were unknown. The mean ages were 43.2$\pm$5.8 and 61.9$\pm$7.7 years among premenopausal and postmenopausal women respectively. Overall, mean weigh, waist and hip circumferences, BMI, total cholesterol level, triglycerides level, significantly increased among premenopausal women: +2.1 kg [95% confidence interval (CI), 1.2 to 3.0], +2.3 cm [95% CI, 1.1 to 3.6], +1.5 cm [95% CI, 0.3 to 2.7], +0.8 kg/m^2 [95% CI, 0.5 to 1.2], +10.1 mg/dl [95% CI, 3.8 to 16.4], +29.0 mg/dl [95% CI, 16.9 to 41.1] respectively. Most of the changes were observed in women receiving hormonal therapy with or without chemotherapy. Among postmenopausal women, mean triglycerides level increase: +24.0 mg/dl [95% CI, 11.6 to 36.3] and a significant decrease of H1Ac, HDL and LDL cholesterol levels: −0.2 [95% CI, −0.43 to −0.03], −5.9 mg/dl [95% CI, −11.4 to −0.5], −9.6 mg/dl [95% CI, −18.4 to −0.8] respectively were the only significant metabolic changes. Adjuvant therapies do not seem to affect glucose, insulin and HOMA score levels in our dataset.
Conclusions: Profound metabolic changes and weight body distribution occur in patients receiving adjuvant therapies after EBC diagnosis. These changes are more relevant in premenopausal women. Use of adjuvant chemotherapy and the onset iatrogenic induced amenorrhea (either with chemotherapy or hormonal treatment) may play a major role. Further follow up is needed to correlate such changes with patient prognosis.
No conflict of interest.

2079 POSTER

Prognosis of breast cancer patients with chemotherapy resistant disease following neo-adjuvant chemotherapy is dependent on luminal status

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Background: Patients who remain heavily node positive (ypN2) after neo-adjuvant chemotherapy may be deemed to have chemotherapy resistant disease. The future prognosis of patients was determined according to luminal status of the primary tumour.
Materials and Methods: All patients who received neoadjuvant chemotherapy, operated in Castle Hill Hospital, Hull, UK between January 2005 and December 2011 for early breast cancer and found to have 4 or more nodes involved on pathological assessment were identified. Neo-adjuvant chemotherapy consisted of 4 cycles of EC followed by 4 cycles of docetaxel. All patients received post-operative radiotherapy to intact breast/chest wall and SCF to a dose of 40 Gy in 15 fractions. Adjuvant endocrine treatment and trastuzumab was prescribed as appropriate. All patients had baseline staging investigations to exclude metastatic disease with CT chest,abdomen, pelvis and isotope bone scan. Luminal status was defined as: a ER/PR + HER2 -; b ER/PR+ HER2+; HER2 ER/PR- HER2+, Basal ER/PR/HER2 -. Disease free and overall survival was assessed using Kaplan–Meier analysis. Median follow-up was 30 months (range 1−92 months).
Results: 65 patients were identified who fulfilled the above criteria. Median age was 50 years (range 27−78 years). Luminal status significantly predicted long term disease free and overall survival. The median disease free survival for basal and HER2 subtypes was poor at 7 and 1 months respectively with median overall survival being 13 months for both groups. On univariate analysis grade, age, luminal status, and lymphovascular invasion significantly predicted for survival. On multivariate analysis using Cox Regression luminal status was the strongest predictor of long term survival ($p < 0.0001$).
Conclusions: In patients who have an initial poor pathological response to neo-adjuvant chemotherapy future prognosis is heavily dependent on luminal status. The prognosis for such patients who are triple negative or ER/PR − HER2+ is extremely poor. Alternative adjuvant strategies for such patients must be explored.
No conflict of interest.

2080 POSTER

Fertility preservation in early breast cancer patients: A survey among Italian oncologists

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Background: Patient's desire for fertility preservation is a frequently underestimated problem in oncology clinical practice. A survey to evaluate how this problem is managed by Italian oncologists has been performed.
Methods: Between April and July 2011, an electronic questionnaire regarding the treatment attitude in early breast cancer in premenopausal women has been completed by 611 Italian oncologists, (female 52%, age range 25−65, 81% from general hospitals, 19% from research institute). We compared the survey results regarding the fertility preservation (examined according to sex, age, working institution and geographic origin) with the recommendations available from guidelines of oncology and gynecology societies.
Results: A pregnancy test before starting chemotherapy is considered mandatory only by 49.5% of oncologists, independently from age and type of treatment.
The results of survey are reported in the table, compared with guidelines recommendation.

	Type of Recommendation for fertility preservation during chemotherapy			
	Eggs freezing	Embryo freezing	Ovarian tissue freezing	LHRH-analogs
ASCO (USA, 2006)	Investigational	Standard	Investigational	Investigational
CASA (Australia, 2012)	Standard	Standard	Investigational	Investigational
AIOM (Italy, 2012)	Standard	Non allowed by law	Special cases	Investigational
Present survey	24.8%	<1%	6%	68.2%

The majority of Italian oncologists considered the administration of LHRH-analog the treatment of choice to maintain fertility (independently from the hormone receptor status of the tumor in 83% of cases), being the monthly injection used in 2/3 of cases. No significant differences as by type of institution, geographic location (north, centre or south Italy), and physician's age has been observed.
Conclusions: The use of LHRH-analog would be the preferred method by Italian oncologists for fertility preservation. A recent analysis of literature regarding the use of LHRH-analogs by Italian Society for Medical Oncology using the GRADE method suggest an important role of this drugs, even if not yet conclusive for their efficacy (level of evidence 1+, Recommendation 'slightly positive'). Potential barriers to other more evidence-based methods can be the limited number of specialized centres for oocyte freezing, and the frequent lack of a multidisciplinary approach to the problem.
No conflict of interest.

2081 POSTER

Experience with aprepitant as antiemetic prophylaxis in combination with anthracycline plus cyclophosphamide: Should we include it from the first cycle?

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Background: Nausea and vomiting are frequent and troubling adverse effects during chemotherapy. This usually affects treatment adherence and could impair the quality of life.
MASCC/ESMO, ASCO, NCCN and SEOM guidelines recommend adding aprepitant from cycle 1 as antiemetic prophylaxis in patients with cyclophosphamide-based chemotherapy plus anthracyclines.
In 2006 aprepitant was authorized in our hospital, in breast cancer patients treated with cyclophosphamide plus anthracycline and refractory to approved protocol (5-HT3 and corticosteroids for prophylaxis of acute emesis and corticosteroids for delayed emesis days 2−3) or in patients with some risk factors (age <55 years, PS>1, sickness or hyperemesis gravidarum and low alcohol consumption).
This study aims to evaluate the effectiveness of aprepitant in the control of nausea and vomiting in patients with TAC (docetaxel, doxorubicin and cyclophosphamide) and the incremental cost that would supposed including aprepitant from the cycle 1 in an antiemetic prophylaxis protocol.
Material and Methods: It's a retrospective observational study, and include patients between 2010 and 2012.
Data collection included health records, chemotherapy regimen, emesis risk factors and presence of nausea and vomiting of any grade on the second visit.
Primary end point: complete response (CR) (no emetic episodes and no use of rescue therapy) over the overall period (0–120 h). Secondary endpoint: incidence of nausea and vomiting and cost.
To assess the incremental cost we calculated the difference between the actual consumption of aprepitant and the cost that would suppose if we had included all patients from the cycle 1.
In patients who had not received aprepitant from the cycle 1, we reviewed if they had started aprepitant in any of the subsequent cycles and how many tablets consumed.
Results: Of the 84 patients receiving TAC, 31 received aprepitant from cycle 1. CR was achieved in 84% patients with aprepitant and 86% in those receiving the original protocol. The incidence of nausea in the aprepitant group was 21/31 and without aprepitant 28/51 (RAR: −12.8 [−34.22, 8.54]). The incidence of vomiting in the aprepitant group was 5/31 and without aprepitant 7/51 (RAR: −2.4 [−18.43, 13.62]). No differences in risk factors for emesis between both groups of patients were found. In addition, there was no correlation between the recommendations for the use of aprepitant in our protocol and usual practise. Aprepitant was added in three patients after cycle 1 (two patients in the second and one in the third). The total cost of aprepitant in the study period was 11.200 €. The cost that would have supposed if we started with aprepitant in all patients would be € 27.552.
Conclusions: According to results, and despite the limitations of the study, we could not recommend the inclusion of aprepitant from baseline in this. Aprepitant was no better than standard therapy in our patients.
No conflict of interest.

2082 POSTER

Presence of breast cancer stem cells (BCSCs) on diagnosis in younger breast cancer patient: A predictor of chemotherapy

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Background: As breast cancer is found to be an extremely heterogeneous disease, we hypothesize that the invasive and mesenchymal properties of Breast Cancer Stem Cells (BCSCs) with $CD44^{+}/CD24^{low}/ALDH1^{+}$ phenotype has made them potential competence that can play a crucial role for the development of specific target therapies by eradicating metastases of primary tumorsin younger breast cancer patientsthus it can be considered as a potential alternative for 'event free survival' in breast cancer.
Materials and Methods: Fifty young breast cancer patients (age<30) were selected randomly. Breast cancer cells were isolated from whole tumor and cultured for in vitro drug sensitivity towards platinum, anthracycline and docetaxel and correlation was drawn between cell differentiation and drug response. BCSCs were also isolated from the whole tumor, cultured and in vitro drug sensitivity was checked and chemotherapy was designed according to the results.
Results: Among positive samples, 70% of patients showed platinum sensitivity and rest were found to be anthracycline sensitive. No sensitivity towards docetaxel was observed. In lieu of this, cisplatin was applied ex vivo and percentage of BCSCs came down to 6.58% from an initial 11.16%.
Conclusion: Thus the primary aim to target BCSCs to control metastasis and relapse of disease was achieved to some extent. We further plan to show a relationship ratio of selected markers present in patients in pre- and post-chemotherapeuticcondition with time to recurrence, mortality, morbidity and progression-free survival.
No conflict of interest.

2083 POSTER

Investigation of the molecular profile of breast carcinoma comparing polychemotherapy vs endocrine therapy in neoadjuvant mode

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Background: Despite of considerable achievements in the management of breast carcinoma (BC), it's still a major public health problem. The current algorithm in selecting therapies for breast cancer is based on a combination of clinical, pathological and molecular factors. An important aspect is the individualization of neoadjuvant treatment. We investigated retrospectively the impact of polychemotherapy (PCT) vs endocrine therapy (ET) to changes in the molecular portrait of BC used in neoadjuvant mode.
Material and Methods: 48 patients with verified BC was performed core-biopsy with immunohistochemical typing of tumors before start of neoadjuvant treatment. The molecular profiles of tumors were evaluated before and after neoadjuvant therapy by clinical response, RECIST-criteria, Allred score and histopathological features. For statistical data processing we used the fourfold tables analysis method and the 2xK tables analysis.
Results: After neoadjuvant treatment tumor's molecular portrait unchanged in 45.8% of patients. Among them Luminal A − 8.3%, Luminal B − 29.2%, Her2 type − 4.2%, Triple negative − 8.3%. In 54.2% of patients changed molecular status of tumor (Table 1).
A decrease in Allred score after neoadjuvant therapy was in 25% of patients. Among them PCT received 83%, ET − 17%.

Table 1.

	PCT	ET	Total
Luminal A»Luminal B	6 (12.5%)	0	6 (12.5%)
Luminal B»Luminal A	8 (16.7)	4 (8.3%)	12 (25.0%)
Luminal»BHer2 type	6 (12.5%)	0	6 (12.5%)
Luminal»Triple negative	2 (4.2%)	0	2 (4.2%)
Total	22 (45.9%)	4 (8.3%)	26 (54.2%)

$p < 0.05$.

Conclusions: Application as induction therapy PCT leads to loss of tumor's steroid receptors, a kind of molecular 'conversion' in less favorable subtypes.
Application of ET in neoadjuvant mode lets to save molecular markers of more prognostic favorable luminal tumor types.
Using as first-line neoadjuvant therapy of BC endocrine medicines does not change the molecular profile, which in its turn may positively effect on the long-term results.
Progression of tumor clone that has no ER/PR, may can be a source of recurrent tumors with poor prognosis.
No conflict of interest.

2084 POSTER

Is adjuvant hormonal therapy in premenopausal breast cancer women linked to gender of oncologist? An Italian survey

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Background: The increasing age of first pregnancy among italian women and the number of available therapy in premenopausal patients make adjuvant hormonal therapy an hot topic justifying a survey on the therapeutical approach of italian oncologists to breast cancer. In particular we wanted investigate if oncologist's gender modifies therapeutic choice.
Material and Methods: From April to July 2012 a 11 items electronic questionnaire was submitted to italian oncologists and 611 filled questionnaires were collected, 294 male (M) and 317 female (F), age range 25−65, 211 from north Italy, 173 form centre and 227 from south; 495 from general hospitals, 116 from research institutes. The results were examined globally and according to sex of the oncologists.
Results: 97.7% of patients aged less than 40 years needing only hormonal therapy would receive both tamoxifen (TAM) and LHRH analog (LHRHa)(97.6% M and 97.8% F); 2.3% TAM or LHRHa alone (2.4% M and 2.2% F). 93.6% of patients aged over 40 years would receive the combination (92.5% M and 94.6% F) whereas TAM or LHRHa was offered to 6.4% of women (7.5% M and 5.4% F).
In patients aged under 40 with chemotherapy induced amenorrhea, the oncologists would prescribe: TAM in 22.4% (25.5% M and 19.6% F), TAM and LHRHa in 68.1% (62.9% M and 72.9% F) with LHRHa prescribed for 5 years in 55.3% (58.4% M and 52.8% F), for 3 years in 22.1% (20.5% M and 23.4% F), for 2 years in 22.6% (21.1% M and 23.8% F), aromatase inhibitor (AI) +/− LHRHa in 6.6% (8.2% M and 5% F), LHRHa alone in 2.9% (3.4% M and 2.5% F). A greater number of patients would be treated with AI among women aged over 40: 11.6% M and 10.4% F.
The reasons to add LHRHa to TAM and the length of treatment would be: higher efficacy of the combination: 45.5% (51% M and 40.4% F); patient's age: 30.1% (26.2% M and 33.75% F); risk of recurrence: 20.8% (20.4% M and 21.1% F); and side effects: 3.6% (2.4% M and 4.7% F).
Conclusions: A high concordance between the Italian Oncologist attitude and the Oncological International guidelines is confirmed by this large survey, nevertheless we note a wide preference for a TAM/LHRHa combination.
No substantial difference was noted in questionnaire responses as regards sex of the oncologists. Nevertheless − although number of responses was small − we observed a larger interest (two fold) between female than male in hormonal side effects when they decide the length of LHRHa prescription.
No conflict of interest.

2085 POSTER

Quality of life in women with breast cancer that receive adjuvant chemotherapy

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Background: Breast cancer and adjuvant chemotherapy adversely affect different aspects of women's lives. Acute side effects of chemotherapy condition a definite impact. The purpose of this study is to analyze the effect of adjuvant chemotherapy on quality of life (QOL) of women.
Material and Methods: A cohort of women with breast cancer eligible to receive chemotherapy (neo)-adjuvant and participants in a randomized clinical trial of non-pharmacological intervention (ClinicalTrials.gov Identifier: NCT00964522) completed questionnaires prospectively validated CV (EORTC QOL -C30, version 3.0 and QOL-BR23), before chemotherapy, and half of it and at the end. We studied the differences according to clinical and biographical variables.
Results: 193 patients were enrolled in the trial of which 49 (25.3%) completed the three questionnaires between January 2007 and December 2009. Differences were identified in the different scales according to clinical

and biographical variables of patients (age, stage, type of chemotherapy, marital status, education level, social status and employment status).
Global health/QOL worsened over time (P = 0.01). Physical functioning (P = 0.0001) and body image (P = 0.002) were more deteriorated scales and asthenia (P = 0.004), nausea/vomiting (P = 0.05), anorexia (P = 0.025), xerostomia (P < 0.0001), conjunctivitis (P < 0.0001) and hot flashes (P < 0.0001), symptoms more temporary impact of chemotherapy. It was noted that the changes in physical functioning and xerostomia (P = 0.01), age influenced (P = 0.04) and conjunctivitis were influenced by the type of chemotherapy (P = 0.006).
Conclusion: Adjuvant chemotherapy worse QoL in patients with breast cancer, primarily in the area of physical functioning and body image. Asthenia, gastrointestinal toxicity, conjunctivitis and hot flashes are the side effects that most affect patients (Funding Health Research Fund # FIS 07/0141).
No conflict of interest.

2086 POSTER

Anthracycline-based regimens and trastuzumab related cardiotoxicity after adjuvant therapy in early breast cancer: A single center experience

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Background: Quality of life of patients who survive breast cancer can be compromised by Anthracycline-based regimens (ABR) and Trastuzumab (TZB) cardiotoxicity-related side-effects. The aim of our retrospective study was to evaluate left ventricular systolic and diastolic function performance in women with early breast cancer (EBC) treated with ABR associated or not to TZB.
Materials and Methods: One hundred and thirteen women, median age 51 (range 25 to 79), without basal alteration of left ventricular ejection fraction (LVEF) and diastolic function were considered.
Forty-four patients received 6 cycles of FAC (n = 19) or 6 cycles of FEC100 (n = 25). Forty-four patients received 4 cycles of EC plus 4 cycles of Docetaxel (D). Twenty-five patients with Her2-positive EBC received 4EC+4D+TZB up to 1 year. Management of cardiac function was assessed by Doppler echocardiogram at baseline (T0) during chemotherapy (T1) and 5-years of follow-up (T2). Cardiac toxicity was defined according to CTCAE-NCI-2.0 and NYHA class.
Results: A decrease of LVEF less than 10% was found in all patients at T1. No cardiac heart failure (CHF) event was observed at T2 for the patients treated with 4EC+4D or 4EC+4D+TZB. Two CHF events occurred in patients treated with FAC and FEC100, 5 years after the end of the FAC treatment (LVEF: 35%) and 2 years after the end of the FEC100 treatment (LVEF: 40%), respectively.
In the group of patients receiving ABR, the incidence of Grade 1 diastolic dysfunction was 37% and 50% at T1 and T2, respectively. In Her2 positive EBC patients treated with TZB, the incidence of diastolic dysfunction was 23% at T1 and it was increased to 27.7% at T2.
Conclusions: Our data show that 4EC+4D regimen has a good cardiac safety related to low cumulative dose of Epirubicin (400 mg/m^2). Cardiotoxicity incidence (1.76%) observed in patients treated with FAC/FEC100 regimens agrees with other studies. The addition of Trastuzumab in HER2+patients has not caused systolic dysfunction. Data on incidence of Grade 1 diastolic dysfunction, compared between the two groups, at T1 and T2, were no statistically significant. Therefore, Trastuzumab treatment does not increase the risk of occurrence of diastolic dysfunction.
No conflict of interest.

2087 POSTER

Outcome in patients treated with primary endocrine therapy and neoadjuvant endocrine therapy for breast cancer: A single centre experience

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Background: Our use of primary endocrine therapy (PET) and neoadjuvant endocrine therapy (NAET) is increasing. The aim of the former is to prevent disease progression, and the latter is used with an aim to downstage tumour prior to surgery. Our study examines the pattern of use, and patient outcome in terms of response and survival.
Methods: Retrospective data analysis was performed using a prospectively maintained database of early breast cancer patients treated with endocrine therapy for a minimum of 4 months (2005–2012). Clinico-pathological parameters, radiological features and reasons for endocrine therapy were determined. Response to endocrine therapy was defined by the change in tumour size from the pre-treatment ultrasound (USS) to the interval USS. Kaplan–Meier survival analysis was performed to determine the overall survival (OS), disease free survival (DFS), and progression free survival (PFS).
Results: 138 patients were treated with endocrine therapy (98 PET and 40 NAET). The reasons for PET were due to co-morbidities (74.7%) and patient choice (25.3%). Median duration of endocrine therapy was 33.5 months (PET) and 7.5 months (NAET). Median patient age was 83 years old (PET) and 71.5 years old (NAET). Tumour characteristics were similar apart from the higher rate of axillary metastasis (55.8% versus 9.2%; p < 0.0001), and larger initial tumour size (30 mm versus 22.5 mm; p = 0.01) in the NAET group. This was reflected by a mastectomy rate of 52.5% in the NAET group. NAET regimen consisted of anastrozole (45%), letrozole (45%), or tamoxifen (10%). Anastozole was used more commonly in the PET group (61.2%), compared to letrozole (27.6%) or tamoxifen (11.2%). Interval USS was selectively performed in 19/40 cases (47.5%) in the NAET group, resulting in a tumour volume reduction of 60.6% (median time to USS: 4.8 months). Similarly, interval USS was selectively performed in 36/98 case (36.7%) in the PET group, resulting in a tumour volume reduction of 49.7% (median time to USS: 14.2 months). 5 year OS of 56.1% was seen in the PET group with PFS of 97%. However, 5 year OS of 82.5% was seen in the NAET group with DFS of 87.5%.
Conclusion: Good outcome is seen in patients treated with PET, reflected by the high rate of PFS. The DFS rate was lower in the NAET group, reflected by the poor prognostic pathological features. The type of regime, timing and indications for interval USS requires standardisation.
No conflict of interest.

2088 POSTER

Efficacy of dose-dense neoadjuvant chemotherapy in patients with stage II or III breast cancers

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Background: This study will evaluate the efficacy of dose-dense neoadjuvant chemotherapy and the safety of this treatment, in potentially operable and locally advanced breast cancers.
Material and Methods: We retrospectively collect data from 50 women with stage II−III breast cancer, from april 2008-november 2012. Patients were treated preoperatively with 4 cycles of doxorubicin 60 mg/m^2 -cyclophosphamide 600 mg/m^2 every 2 weeks, with filgrastim at 5 g/kg days 3 to 10 of each cycle, followed by 4 cycles of docetaxel 100 mg/m^2 every 3 weeks, with or without trastuzumab 6 mg/kg (loading dose of 8 mg/kg) every 3 weeks, according to human epidural growth factor receptor 2 status(HER2).
Results: Median age was 46 years, 72% were stage II and 28% stage III, 64% were clinically node positive. Tumours were classified into four phenotype subtypes. 90% of patients received complete treatment. 22% included trastuzumab preoperatively.
The primary study end point was to evaluate rate of pathologic complete response (pCR), defined as the absence of invasive cancer in the breast and nodes at the time of surgery, 15 patients(30%) achieved pCR rate.

Tumour phenotype	N (%)	Pathologic response (N+T)*	
		pCR, 15 (30%)	Non pCR, 35 (70%)
Luminal A	6 (12)	2 (33.3%)	4 (66.7%)
Luminal B	24 (48)	6 (25.0%)	18 (75.0%)
Her 2	3 (6)	2 (66.7%)	1 (33.3%)
Basal Like	17 (34)	5 (29.4%)	12 (70.6%)

*When Pearson's χ^2 test was performed, no statistical association was found between pCR and tumour phenotype, nor with age, tumour size, lymph node status, ki 67, hormonal receptor and HER2. Pathologic complete response was significantly associated with stage II (p = 0.02) and high tumor grade (p = 0.04).

Secondary objectives: pathologic tumor complete response was observed in 17 patients (34%), and high tumor grade was significantly corre-

lated with this (p = 0.02).18 patients (36%) achieved clinical complete response (cCR). cCR was correlated with small tumor size, (p = 0.04) and high tumor grade (p = 0.01).
Breast-conserving surgery was possible in 35 patients (70%). The reported grade 3/4 toxicities were: asthenia 7(14%), skin toxicities including hand and foot syndrome 4(8%), nausea and vomiting 5(10%), 14(28%) neutropenia, less than 4(8%) of patients reported febrile neutropenia.
Conclusions: Our results indicate that dose dense neoadjuvant chemotherapy is highly active for breast cancer and is not accompanied by an increase in toxicity.
No conflict of interest.

2089 POSTER

Effect of oral cyclophosphamide use on pathologic complete response rate in the neoadjuvant treatment of breast cancer

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Background: Continuous exposure to cyclophosphamide (C) can result in selective cytotoxicity for endothelial cells, followed by antiangiogenic effects on tumor cells. In this study we analyzed the pathological complete response (pCR) rate in a cohort of patients (p) diagnosed with locally advanced breast cancer (LABC) treated with neoadjuvant chemotherapy (CT) based on anthracyclines and taxanes, depending on the route of administration of C (intravenous (IV) and oral arms).
Material and Methods: We retrospectively studied a consecutive series of p. with LABC treated with neoadjuvant CT in 2 hospitals in Asturias. The regimens used were CE100F, FA60C, AC (regimens with IV C) or oral CAF (C 100 mg/m^2/day orally x 14 days, doxorubicin 30 mg/m^2 day 1 and 8 and 5-FU 500 mg/m^2 days 1 and 8 every 28 days) x 4 cycles. The anthracycline regimen was followed by weekly paclitaxel or docetaxel every 3 weeks. If HER2 overexpression, trastuzumab was given in combination with the taxane.
Results: We identified 170 p., 128 of them treated with oral C and 42 with IV C (CEF 3 p., FAC 6 p. and AC 33 p.). The median age was slightly higher in the p. treated with C IV (52.0 vs. 48.5, p = 0.036), which also received a higher number of cycles (7.2 vs. 6.7, p = 0.006) and a higher anthracycline dose intensity (93.6% vs 88.5%; p < 0.001). There were no significant differences in tumor size, lymph node involvement, grade, estrogen receptor (ER) or HER2. The rate of pCR was significantly higher in p. receiving oral C (38.9% vs 10%, p < 0.001). Grade 3, negative, estrogen receptors and HER2 were also significantly associated with a higher rate of pCR. On multivariate analysis only oral C, ER negative and HER2 positive were independent factors associated with pCR. With a median follow up of 25.5 months (95% CI 22.4 to 28.6), there have been 37 recurrences, 21 (16.4%) in the continuous arm and 16 (29.6%%) in the standard arm, without significant differences in disease free survival.
Conclusions: Our results suggest that the pCR rate can be higher using oral C in the neoadjuvant treatment of LABC based on anthracyclines and taxanes. This hypothesis should be confirmed in a randomized and prospective study.
No conflict of interest.

2090 POSTER

Comparison of dose dense adjuvant chemotherapy with conventional three weekly chemotherapy in triple negative early breast cancer patients in Indian population

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Background: Patients with triple negative breast cancer tend to present at a younger age, with higher histologic grade, higher relapse rates and poorer survival than other subtypes. At present, even though it is an aggressive disease, the adjuvant chemotherapy used in this subgroup is the same as in hormonal receptor positive patients.
Materials and Methods: At our institution 128 patients with triple negative early breast cancer who underwent surgery followed by adjuvant chemotherapy were identified. We compared two groups of patients based on the adjuvant chemotherapy received. The dose dense adjuvant chemotherapy **(DD)** group received 4 cycles of AC (Adriamycin, Cyclophosphamide) − two weekly followed by 4 cycles of Paclitaxel − two weekly. The conventional chemotherapy **(CC)** group had three weekly regimen; 3 cycles of FEC 100 (5-fluorouracil, Epirubicin, Cyclophosphamide) followed by 3 cycles of Docetaxel or six cycles of TAC (Taxol, Adriamycin, Cyclophosphamide). Radiotherapy was given to patients as indicated. We retrospectively evaluated patients in both groups for age, stage at presentation, pathology, relapse rates, mortality rates and 5 year disease free survival (DFS) and overall survival (OS).
Results: The median age at diagnosis, pathology and stage at presentation were matched in both groups. 60 (46.87%) patients were pre-menopausal. 66 (51.56%) patients belonged to DD group and 62 (48.44%) patients belonged to CC group. Neuropathy was higher in DD arm, while fatigue, vomiting and neutropenia were higher in CC arm. The median follow up of was 98 months. 30 patients (23.43%) were diagnosed to have systemic relapse. Recurrence was more common in the CC group 18 patients (60%) than in DD group 12 (40%). The common sites of relapse were bones (17%), lungs (19%) and brains (12%). The 5 year relapse free rate was significantly better in DD group (81.81% vs 70.97%, P = 0.014). The 5 year DFS was significantly longer in DD group than CC group (30.83 vs 26.72 months P = 0.004). The 5 year mortality rate was slightly better in DD group (9.1% vs 14.5%, P = 0.340). The 5 year OS although longer in DD group, was not statistically significant (52.50 vs 48.56 months, P = 0.647).
Conclusion: In early stage triple negative breast cancer, patients who received dose dense adjuvant chemotherapy had lower relapse rates with prolonged DFS in comparison to conventional chemotherapy. But OS was the same in both groups.
No conflict of interest.

2091 POSTER

Tumor immune subtypes distinguish tumor subclasses with clinical implications in breast cancer patients

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Background: Various interactions underlie the balance between immune control and tumor immune escape. We defined tumor immune subtypes and investigated their prognostic effect in a training and validation cohort of breast cancer patients.
Material and Methods: Our training and validation cohort (n = 822) consisted of all early breast cancer patients primarily treated with surgery in our center between 1985 and 1996. Patients diagnosed with breast cancer between 1985 and 1990 (n = 440) were selected as the training cohort; between 1990 and 1996 (n = 382) as the validation cohort. Sections of formalin-fixed paraffin-embedded tumor tissue were immunohistochemically stained for CD8 (CTL) and PEN5 (NK cells) to determine tumor-infiltrating immune cells. Tumor expression of classical and non-classical HLA class I, and tumor-infiltrating Tregs were previously determined. Tumor immune subtypes were constructed based on quantification of these markers and biological rationale.
Results: Patients with data available for all mentioned immune markers were analyzed for tumor immune subtypes for the training cohort (n = 293) and validation cohort (n = 219). High, intermediate and low immune susceptible tumor immune subtypes were found in respectively 16%, 63% and 20% of patients in the training cohort and respectively 16%, 71% and 13% in the validation cohort. Tumor immune subtypes showed to be statistically significant prognostic for relapse free period (RFP) (p < 0.0001, intermediate versus high immune susceptible: hazard ratio (HR) 1.95 95% confidence interval (CI) 1.13–3.39; low versus high immune susceptible HR 2.98 95% CI 1.62–5.48) and relative survival (RS) (p = 0.006, low versus high immune susceptible HR 3.84 95% CI 1.62–9.09; intermediate versus high immune susceptible: HR 4.26 95% CI 1.70–10.70), independent of known clinicopathological parameters and with high discriminative power. Validation of these outcome analyses confirmed the independent prognostic associations for RFP (p = 0.025) and RS (p = 0.040).
Conclusion: The tumor immune subtypes that we present here represent a prognostic profile with solid underlying biological rationale and with high discriminative power. In addition, results were validated in a separate cohort, confirming the statistically significant relations with patient outcome. Tumor immune subtype profiling is a promising method for prognosis prediction and may aid in achievement of tailored treatment for breast cancer patients.
No conflict of interest.

2092 POSTER

Breast cancer survival of young patients: The impact of BRCA1/2 germline mutations

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The pathological biology of *BRCA1/2*-associated tumors supports the hypothesis that patients carrying a germline *BRCA1/2* mutation might have a worse breast cancer prognosis compared to non-carriers. Earlier studies showed inconsistent results and *BRCA1/2* mutation status is currently not taking into account, outside e.g. PARP-inhibitor trials, for primary breast cancer treatment. The aim of this study was to evaluate the impact of *BRCA1/2* mutations on breast cancer outcome in a multicenter, consecutive cohort of breast cancer patients.

We included invasive pathologically-confirmed breast cancers, diagnosed before <50 years of age, in the period 1970–2002, in ten Dutch centers, in patients with no previous malignancies. DNA for *BRCA1/2* analyses was isolated from formalin-fixed, paraffin-embedded tissue blocks containing normal (non-tumor) tissue. A selection of most frequently occurring *BRCA1/2* mutations was analyzed, capturing ~70% of all Dutch pathogenic mutations. Clinico-pathological data and follow-up were collected and part of the tumor characteristics (grade, ER, PR, HER2) was obtained by revision. Metastasized patients were excluded. Hazard Ratios (HRs) from cox proportional hazard models were adjusted for grade, size, nodal status, adjuvant treatment, ER (if applicable) and age.

Among 5391 breast cancer patients we found 3.5% *BRCA1* and 1.2% *BRCA2* mutation carriers. Mean follow-up of the cohort was 11.3 years. *BRCA1* and *BRCA2* carriers had worse 15-year overall survival (OS) compared to non-*BRCA*; HR unadjusted 1.4 (95% CI: 1.1−1.8) p = 0.002 and 1.4 (1.0−2.1) p = 0.054, respectively; HR adjusted 1.2 (1.0−1.5) p = 0.116 and 1.3 (0.9−1.9) p = 0.145, respectively. The proportions of ER-positive breast cancers in non-*BRCA*, *BRCA1* and *BRCA2* mutation carriers were 68%, 29% and 82%. Within ER-positive tumors OS was significantly worse in *BRCA2* mutation carriers (HR 1.8 (1.1−2.8) p = 0.011; HR adjusted 1.5 (1.0−2.4) p = 0.059) but we found no evidence for a worse OS in *BRCA1* carriers. Within ER-negative tumors there was a tendency for worse OS in *BRCA1* (HR 1.2 (0.8−1.6) p = 0.358; HR adjusted 1.3 (0.9−1.8) p = 0.101); for *BRCA2* analysis there was insufficient power. Adjuvant chemotherapy was found to be an important confounder in the analyses.

Results are preliminary and further tumor subtype and treatment analyses including breast cancer-specific and recurrence-free survival will be presented after update of follow-up. To our knowledge this is the first large unselected breast cancer cohort in the Netherlands in which *BRCA1/2* has been genotyped and breast cancer outcome evaluated. We found evidence for difference in outcome for *BRCA1/2* germline mutation carriers in specific tumor subtypes. If confirmed this might be used in treatment decisions for *BRCA1/2* mutation carriers.

No conflict of interest.

2093 POSTER

Mesenchymal phenotype of CTCs-enriched blood fraction and lymph node metastasis formation potential

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Background: The occurrence of epithelial–mesenchymal transition might influence the seeding potential and aggressiveness of tumor cells. It is not well known how this process affects molecular characteristics of tumor cells present in different compartments.

The aim of this study was to analyze the expression of epithelial, mesenchymal and invasion/metastasis related genes in CTCs-enriched blood factions, a subset of matched primary tumors and lymph node metastases from breast cancer patients and correlate it with each other and clinico-pathological data.

Materials and Methods: Blood samples (n = 94), formalin-fixed, paraffin embedded (FFPE) primary tumors (PT) (n = 25) and FFPE lymph node metastases (LNM) (n = 14) were collected from 94 breast cancer patients (pT1−4, pN1−3) before therapy initiation. Blood samples were subjected to CTCs enrichment by density gradient centrifugation and immunomagnetic depletion of CD45-positive cells. Expression of mammary epithelial: cytokeratin 19 (*CK19*), mammaglobin 1, as well as mesenchymal: vimentin (*VIM*), *TWIST1, SNAIL, SLUG* and invasion/metastasis-related genes: *HER2, CXCR4, uPAR* was measured with qRT-PCR. As a control material blood samples from nine healthy controls, sections of healthy FFPE breast and lymph nodes were analyzed and processed the same way as patients' samples. Gene expression level was analyzed in a relative manner using two reference gene (*GAPDH* and *YWHAZ*) and a calibrator using qBase^{PLUS} software.

Results: Expression of *CK19* and/or *VIM* in CTCs-enriched blood fractions was associated with lymph node involvement (p = 0.002). Mesenchymal status of CTCs-enriched blood fraction correlated with higher number (>5) of involved lymph nodes (p = 0.0008). Moreover, CTCs-enriched blood fraction of N1 patients, in comparison to N0 patients, were more frequently positive for *CXCR4* (52% vs. 33%, p = 0.07) and *uPAR* (73% vs. 50%, p = 0.02). Expression of *CXCR4* and *uPAR* was associated with increased hazard of developing lymph nodes metastases HR 2.4 (CI 1.03−5.5, p = 0.02) and HR 2.2 (CI 1.1−4.3, p = 0.02), respectively. Interestingly, the percentage of samples positive for *CXCR4* and *uPAR* decreased from PT to LNM with respective 55% (6/11) and 27% (3/11) conversion rates in matched samples.

Conclusions: Mesenchymal phenotype (*CK19-/VIM+*) of CTCs-enriched blood fraction contains cells more potent in lymph node metastases formation, which might be related to the increased expression of CXCR4 and *uPAR* receptors. Significance of these receptors seems to be of lower importance in LNM.

No conflict of interest.

2094 POSTER

The impact of baseline and genetic parameters on progression free survival and overall survival in breast cancer patients receiving neoadjuvant or adjuvant chemotherapy with fluorouracil, epirubicin, cyclophosphamide (FEC) and docetaxel (D)

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Background: Several studies assessed the influence of genetic variability on outcome in breast cancer patients, but most studies were small or were limited to a few genes only. We assessed the impact of a wide range of patient-, tumor- and chemotherapy-related factors on progression-free survival (PFS) and overall survival (OS) in patients receiving fluorouracil, epirubicin, cyclophosphamide and docetaxel (FEC-D).

Methods: Female patients with early breast cancer receiving neoadjuvant or adjuvant chemotherapy with 3 cycles FEC and 3 cycles D were eligible. Patient-related factors (age at diagnosis, body mass index, body surface area and germ line genetic polymorphisms), chemotherapy-related factors (cycles received and growth factor use), baseline biochemical variables (white blood cell count, absolute neutrophil count, platelets, aspartate aminotransferase, alanine aminotransferase, total bilirubin and creatinine), tumor-related factors (stage and subtype) and severe toxicity occurrence (febrile neutropenia) were assessed (missing data <10%). The germ line genetic polymorphisms were selected based on our recent publication describing the impact of genetic variability on toxicity of FEC (Vulsteke et al, Ann Oncol. 2013 Feb 7). Univariate survival analysis of OS and PFS were performed.

Results: Among 529 patients planned to receive 3 cycles of FEC followed by 3 cycles of D during a mean follow-up of 4.2 years, 54 (10.2%) developed distant metastasis, 8 (1.5%) had a locoregional relapse and 26 (4.9%) died. In the univariate analysis, significant associates with a better OS and a better PFS were: higher relative dose intensity (RDI) of epirubicin (p < 0.04), lower stage (p < 0.003), luminalA or luminalB subtype (p < 0.0001) and homozygous carriers of the C-allele of rs2107538 in the RANTES gene (p < 0.01). Higher absolute neutrophil count, carriers of the T-allele of rs1801133 in the MTHFR gene, carriers of the C-allele of rs1800566 in the NQO1 gene and carriers of the TA-allele of rs2032582 in the MDR1/ABCB1 gene were significantly associated with worse OS (p < 0.05), whereas no growth factor use and carriers of the homozygous A-allele of rs776746 in the CYP3A5 gene were significantly associated with a better PFS (p < 0.03).

Conclusions: In this study, genetic variability, chemotherapy-related factors and tumor-related factors were significantly associated with OS and PFS in a large cohort of early breast cancer patients treated with 3 cycles of FEC followed by 3 cycles of D. A multivariate analysis will be performed to confirm the results and the findings will be presented at the meeting.
No conflict of interest.

2095 POSTER

Tamoxifen pharmacokinetics influenced by circadian rhythm?

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Background: The anti-oestrogen tamoxifen (Tam) is extensively metabolised, involving activation to endoxifen, and inactivation to conjugates, catalysed by cytochrome P450 iso-enzymes and phase II enzymes, respectively. Variability in pharmacokinetics (PK), which may contribute to variable clinical response, may be caused by *CYP2D6* polymorphisms, co-medication, but possibly also by the circadian clock. Due to daily variation in physiological functions, Tam PK may vary depending on time of administration. To investigate whether Tam shows circadian time-dependent PK, both a preclinical study in mice and a prospective clinical study were initiated.
Material and Methods: Tam PK was studied in mice, dosed at 6 different times at 4 hour intervals during the day. Mice were housed under a 12 h light-dark cycle and were given 4 mg Tam orally. PK measurements were based on 6 time points of blood collection (3 mice/time point). In patients on steady state Tam, a PK crossover study was performed. During two 24 h-periods, once after Tam dosing at 8 AM and once after dosing at 8 PM, for at least 4 weeks, blood samples were collected for PK measurements. Tam and its major metabolites were analysed by a validated LC-MS/MS method. Differences in PK between morning and evening administration were compared using a paired *t*-test.
Results: In mice, a 34% difference in Tam $AUC_{0-20\,h}$ was observed between 8 AM and 8 PM dosing, while the highest exposure was reached after dosing at midnight. Up till now, 12 patients completed both study periods. The area under the curves ($AUC_{0-12\,h}$) of Tam and its metabolites were higher after dosing at 8 AM compared to 8 PM ($p < 0.02$), with endoxifen $AUC_{0-12\,h}$ being 20% higher following dosing at 8 AM ($p = 0.006$). Peak concentrations (C_{max}) of Tam, ND-Tam and 4-OH-Tam, but not of endoxifen, were 18−27% higher ($p = 0.001$–0.03) and were reached earlier after dosing at 8 AM.
Conclusions: Both in mice and humans, circadian changes in Tam PK were observed. Differences in AUC, C_{max} and t_{max} between morning and evening dosing in patients are most probably due to variation in absorption and may be clinically relevant. Circadian variation in gastric emptying and gastrointestinal blood flow may be underlying mechanisms, although differences in metabolism are currently not excluded.
No conflict of interest.

2096 POSTER

Androgen receptor expression and outcomes in early breast cancer: A systematic review and meta-analysis

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Background: The androgen receptor (AR) is expressed frequently in breast cancer, but its prognostic significance is unclear. Preclinical data suggest that expression of AR may modify clinical outcomes in early breast cancer with an improved prognosis seen in estrogen-receptor (ER)-expressing tumors and a worse prognosis in ER-negative disease.
Methods: A systematic review of electronic databases was conducted to identify publications exploring the association between AR expression and both overall survival (OS) and disease free survival (DFS) in women diagnosed with early breast cancer. The odds ratio for OS and DFS at 5 years were calculated and then weighted and pooled in a meta-analysis using Mantel-Haenszel random-effect modeling.
Results: Nineteen studies involving 7693 women were included in our analysis. AR expression was documented in 58% of patients. ER-positive tumors were more likely to express the AR than ER-negative tumors (75% vs 31%, p for difference <0.001). AR expression was more common among progesterone receptor (PR) positive tumors than PR negative tumors (58% vs 42%, p for difference =0.001). There was a highly significant association between AR expression and low Ki-67 ($P < 0.001$). Overall, AR-expression was associated with improved OS and DFS irrespective of ER-expression. Odds ratio for OS and DFS were 0.45 (95% CI 0.31–0.64, $P < 0.001$) and 0.34 (95% CI= 0.20–0.57, $P < 0.001$) respectively. Co-expression of the ER did not influence these results (p-values for subgroup differences 0.79 and 0.75 for DFS and OS respectively). Sensitivity analysis removing of studies using radioimmunoassay or reverse-phase protein array rather than immunohistochemistry (IHC) did not affect either OS or DFS. Among studies utilizing IHC, there was no statistically significant difference for the 1% or 10% thresholds at either OS (p for difference =0.09) or DFS (p for difference =0.38). Only 2 studies reported the influence of AR-expression on HER2/neu-positive breast cancer. No apparent association was seen for either OS (OR=1.58, 95% CI =0.09–27.26, $P = 0.75$) or DFS (OR=0.92, 95% CI: 0.34–2.52, $P = 0.87$), but CI were wide and the possibility of an association in either direction cannot be excluded.
Conclusion: Expression of AR in women with breast cancer is associated with better DFS and OS irrespective of co-expression of ER.
No conflict of interest.

2097 POSTER

Biomarkers for predicting taxane efficacy in ER+/HER2− breast cancer patients: From in-vitro chemosensitivity screening to clinical validation in the GEICAM/ 9906 trial

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Background: Taxanes are among the most active agents for breast cancer (BC) patients, but the benefit of taxane-based treatment has to be balanced against side-effects. Therefore, there is a great need for novel predictive markers. Here we present the clinical validation of marker genes identified in an *in-vitro* chemosensitivity study, in order to select the ER+/HER2− BC patients who have a benefit from the inclusion of a taxane in the chemotherapy regimen.
Material and Methods: Tumor cells from 29 ER+/HER2− BC samples were incubated *in-vitro* with Paclitaxel (P), 5-Fluorouracil (F) and Epirubicin (E). An area under the dose-response curve (AUC) was determined for all tumor samples and all agents, respectively. RNA was extracted from the same tissue specimens and used for gene expression profiling. Promising predictive markers from the *in-vitro* chemosensitivity study were validated in 555 node-positive ER+/HER2− BC patients from the GEICAM/ 9906 trial; including patients that were either treated with F, E, and Cyclophosphamide (FEC) or with FEC followed by weekly P (FEC-P). Distant metastasis rates were estimated using the Kaplan–Meier method.
Results: *In-vitro* chemosensitivity data were used to calculate a taxane-response score (higher likelihood of P benefit in comparison to F and E) in ER+/HER2− BC patients. Gene expression levels from the microarray data were correlated with the taxane-response score and two genes − S100P and PCSK6 − were selected due to their significant correlation ($p < 0.05$). Since both genes exhibited an independent predictive information, a metagene was defined resulting in a better correlation (Pearson $r = 0.63$, $p < 0.05$). Validation of the metagene in the GEICAM/ 9906 trial demonstrated that tumors with a high metagene expression (>75% percentile) had a significant benefit from taxane-based treatment (log-rank $p < 0.003$, FEC vs. FEC-P − absolute risk reduction of distant metastasis: 27.3%), whereas there was no effect in the low-metagene group.
Conclusions: Single agent *in-vitro* chemosensitivity data can be validated in a clinical study. Additional studies are needed to validate the cut-offs levels for the predictive marker genes.
Conflict of interest: *Other substantive relationships: Dr. JC Brase is employed at Sividon Diagnostics GmbH. No conflict of interests to declare by rest of authors.*

2098 POSTER

TP53 mutation-regulated DNA repair genes mediate different sensitiveness to chemotherapy in ER+ and ER− breast tumors

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Background: Breast cancers molecular subtypes carry specific *TP53* mutations that can influence gene expression and clinical outcomes. Furthermore, TP53 has been shown to regulate important DNA repair pathways. In the present study we aimed to identify DNA repair gene signatures driven by *TP53* mutations and to assess their clinical relevance in ER-positive (ER+) and ER-negative (ER-) breast cancers (BC).
Methods: Publicly gene expression data analyzed with Affymetrix technology from 5 independent BC datasets (ER+ n = 511, and ER− n = 184) with known *TP53* status were used. The raw array data was normalized in the R environment using the affy Bioconductor package. In the discovery cohort, ROC analysis was performed for each gene separately and the genes were ranked by AUC values. Kaplan–Meier analysis was performed by KM-plotter software(1) using 635 neoadjuvant taxanes and anthracyclines-based chemotherapy treated patients. Statistical significance was set at $p < 0.01$. Pearson correlations and GSEA analyses were assessed in each molecular BC subtype. siRNAs were performed for the top 12 DNA repair genes and sensitivity for different treatments was tested in several BC cell lines.
Results: *TP53* mutations, particularly deletions/nonsense and frame shift mutations were more frequent in ER− tumors. *TP53* mutations types did not affect prognostic values. Importantly, *TP53* mutations (deletions/nonsense > frameshift > missense) were associated with a significant higher number of deregulated DNA repair genes particularly in ER− tumors (*P <0.001*). Specific genes were able to categorize patients with high and low risk of relapse in ER+ tumors only. The most significant TP53-mutated regulated within ER+ were: *TPX2* (0.803) *CENPA* (0.801), *AURKA* (0.800), and *RRM2* (0.79), and among ER-: *MSH2* (0.73), *DEK* (0.73), *RAD51AP1* (0.73), *MCM2* (0.72), *ASPM* (0.72). All of the top TP53-regulated genes correlated with survival. However, only genes within the ER+ tumors were associated with shorter survival in neoadjuvant-treated BC patients. siRNAs for TPX2 and DEK showed increased sensitivity of BC cells to HDAC and KSP inhibitors.
Discussion: We identified different *TP53*-mutation driven DNA repair genes in ER+ and ER− breast tumors. Deletions/nonsense mutations were associated with a higher frequency of deregulated DNA repair genes particularly in the ER− tumors. Specific *TP53*-mutated regulated DNA repair genes correlates with different prognosis and with different sensitivity to selected pharmacological treatments.
No conflict of interest.

2099 POSTER

The role of interleukin-8 (IL-8), matrix metalloproteinase −2 and −9 (MMP-2 and MMP-9) in breast cancer progression

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Background: IL-8 is a chemokine that is involved in breast cancer progression by multiple mechanisms, including attracting inflammatory cells that produce growth factors, angiogenic factors and proteinases such as MMP-2 and MMP-9. The aim of the study was to investigate the relations between IL-8/MMP-2/MMP-9 and other prognostic variables in lymph node-negative (N0) untreated breast cancer patients, with emphasis on their relation to steroid receptor status, and to determine the prognostic value of these potential biomarkers in terms of relapse free survival (RFS).
Material and Methods: The study included 135 N0 untreated breast cancer patients with known clinicopathological parameters. The median follow-up time was 111 months. IL-8, MMP-2 and MMP-9 levels were determined by ELISA in primary tumour tissue lysates.
Results: There were no significant relations between IL-8/MMP-2/MMP-9 expression and available clinicopathological parameters (patient's age, menopausal status, tumour size and tumour grade), except for MMP-9 expression being significantly higher in patients with invasive ductal carcinoma as well as in patients with higher levels of IL-8 according to median IL-8 level (M = 102.27 pg/mg, Mann-Whitney rank sum test, $p = 0.004$ and $p < 0.001$, respectively). ER− patients had higher levels of both IL-8 and MMP-9 (Mann-Whitney rank sum test, $p = 0.006$ and $p = 0.04$, respectively) compared to ER+ patients, but PR+ patients had higher levels of MMP-2 than PR− patients ($p = 0.03$). There was a significant negative correlation between ER and IL-8 expression (Spearman rank order test, $p = 0.02$) and significant positive correlation between IL-8 and MMP-9, as well as between PR and MMP-2 expression ($p < 0.001$ and $p = 0.05$, respectively). Among investigated biomarkers, only IL-8 had a statistically significant prognostic value in terms of RFS (Log rank, $p < 0.001$). Patients with IL-8 levels higher than median value had worse prognosis.
Conclusions: Expression of IL-8 and consequently expression of MMP-9/MMP-2 could be hormonally regulated in breast cancer. However, different expression of MMP-2 and MMP-9 regarding differential hormonal receptor expression, indicate distinct mechanisms of their regulation. Besides being a marker of more aggressive, ER− breast cancer phenotype, IL-8 seems to be a strong and independent unfavourable prognostic parameter in N0 breast cancer. Such patients with higher levels of IL-8 should be treated with adjuvant, especially IL-8 targeted therapy.
No conflict of interest.

2100 POSTER

Serum vascular endothelial growth factor (VEGF) in women with stage I−II breast cancer

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Background: In patients with breast cancer (BC) a number of prognostic and predictive factors have been reported including age, staging, hormone receptor status, and human epidermal growth factor 2 (HER2) and Ki-67 overexpression. Ki-67 is a nuclear protein tightly linked to the cell cycle and a marker of cell proliferation found in several epithelial malignancies, including BC. Angiogenesis is essential for the growth of tumor and spread of metastases, and cancer cells overexpressing cyclooxygenase-2 (COX-2), an inducible enzyme involved in prostaglandin biosynthesis, produce angiogenetic factors, such as vascular endothelial growth factor (VEGF). It has also been shown that inhibition of COX-2 leads to inhibition of angiogenesis in cancer tissue, and that elevated serum VEGF can be considered a negative prognostic factor in patients with cancer. The aim of this study was to analyze the predictive value of VEGF and Ki-67 in patients with invasive BC.
Material and Methods: Data from a group of 59 women (median age 60 years, range 32−68 years) with confirmed stage I−II BC who underwent curative surgery were reviewed. For evaluation of the preoperative serum VEGF values commercially available quantitative enzyme-linked immunosorbent sandwich assay (ELISA) kit for human VEGF 165 was used. All measurements were performed in twice. Ki-67 immunohistochemistry using the MIB-1 antibody was performed on sections cut from archival formalin-fixed, paraffin-embedded specimens. Pearson's correlation coefficient (R) calculation was used to evaluate the relationship between pairs of variables, and the 95% confidence interval (95% CI) was calculated, when appropriate.
Results: At 5-year follow-up, 51 (96.5%) patients were still alive, while 11 (18.6%) experienced recurrence of their disease. The 3- and 5-year survival probability estimates were 0.95 (95% CI 0.85–0.99) and 0.81 (95% CI 0.68–0.90), respectively. As expected, there was a significant ($p < 0.01$) inverse relationship between MIB-1 rate and disease-free survival (DFS), while no correlation (p=NS) was found between serum VEGF and survival or DFS.
Conclusions: Although plasma VEGF level has a clinical significance, its measurement was unlikely to provide clinically useful prognostic information, in our experience, for patients with early BC.
No conflict of interest.

2101 POSTER

Clinical prognostic value of HLA-E and HLA-G expression in early breast cancer

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Background: The immune system affects growth of tumors, including breast cancer. We studied the clinical prognostic value of the expression level of non-classical HLA class I, E and G alleles in early breast cancer.
Material and Methods: In our study we included tumors from 350 patients with early breast cancer (BC) (cancer *in situ*: 35 cases, 10%; T1N0M0 stage: 315 cases, 90%) treated in Russia between 1985 and 2009 (RCRC, RMAPE, Moscow). Median age of patients included was 53 years (range: 26−88 years). Patients had radical surgery (mastectomy: 161 cases, 46%; breast-conserving surgery: 189 cases, 54%) and on recommendation also adjuvant treatment (radiotherapy- 180 cases, 51.4% or/and systemic therapy- 225 cases, 64.3%). Median time of follow-up 72 months (range: 12–216 months). BC progression was seen in 85 patients (24.2%), with median time to progression being 33 months (range: 7–168); 9.1% presented with local recurrence; 2.3% with regional recurrence; and 12.9% with distant recurrence. During follow-up 54 patients died: 43 patients (12.2%) from breast cancer and 11 (3.1%) from any other reason. A Tissue Micro Array (TMA), with triplicate 1 mm tumor tissue punches of all patients was constructed. Subsequently, sections were immunohistochemically stained for HLA-E and HLA-G. Expression was quantified for HLA-E in 334 cases, in 342 cases for HLA-G.
Results: HLA-E expression was absent in only 4 tumors (1.2%) and present in 330 tumors (98.8%), median rate of expression of HLA-E (percentage of positive tumor cells within a sample) was 90% (range 0–100%). We divided patients into: low expression (HLA-E*low*): 0−90% positive tumor cells, 152 cases (45.5%); and high expression (HLA-E*high*): >90% positive tumor cells, 182 cases (54.5%). HLA-G expression was absent in most tumors (225, 65.8%). 117 tumors (34.2%) expressed HLA-G (1−90% positive tumor cells per patient). Expression of HLA-E and G did not correlate with progression of BC or survival time for the whole group. In the invasive cancer patients a correlation between high expression HLA-E and progression of BC was seen ($p = 0.05$). Furthermore, combined HLA-E*low*/-G*negative* significantly ($p < 0.05$) correlated with a favorable clinical prognosis (16.3% relapses *vs* >25% in all other combinations).
Conclusion: We conclude that both HLA-E and G expression have clinical prognostic value in stage I tumors, suggesting an involvement of the immune system in counteracting tumor development already in very early stages of BC.
No conflict of interest.

2102 POSTER

Expression levels of HER2−2 dimer in proximity ligation assays is associated with trastuzumab-sensitivity in HER2-positive breast cancer

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Background: Expression of HER2-containing dimer could be a reliable predictive factor of HER2-targeting antibody trastuzumab in HER2-positive breast cancer. We investigated the association between expression of HER2-containing dimer and response to trastuzumab in HER2-positive breast cancer.
Method: The expression levels of HER2-containing dimer were evaluated in series of HER2-positive breast cancer cell lines. We also evaluated the association between expression of HER2-containing dimer and trastuzumab-sensitivity in breast cancer patients who underwent trastuzumab-containing neoadjuvant chemotherapy. HER2-containing dimer was evaluated by proximity ligation assays (Duolink in situ, Olink®).
Results: There were higher expression levels of HER2−2 dimer in trastuzumab-sensitive cell lines compared to the resistant cell lines (sensitive vs. resistant, 65 vs. 15, $p<0.01$). In acquired trastuzumab-resistant model by long-term exposure of trastuzumab, significant decrease in expression level of HER2−2 dimer was recognized irrespective of maintain similar levels of HER2-receptor. In a cohort of 23 HER2-positive breast cancer patients treated with trastuzumab-containing neoadjuvant chemotherapy, high HER2−2 dimer expression cohort showed significantly higher rate of quasi-pathological complete response compared with low HER2−2 dimer expression cohort (high vs. low, 12/16, 75% vs. 1/7, 14%, $p = 0.006$).
Conclusion: Expression level of HER2−2 dimer by proximity ligation assays can be a reliable predictive marker of trastuzumab-sensitivity in HER2-positive breast cancer in vitro and vivo. Further examination is warranted in larger population, especially from prospective randomized clinical trials.
No conflict of interest.

Variables		expression level of HER2−2 dimmer		p value
		Low (n = 7)	High (n = 16)	
T	1	2	4	0.86
	2,3,4	5	12	
N	0	1	4	0.57
	1,2,3	6	12	
Grade	1,2	3	3	0.23
	3	4	13	
ER	positive	2	9	0.22
	negative	5	7	
HER2 IHC	1+,2+	2	2	0.35
	3+	5	14	
HER2 FISH	average	6.3	6.1	0.88
QpCR	yes	1	12	0.006
	no	6	4	
HER2−3 dimer	positive	0	3	0.22
	negative	7	13	

2103 POSTER

The impact of baseline and genetic parameters on progression free survival and overall survival in breast cancer patients receiving neoadjuvant or adjuvant chemotherapy with fluorouracil, epirubicin and cyclophosphamide

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Background: Several studies assessed the influence of genetic variability on outcome in breast cancer patients, but most studies were small or were limited to a few genes only. We assessed the impact of a wide range of patient-, tumor- and chemotherapy-related factors on progression-free survival (PFS) and overall survival (OS) in patients receiving fluorouracil, epirubicin and cyclophosphamide (FEC).
Methods: Female patients with early breast cancer receiving neoadjuvant or adjuvant chemotherapy with 6 cycles FEC were eligible. Patient-related factors (age at diagnosis, body mass index, body surface area and germ line genetic polymorphisms), chemotherapy-related factors (cycles received and growth factor use), baseline biochemical variables (white blood cell count, absolute neutrophil count, platelets, aspartate aminotransferase, alanine aminotransferase, total bilirubin and creatinine), tumor-related factors (stage and subtype) and severe toxicity occurrence (febrile neutropenia) were assessed (missing data <10%). The germ line genetic polymorphisms were selected based on our recent publication describing the impact of genetic variability on toxicity of FEC (Vulsteke et al, Ann Oncol. 2013 Feb 7). Univariate survival analysis of OS and PFS were performed.
Results: Among 462 patients planned to receive 6 cycles of FEC, 66 (14.3%) developed distant metastasis, 24 (5.2%) had a locoregional relapse and 44 (9.5%) died during a mean follow-up of 6.3 years. The median age was 50 years (range: 23−72 years) and 24 (5%) of the 462 patients received neoadjuvant chemotherapy. In the univariate analysis, patients with febrile neutropenia had a significantly better OS ($p = 0.03$) and patients with increasing tumor stage had a worse OS ($p = 0.002$). Univariate significant associations with a worse PFS were: higher tumor stage ($p = 0.0020$), less FEC cycles received ($p = 0.02$), higher white blood cell count ($p = 0.03$), no growth factor use ($p = 0.04$), HER2like and triple negative subtype ($p = 0.01$), C-allele carriers of rs1138272 in the GSTP1 gene ($p = 0.03$) and T-allele carriers of rs4673 in the MRP1 gene ($p = 0.01$). On the CYP2C9

gene, carriers of the homozygous C-alleles of rs1057910 were significantly associated with a worse OS and PFS ($p < 0.0001$).
Conclusions: Tumor-related factors but also genetic variability, baseline biochemical variables and chemotherapy-related factors significantly impacted on OS and PFS in a large cohort of early breast cancer patients treated with FEC only. A multivariate analysis of these putative predictive factors is now ongoing and the findings will be presented at the meeting.
No conflict of interest.

2104 POSTER

CHD1L protein is overexpressed and a marker for aggressive tumor biology in human breast cancer

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Background: The chromodomain helicase/adenosine triphosphatase DNA binding protein 1-like gene (CHD1L) is a recently identified oncogene localized at 1q21. Overexpression of CHD1L protein in primary hepatocellular carcinoma is correlated with enhanced apoptosis inhibition, and could probably lead to reduced chemosensitivity and shortened patient survival. However, CHD1L protein status in primary breast cancer and its clinical significance remains obscure.
Material and Methods: In this study, immunohistochemistry (IHC) for CHD1L was performed on a tissue microarray (TMA) containing 179 primary invasive breast cancer. CHD1L status was determined by a scoring system using both the proportion score and the intensity score. Clinicopathologic features of the breast cancer patients were collected and compared between different CHD1L status.
Results: CHD1L overexpression was observed in 87 of the 179 breast cancers (48.6%). CHD1L overexpression was associated with a younger age ($P = 0.011$), higher grade ($P = 0.004$) and HER2 positive status ($P = 0.037$). No other clinicopathologic features were significantly correlated with CHD1L expression(Table 1).
Conclusions: CHD1L overexpression is more significantly associated with aggressive tumor biology rather than large tumor burden in breast cancer. The prognostic significance of CHD1L expression needs to be further studied.
No conflict of interest.

Table 1. Patient characteristics, stratified by CHD1L expression.

Characteristic	CHD1L expression (%)		*P* value
	Negative (N = 92)	Positive (N = 87)	
Age			0.011
⩽55	34 (37.0)	49 (56.3)	
>55	58 (63.0)	38 (43.7)	
AJCC T Stage			0.204
1	42 (45.7)	47 (54.0)	
2	48 (52.2)	35 (40.2)	
3–4	2 (2.2)	5 (5.7)	
AJCC N Stage			0.928
0	52 (56.5)	50 (57.5)	
1	24 (26.1)	23 (26.4)	
2	12 (13.0)	9 (10.3)	
3	4 (4.3)	5 (5.7)	
Grade			0.004
1	29 (31.5)	11 (12.6)	
2	45 (48.9)	46 (52.9)	
3	18 (19.6)	30 (34.5)	
ER			0.264
Positive	26 (28.3)	32 (36.8)	
Negative	66 (71.7)	55 (63.2)	
PR			0.456
Positive	40 (43.5)	43 (49.4)	
Negative	52 (56.5)	44 (50.6)	
HER2			0.037
Positive	80 (87.0)	64 (73.6)	
Negative	12 (13.0)	23 (26.4)	

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

2105 POSTER

Immunogenicity of balugrastim and pegfilgrastim in breast cancer patients: An integrated analysis from phase I, II, and III studies

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Background: Balugrastim is a once-per-cycle, fixed-dose protein composed of human serum albumin (HSA) and granulocyte-colony stimulating factor (G-CSF) under review for the prevention of severe neutropenia in cancer patients receiving chemotherapy (CTx). Like any protein-based therapeutic, balugrastim may elicit an anti-drug antibody (ADA) response that could affect drug safety and efficacy. The immunogenicity of balugrastim versus pegfilgrastim and the impact of ADAs on the pharmacokinetics (PK), clinical efficacy, and safety of balugrastim were assessed in patients with breast cancer receiving CTx.
Methods: Patients received a subcutaneous injection of balugrastim or pegfilgrastim 6 mg on Day 2 of each CTx cycle. Balugrastim doses were: 50, 150, 300, or 450 μg/kg (Phase I); 30, 40, or 50 mg (Phase II); or 40 mg (Phase III). Serum samples for analysis of antibodies to balugrastim were obtained before dosing of balugrastim for each CTx cycle and at the end of the study (15−30 days after the last dose). Follow-up samples were collected 6 and 12 months after the last dose for the Phase II study and 4 and 10 months after last dose for the Phase III study. Samples were screened for antibodies specific to each study drug using ELISA assays. ADAs were confirmed using an immunocompetition approach and analyzed for titers and neutralizing activity in a cell-based assay. Antibodies to human albumin were also assessed using a separate ELISA with enhanced tolerance for serum albumin.
Results: A total of 764 patients from three clinical studies were tested for ADAs to balugrastim (n = 502) or pegfilgrastim (n = 262). Two patients were observed to have positive ADA responses to pegfilgrastim and three were observed to have positive ADA responses to balugrastim. All positive ADA samples had low antibody titers, and no neutralizing activity was observed in the cell-based assay. Antibodies to human albumin related to balugrastim administration were detected in seven patients at only one time point in each patient. Serum ADA status was not observed to correlate with the PK, clinical safety, or efficacy of balugrastim.
Conclusions: A low immunogenicity incidence was observed in the 502 breast cancer patients treated with balugrastim. All positive ADA responses had low antibody titers and lack of neutralizing activity for balugrastim. The incidences of confirmed positive anti-balugrastim or anti-pegfilgrastim binding antibodies were comparable between treatment groups.
Conflict of interest: *Ownership: Laurie Pukac, Shane Clark, Natasha Bukreyeva, Steven Barash, Anton Buchner, Liat Adar, Noa Avisar, Patrick Liu, are all employees of Teva Pharmaceuticals*

2106 POSTER

Frequency of triple-negative breast cancer in women with different genotypic variants in BRCA, TP53

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Background: Triple-negative breast cancer (TNBC) is a tumor characterized by lack of estrogen receptor, progesterone receptor, and HER2/neu. Frequency of TNBC is about 15% of all invasive breast cancers. Triple-negative breast cancer is associated with the presence of a germline *BRCA*-mutations and poor prognosis. The purpose of this study was to analyze the frequency of TNBC in women with polymorphisms and mutations in *BRCA* and *TP53* genes.
Material and Methods: At the first stage *BRCA1*, *BRCA2*, *TP53* genes from 242 women with breast cancer were scanned for mutations and polymorphisms.
242 women with breast cancer enrolled in this study were divided: 184 women (76%) with hereditary breast cancer, associated with allelic variants in *BRCA1/2* [haplotype B (IVS1–103T/C, IVS1–115T/C, IVS8−58delT, D693N, S694S, L771L, P871L, E1038G, K1183R, S1436S, IVS14−63C/G, S1613G) − 24.8% (n = 60), Q356R − 5.4% (n = 13), *BRCA1*-mutations − 23.5% (n = 57), N372H − 8.3% (n = 20)], *TP53* [R72P − 4.5% (n = 11), In3dup16−4.1% (n = 10)] genes and 58 cases (24%) with sporadic breast cancer (wt*BRCA*/*TP53*) were included in control group.
Results: Triple-negative breast cancer in women with allelic variants was identified in 7.7% − 49.1% cases. Multiple studies have indicated that

triple-negative breast cancers in younger women are frequently *BRCA1*-related. We have also shown that TNBC is statistically-valid presented in women with *BRCA*-mutation − 49.1% compared to other breast cancers associated with or without allelic variants ($p < 0.05$). Less frequently TNBC was observed in women with haplotype B (*BRCA1*) − 18.3% and with missense variant R72P (*TP53*) − 18.2%.
Another fascinating fact is the detection of TNBC in patients with wt*BRCA*/*TP53* − 15.5% cases. TNBC was extremely rare indicated in women with polymorphism Int3dup16 (*TP53*) − 10% and with missense variant Q356R (*BRCA1*) − 7.7%. There is no one case of TNBC in women with missense variant N372H in *BRCA2*.
Conclusions: The study demonstrated different frequency of triple-negative breast cancer depending on *BRCA*- and *TP53*-genotype; TNBC is statistically-valid presented in women with germline mutation in *BRCA1*.
No conflict of interest.

2107 POSTER

Is there a correlation between CDKN1A and CDKN1B gene polymorphisms and Turkish breast cancer patients?

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Background: We assessed whether C120T in CDKN1A; C279T and Gly109Val in CDKN1B gene polymorphisms predicted clinical outcome in breast cancer patients.
Material and Methods: DNA was isolated from peripheral blood by standard phenol/chloroform extraction method for genotyping. The data were statistically analysed using SPSS software version 17.0 for Windows. Statistical significance of the observed genotype frequencies was evaluated according to Hardy–Weinberg rule.
Results: A total of 73 breast cancer patients with performance status of 0−2 were enrolled in this study. We determined the Ser31Arg and C120T in CDKN1A; C279T and Gly109Val in CDKN1B single nucleotide gene polymorphisms. Median age was 49 years (range 25−80 years) and all patients were female. Anthracycline or anthracycline plus taxane based chemotherapy were given At diagnosis lymph node involvement was detected in 41 patients (56.2%) and in 27 (37%) of the patients no involvement was detected. Her-2 positivity was recorded in 35 (47.9%) patients and negativity in 35 (47.9%) patients. Hormone reseptor positivity was found in 35 (47.9%) of the patients. We found polymorphisms of Ser31Arg in CDKN1A gene AC, AA, CC genotype and C,A allele frequencies in breast cancer patients as 46.6%, 35.6%, 17.8% and 36.7%, 63.3%; for C120T in CDKN1A gene, CC, CT, TT genotype and C, T allele frequencies as 71.2%, 27.4%, 1.4%, 84.9%, 15.1%; for C279T in CDKN1B gene CC, CT, TT genotype and C,T allele frequencies as 57.5%, 32.9%, 9.6%, 74.0%, 26.0%; for Gly109Val polymorphism in CDKN1B gene GT,TT,GG genotype and T,G allele frequencies as 47.9%, 45.2%, 6.8%, 69.2%, 30.8%, respectively. Patients with polymorphism of Ser31Arg in CDKN1A gene AA genotype had a longer survival (140.94 $\pm$12.57 months, 95% CI 116.32–165.56) than all of the other genotypes. However, this difference is not statistically significant ($p = 0.530$). We didn't find any significant correlation between overall survival and Ser31Arg and C120T in CDKN1A; C279T and Gly109Val in CDKN1B genotypes ($p = 0.411$, $p = 0.942$, $p = 0.754$, $p = 0.325$ respectively). Cox regression analysis for overall survival showed that only exist of metastasis was statistically significant (HR = 3.087, 95% CI=0.009–0.238, $p < 0.001$); it was the most important prognostic factor. The frequency of genotypes in these genes in patients did not show a significant deviation from Hardy–Weinberg equilibrium.
Conclusions: We could not find any significant association between the genotypes and clinicopathologic parameters. Further large and functional studies are needed to explore these gene polymorphisms in Turkish population.
No conflict of interest.

2108 POSTER

The significance of urokinase system in postmenopausal breast cancer patients

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Background: Due to heterogeneous nature of breast cancer, individual adjuvant therapy is not successful in all patients. For that reason 30% of all patients with early-stage breast cancer will develop metastasis. Urokinase system has a central role in the process of migration, invasion, extracellular turnover and proliferation of malignant cells.
Material and Methods: Our analysis included 49 patients with histologically verified primary breast cancer. All of the investigated patients were postmenopausal women who received adjuvant tamoxifen therapy according to protocols at the time of diagnosis. At time of primary therapy, no patients had any clinical evidence of distant metastasis. The course of disease was followed for 30 months or until the recurrence of disease (emergence of distant metastasis).
Results: We determined cut off points by a method of minimal p values. Cut off value for PAI-1 was determined at 4.5 ng/mg. A strong trend for uPA was obtained at 0.26 ng/mg. Analysis of disease free intervals (DFI) probabilities showed that patients with high concentration of uPA or low concentration of PAI-1 in their tumors, have much higher chance of developing distant metastasis in the period of 30 months after the surgery. Analysis of DFI probabilities for quantitative values of ER and PR showed a cut off value of 5 fmol/mg in the case of both molecular biomarkers. Patients with high concentration of PR among uPA+ had better DFI, and patients with low uPA concentration in the PR- had a higher chance of recurrence. In the subgroup of PAI-1+ patients, those with ER− or pT2 tumors had a worst prognosis compared with ER+ and pT1. A strong positive correlation was found between ER and PR ($r = 0.6$, $p=<0.001$) and uPA and PAI-1 ($r = 0.35$, $p = 0.02$).
Conclusions: uPA and PAI-1 are significant predictive factors in the period of the first 30 months after surgical treatment. Both ER and PR were confirmed as predictive markers in regard to tamoxifen therapy. These markers, combined with other clinicopathological parameters, revealed subgroups of patients with increased risk of early metastasis occurrence.
No conflict of interest.

2110 POSTER

Prognostic value of tumor infiltrating lymphocytes (TILs) on residual disease after primary chemotherapy for triple-negative breast cancer (TNBC) patients

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Introduction: Patients (pts) with TNBC not achieving a pathological complete response (pCR) after neoadjuvant chemotherapy (NACT) show a poor prognosis. Previous data suggest that chemotherapy induces immune response and that TILs on primary tumor are associated with prognosis. Aim of the present study is to investigate the prognostic value of TILs on residual disease after NACT for TNBC pts not achieving pCR.
Methods: HES slides from surgical specimens of 308 TNBC pts without pCR after NACT were retrieved from 3 centers (European Institute of Oncology, Institut Gustave Roussy, Modena University Hospital). Samples were evaluated for the % of intratumoral (IT) and stromal (ST) TILs adopting Denkert et al's methods (J Clin Oncol, 2010). Samples were classified as high-TILs if IT and/or ST >60%. Overall survival (OS) was defined as the delay between BC surgery and death/last follow up (FU) and disease-free survival (DFS) as the delay between BC surgery and relapse (local/distant whatever occurred first) or death/last FU. Those factors significantly correlated with OS in univariate analysis were included in a multivariate model.
Results: 291 out of 308 pts resulted evaluable for at least one TIL variable and were included in the analysis. Median age was 48 yrs. Median FU was 5.7 yrs. 44% and 49% of the pts received anthra/tax- and anthra-based NACT, respectively. Among the latter, 38% received adjuvant taxanes. IT and ST values were correlated (Spearman's coefficient 0.72). Both IT and ST as continuous variables were associated with OS (23% and 21% reduction in death risk for a 10% increase in IT and ST, respectively;

p < 0.0001). 9.6% of cases were classified as high-TIL. Both DFS and OS were significantly better for high-TIL pts vs low-TIL pts (5 yrs-DFS rate 84% vs 46%, HR 3.64 95% CI 1.49–8.89, log-rank p = 0.002; 5 yrs-OS rate 90% vs 56%, HR 5.02 95% CI 1.59–15.80, log-rank p = 0.002). TIL as continuous variable (defined by considering the highest value between IT and ST for each case) was still significantly associated with both DFS and OS in the multivariate analysis adjusted on clinical stage at diagnosis, node status and tumor size after NACT (p = 0.02).
Conclusion: These data suggest that high-TIL on residual disease predict good outcome for TNBC pts. TIL may be a useful tool to stratify pts at different outcome after NACT in addition to pCR and could help in guiding clinical decisions. This study feeds the hypothesis that chemotherapy can induce immune response.
No conflict of interest.

Proffered Papers Session (Sat, 28 Sep)
Gastrointestinal Malignancies − Colorectal Cancer I

2150 ORAL

Laparoscopic versus open surgery for rectal cancer: Short-term outcomes of a multicentre, open label, randomised controlled trial

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Background: Laparoscopic surgery is considered an alternative to open surgery in patients with rectal cancer, but no sufficiently powered trial has unequivocally demonstrated oncological safety of laparoscopic resection of rectal cancer.
Materials and Methods: A non-inferiority phase III trial was undertaken at 30 centres worldwide. In total, 1103 patients with rectal carcinoma within 15 cm from the anal verge were randomly assigned to either open or laparoscopic surgery in a 1:2 ratio. Clinical and pathology variables were recorded.
Results: 1044 patients were eligible for analyses, 739 patients were assigned to laparoscopic surgery and 345 to open surgery. Laparoscopic surgery was associated with less blood loss (median 200 mL vs 400 mL after open surgery), but lasted 52 minutes longer (both p < 0.0001). Furthermore, laparoscopic approach was followed by earlier restoration of bowel function (p < 0.0001) and shorter hospital stay by 1 day for both. Hospital stay was 8 days after laparoscopic and 9.0 days after open surgery (p = 0.036). Macroscopically completeness of the resection was not significantly different between both groups (88% vs 92% for laparoscopic and open surgery, p = 0.250). In both groups a positive circumferential margin was noted in 10% (p = 0.850). 278 patients (40%) in the laparoscopic group had complications compared with 128 patients (37%) in the open group, (p = 0.424,). Mortality rates, 1.1% in the laparoscopic group and 1.7% in the open group were comparable in both arms, p = 0.409.
Conclusion: Short-term results show that Laparoscopic surgery for rectal cancer is similar to open surgery regarding safety and radicality of surgery while recovery after laparoscopic surgery was improved.
No conflict of interest.

2151 ORAL

Intensified follow-up in colorectal cancer patients using frequent carcino-embryonic antigen (CEA) measurements and CEA-triggered imaging

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Background: For colorectal cancer (CRC), there is need for an evidence-based follow-up schedule defining frequency of blood tests and imaging to detect recurrent disease as early as possible. The trial CEA Watch assesses the value of frequent CEA measurements and CEA-triggered imaging in detecting recurrent disease in CRC patients and aims to increase the rate of curable recurrences amongst all detected recurrences from 10 % to 25%.
Methods: This was a randomized-controlled multicenter prospective study using a stepped wedge cluster design. From October 2010 and on, 11 hospitals in the Netherlands were timed to change their follow-up care as usual into an intensified follow-up schedule for all patients in follow-up after non-metastasized CRC operated from January 2007. The moment of the follow-up switch was randomized per cluster. The inclusion has been stopped October 2013 and the study is in progress.
The intervention protocol consisted of CEA measurements every 2 months, with repetition of the CEA measurement after 1 month in case of a 20% rise and imaging in case of 2 subsequent rises. A sample size calculation was performed and 1600 patients were needed given a recurrence rate of 25%.
Results: 3223 patients were included; 243 recurrences were detected (7.5%), 104 (43%) recurrences were found while the patient participated in the control follow-up and 139 (57%) recurrences in the intervention follow-up. In total, 90 (37.0%) of the found recurrences could be treated with curative intent. The time between the operation and diagnosis of recurrent disease was the same amongst groups. The curability of detected recurrences was significantly higher for the intervention protocol than for the control protocol (42% v 30%, p = 0.04).
Conclusions: The CEA watch protocol detects recurrent disease after colorectal cancer in a phase that a significantly higher proportion of recurrences can be treated with curative intent.
Trial sponsor: The Netherlands Organisation for Health Research and Development.
Trial Registry Number 2182.
Participating hospitals: Medisch Spectrum Leeuwarden, Medisch Spectrum Twente, Nij Smellinghe Drachten, Albert Schweitzer Dordrecht, Martini Hospital Groningen, Jeroen Bosch Hospital Den Bosch, Catharina Hospital Eindhoven, Meander Amersfoort, Gelre Apeldoorn, Medisch Centrum Haaglanden, and Elisabeth Hospital Tilburg
No conflict of interest.

2152 ORAL

Differences in circumferential resection margin involvement after abdominoperineal excision and low anterior resection no longer significant

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Introduction: The oncologic inferiority of the APE technique in comparison with LAR has been widely reported in literature. However, due to large evolvement in rectal cancer care, outcomes after APE may have improved since.The aim of this study was to evaluate whether the abdominoperineal excision (APE) is associated with an increased risk of circumferential resection margin involvement (CRM) after rectal cancer surgery in comparison with low anterior resection (LAR).
Material and Methods: The population-based dataset of the Dutch Surgical Colorectal Audit (DSCA) was used selecting 5017 patients with primary rectal cancer undergoing surgery in 2010–2011. Propensity scores were calculated for the likelihood of performing an APE given relevant patient- and tumour characteristics, and used in the multivariate analysis of CRM involvement.
Results: A LAR was performed in 2969 patients (71%), an APE in 1245 patients (29%). After LAR, a deviating ostomy was constructed in 68% of patients. Factors associated with the performance of an APE were male gender, advanced cT stage, and tumours close to the anal verge (0−3 cm). The APE was associated with a slight, non-significant, increased risk of CRM involvement [OR 1.33; CI 0.93–1.90]. Absolute percentages of CRM involvement were 8 and 12 percent after LAR and APE respectively. In subgroup analysis, advanced rectal tumours (cT3,4) were associated to a higher risk of CRM involvement after APE (OR 1.61; CI 1.05–1.90), whereas smaller tumours (cT1,2) were not [OR 0.62, CI 0.27–1.40].
Conclusion: The results suggest that on a national level the APE procedure itself is not a strong predictor anymore for CRM involvement after rectal cancer surgery. However, in advanced tumours, results after APE are inferior to LAR.
No conflict of interest.

2153 ORAL

Preoperative radiotherapy with a simultaneous integrated boost compared to chemoradiotherapy for T3−4 rectal cancer: Interim analysis of a multicentric randomized trial

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Background: The addition of chemotherapy to preoperative radiotherapy (RT) has been established as the standard of care for patients with cT3−4 rectal cancer. As an alternative strategy, we reported previously in a phase II study a limited toxicity and high 5-year local control rate with preoperative image-guided and intensity-modulated RT (IG-IMRT) with a simultaneous integrated boost (SIB), without concomitant chemotherapy. Here, we compared this strategy to chemoRT in a multicentric randomized trial (NCT 01224392).
Methods: cT3−4 rectal cancer patients were randomly assigned to receive either preoperative IG-IMRT (46 Gy in 23 fractions of 2 Gy) with a SIB to the rectal tumor up to a total dose of 55.2 Gy (boost-arm) or preoperative IG-IMRT (46 Gy in 23 fractions of 2 Gy) plus capecitabine (825 mg/m^2 twice daily) (chemo-arm). Surgery was performed 6−8 weeks after completion of preoperative treatment. Metabolic tumor activity reduction, assessed by comparing the maximal standardized uptake value (SUV_{max}) on sequential 18-fluorodeoxyglucose positron emission tomography (FDG-PET), was the primary endpoint. Acute side effects were scored using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.
Results: Eighty patients were randomly assigned to the boost-arm (n = 37) or chemo-arm (n = 43). Acute grade 3 toxicity occurred in 3% of the patients in the boost-arm compared to 7% in the chemo-arm (p = 0.37). No acute grade 4 toxicities were observed. Acute grade 2 enteritis was significantly lower in the boost-arm (22% vs 44%; p = 0.03). Surgery was performed in 95% of patients in both arms. The R0 resection rate was 97% and 98% for patients in the boost- and chemo-arm, respectively. Pathologic complete response rate (ypCR, Dworak grade 4) was 12% in the boost-arm compared to 24% in the chemo-arm (p = 0.15). Dworak regression grade 3−4 was not different between both arms (45% vs 46%, p = 0.56). The mean fractional change in SUV_{max} at 5 weeks after completion of preoperative RT as compared to baseline was − 49.0% $\pm$ 20.8% and − 50.9% $\pm$ 27.6% for patients in the boost-arm and chemo-arm, respectively (p = 0.40).
Conclusions: The implementation of preoperative IG-IMRT resulted in limited acute grade $\geqslant$3 toxicity in both arms. As compared to chemoRT, patients receiving a boost experienced less acute grade 2 enteritis. In terms of downstaging, impressive rates of major histomorphologic regression (Dworak grade 3−4) were recorded in both treatment arms, with a higher ypCR rate for patients receiving chemoRT. No differences in metabolic response were observed.
No conflict of interest.

2154 ORAL

Health-related quality of life of patients 14 years after short-term preoperative radiotherapy and total mesorectal excision for rectal cancer: Report of a multicenter randomized trial

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Background: Local recurrence is a major problem in rectal cancer treatment. Preoperative short-term radiotherapy (PRT) has shown to improve local control but not survival in combination with total mesorectal excision (TME). Therefore, we assessed the very long-term health-related quality of life (HRQL) of patients treated in the TME trial still alive more than 10 years after diagnosis.
Material and Methods: In the TME trial (1996–1999) 1530 Dutch patients with rectal cancer were treated with TME and randomly assigned to PRT (5 x 5 Gy). In 2012 HRQL was evaluated in all surviving patients (n = 583) using a questionnaire combining EORTC QLQ-C30, EORTC QLQ-CR29 and additional questions. To correct for multiple testing, a p-value of 0.01 was considered statistically significant.
Results: Results were obtained from 478 patients (response rate 82%), with a median follow up of 14.6 years (range: 12.5–16.6). Overall, no significant differences could be detected in global HRQL and functioning scores between the two treatment arms (table 1). For individual symptoms however, irradiated patients reported significantly more bowel dysfunction and increased use of incontinence material. In addition, irradiated male patients more often reported erectile dysfunction. Urinary function however, was not different between the two groups.

Table 1. Overview of prominent results

	Mean score		*P*
	PRT (N = 241)	TME (N = 237)	
Physical functioning	77.4	80.9	0.08
Role functioning	79.4	81.4	0.30
Emotional functioning	86.1	85.8	0.35
Cognitive functioning	83.3	84.0	0.33
Social functioning	86.8	87.7	0.59
Global health status	77.2	78.5	0.16
Stool frequency	26.3	19.4	<0.01
Faecal leakage	22.5	10.1	<0.001
Frequency of use of pads for faecal leakage	56.4	38.4	<0.001
Involuntary urine loss	41.8	41.3	0.88
Frequency of use of pads for urine loss	46.5	44.1	0.73
Sexually active	38.0	41.3	0.08
Difficulty getting or maintaining an erection	79.3	66.8	<0.01

PRT, preoperative short-term radiotherapy; TME, total mesorectal excision.

Conclusions: Long-term HRQL evaluation shows that short-term PRT is still associated with increased bowel dysfunction and increased erectile dysfunction 14 years after diagnosis. However, PRT does not affect global HRQL and functioning (EORTC QLQ-C30). To facilitate shared decision making, these long-term results should be discussed with newly diagnosed patients before start of treatment.
Supported by the Dutch Cancer Society (CKVO 95−04) and the Dutch National Health Council (OWG 97/026).
No conflict of interest.

2155 ORAL

Phase III trial of treatment duration for oral uracil and tegafur/ leucovorin adjuvant chemotherapy for patients (pts) with stage IIB/III colon cancer: Final results of JFMC33–0502

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Background: JFMC33–0502 study (Kondo et al. ESMO 2012, Abstract 552) seemed to offer no significant superiority of 18 months treatment of oral UFT/LV adjuvant chemotherapy to 6 months treatment with respect to the primary endpoint of disease free survival (DFS) in patients with stage IIB/III colon cancer at the interim analysis. Here, we report the final results of this study.
Material and Methods: Patients with curatively resected stage IIB/III colon cancer (PS, 0 to 1; age, 20 to 75 years; no other therapy) were randomly assigned to receive UFT (300 mg/m^2/day)/LV (75 mg/day) for 28 out of 35 days for 6 months (Control (C) arm) or for 5 consecutive days per week for 18 months (Study (S) arm). The primary endpoint was the DFS, and the secondary endpoints were overall survival (OS) and safety. Patient information was fixed in February 2013.
Results: At the time of this final analysis, median follow-up was 61 months with 334 DFS events out of 1060 pts. The 5-year DFS for the primary endpoint was 69% in the S arm and 69% in the C arm. The 5-year OS was 85% in the S arm and 85% in the C arm. The 5-year DFS for the patients with stage IIB, III disease were 79%, 67% in the S arm and 80%, 67% in the C arm, respectively. In toxicity for 6 months, S arm was more feasible than C arm with respect to symptom.
Conclusion: Superiority of prolonging the treatment duration of adjuvant chemotherapy was not demonstrated in Japanese patients with stage IIB/III colon cancer. DFS and OS in both arms were compatible with those of FOLFOX treatment previously reported in MOSAIC and NSABP C-08 trials after follow-up. UFT/LV for 6 months had low recurrence rate and less toxic chemotherapy for patients with stage IIB/III colon cancer.
No conflict of interest.

2155A ORAL

Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: Response to the local treatment after chemoradiation and surgery as secondary endpoint

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Background: The PETACC-6 trial investigates whether the addition of oxaliplatin to preoperative oral fluoropyrimidine-based chemoradiation (CRT) followed by postoperative adjuvant fluoropyrimidine-based chemotherapy (CT) improves disease-free survival (DFS) in locally advanced rectal cancer. We report on pathological staging and sphincter preservation following preoperative CRT.
Methods: Between 11/2008 and 09/2011, patients with rectal cancer within 12 cm from the anal verge, T3/4 and/or node-positive, with no evidence of metastatic disease and considered either resectable at the time of entry or expected to become resectable, were randomly assigned to receive 5 weeks of preoperative CRT (45 Gy in 25 fractions with an optional boost to a total dose of 50.4 Gy) with capecitabine (825 mg/m^2 twice daily), followed by 6 cycles of adjuvant CT with capecitabine (1000 mg/m^2 twice daily/days 1−15 every three weeks) (arm 1) or to receive the same regimen with the addition of oxaliplatin before (50 mg/m^2/days 1, 8, 15, 22, 29) and after surgery (130 mg/m^2/day 1, every three weeks) (arm 2). Pathological down-staging (ypT0−2N0) rate, complete remission (ypT0N0) rate and tumor regression grade according to Dworak were secondary endpoints. The assessment was based on the review of the specimen and scoring by the local pathologist. Patients not operated or not resected were scored as failures (intent-to-treat analysis).
Results: 1094 patients were randomized (547 in each arm). 98% and 92% of patients respectively, received at least 45 Gy of preoperative RT in arms 1 and 2. More than 90% of full dose concurrent CT was delivered in 91% and 63% of patients in arm 1 and arm 2 respectively. R0 resection rate was 92.0% in arm 1 and 86.3% in arm 2. The ypT0N0 rate was equal in both arms with 11.3% in arm 1 and 13.3% in arm 2 (p = 0.31). There was no difference in pathological down-staging rate (43.5% in arm 1 vs. 41.5% in arm 2). In arm 2, the tumor regression according to Dworak was minimal in 13.7% of patients, moderate in 35.5%, good in 20.5% and total in 13.5%. In arm 1, the percentages were 19%, 36.2%, 19.4% and 12.4% respectively. The anal sphincter was preserved in 70% vs. 65% (p = 0.09) in arms 1 and 2. Definitive numbers will be presented at the congress.
Conclusions: The addition of oxaliplatin to preoperative fluoropyrimidine-based CRT led to decreased treatment compliance and did not result in any improvement in tumour down staging or in anal sphincter preservation.
Conflict of interest: *Advisory board: H.J. Schmoll, R. Hofheinz, T. Price have a consultant or advisory role for Roche to disclose. H.J. Schmoll has a consultant or advisory role for Sanofi and Bayer to disclose. Corporate-sponsored research: H.J. Schmoll, E. Van Cutsem, K. Haustermans, R. Hofheinz have research funding from Roche to disclose. H.J. Schmoll has research funding from Merck to disclose. E. Van Cutsem has research funding from Sanofi to disclose. Other substantive relationships: H.J. Schmoll, R. Hofheinz have honoraria from Roche to disclose.*

Proffered Papers Session (Sun, 29 Sep)
Gastrointestinal Malignancies − Colorectal Cancer II

2156 ORAL

Effects of regorafenib therapy on health-related quality of life in patients with metastatic colorectal cancer in the phase III CORRECT study

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Background: In the phase III CORRECT trial (NCT01103323), the multikinase inhibitor regorafenib (REG) showed significant improvement in overall survival and progression-free survival *vs* placebo (P) in patients (pts) with metastatic colorectal cancer (mCRC) whose disease had progressed on other standard therapies. The most frequent grade 3 adverse events (AEs) seen with REG were hand–foot skin reaction (HFSR), fatigue, diarrhea, hypertension, and rash. We examined the impact of REG efficacy and tolerability on quality of life (QoL).
Materials and Methods: CORRECT was an international multicenter, randomized, placebo-controlled trial sponsored by Bayer HealthCare. Adults with mCRC progressing after all standard therapies were randomized 2:1 to receive REG 160 mg (n = 505) or P (n = 255) once daily for the first 3 weeks of each 4-week cycle. Prespecified QoL analyses were undertaken using the European Organisation for the Research and Treatment of Cancer QoL questionnaire (EORTC QLQ-C30) and the EuroQol-five dimension health utility index (EQ-5D). QoL outcomes were expressed as time-adjusted area under the curve (AUC) to allow descriptive evaluations of QoL in the REG and P groups across the entire treatment period. Individual domains were compared using descriptive statistics.
Results: Overall, changes in QoL were similar in the REG and P groups: difference in least-squares (LS) mean time-adjusted AUC of EORTC QLQ-C30 score: −1.19 (95% confidence interval [CI] −3.13 to 0.75); differences in LS mean time-adjusted AUC for EQ-5D index and visual analog scale (VAS) scores: 0.00 (95% CI −0.03 to 0.03) and −1.21 (−3.04 to 0.61), respectively. Changes from baseline did not differ between Reg and P on most of the 15 domains assessed in the EORTC QLQ-C30. Change from baseline on the role functioning scale was similar overall in both groups, although scores appear to differ between REG and P at cycles 3 and 4 for the diarrhea subscale and at cycle 4 for the social functioning subscale.
Conclusion: No substantial differences in overall change in QoL were seen between REG-treated pts and P recipients. Role functioning may be impaired by AEs, but remained similar in both groups; management of AEs with dose modifications may improve role functioning and diarrhea in REG-treated pts.

LS mean time-adjusted AUC (95% CI)	P	REG
EORTC QLQ-C30	58.13 (55.72–60.53)	56.93 (54.79–59.08)
EQ-5D index	0.67 (0.64–0.70)	0.67 (0.64–0.70)
EQ-5D VAS	61.84 (59.59–64.09)	60.62 (58.62–62.63)

Conflict of interest: *Ownership: (stock ownsership) Bayer HealthCare Pharmaceuticals. Advisory board: Bayer, Amgen, Celgene, Genomic Health, Roche, Sanofi-Aventis, Merck, Takeda. Board of directors: n/a. Corporate-sponsored research: Amgen, Bayer, Roche, Merck, Taiho, Daiichi-Sankyo, ImClone. Other substantive relationships: (employment) Bayer HealthCare Pharmaceuticals*

2157 ORAL

Enteral nutrition and prevention of anastomotic leakage: A possible role for conditional essential amino acids? Results of a randomized clinical trial

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Background: Early enteral nutrition after abdominal surgery decreases infectious complications and mortality. Amino acids play an important role as metabolic fuel for rapidly dividing cells. Low plasma L-glutamine concentrations for example, represent poor prognosis in ICU-patients. Furthermore, it has been established that the route of feeding (enteral vs. parenteral) has implications for the metabolism of amino acids.
Methods: A total of 123 patients with rectal carcinoma were included in this prospective randomised controlled trial. Preoperatively, patients were randomised into two groups: early postoperative enteral feeding through a nasojejunal tube (EEN, n = 61) or parenteral feeding through a jugular vein catheter (EPN, n = 62). 8 hours after the surgical procedure feeding was started in hemodynamically stable patients. Both groups were stimulated to normal oral diet. Parenteral feeding was chosen as a control to ensure caloric equivalence between both groups. Blood samples were collected preoperatively and at POD +1 and +5. Plasma L-glutamine, L-citrulline and L-arginine levels were analysed using a validated UPLC-tandem mass spectrometric method.
Results: Baseline amino acid levels were comparable for both groups. Directly after rectal surgery, a decrease in all amino acid concentrations was seen. Plasma L-glutamine levels were higher in the EPN group compared to the EEN group both on postoperative day 1 (401.6 μmol/l ± 94.3 vs. 351.4±123, p = 0.013) and day 5 (441.6 μmol/l ± 119.7 vs. 395.5±110.7, p = 0.006). L-citrulline levels did not differ. L-arginine levels were significantly elevated in the EPN group compared to the EEN group at both day 1 (51.5 μmol/l ± 15.3 vs. 40.4±13.7, p = 0.008) and day 5 (77.4 μmol/l ± 27.7 vs. 61.6±21, p = 0.008). Because the EEN group showed a significantly lower number of anastomotic leakages (n = 1) compared to the EPN group (n = 9, $p = 0.009$), plasma amino acid levels were correlated with infectious complications. An inverse relation between the amino acid levels at day 5 and the occurrence of infectious complications was found. Moreover, the longer the surgical duration, the more blood loss was observed both inversely related to plasma L-citrulline and L-arginine on day 1.
Conclusion: Directly after major rectal surgery a strong decrease in plasma amino acid concentrations occurs. After early feeding plasma concentrations increase in both groups. Lower plasma L-glutamine and L-arginine levels were associated with characteristics of major surgery, e.g. longer duration of surgery, more blood loss and more infectious complications. Early parenteral feeding was associated with higher plasma glutamine, citrulline and arginine concentrations. We previously showed that enteral nutrition resulted in less anastomotic leakage, infectious complications and a shorter hospital stay than parenteral nutrition. Therefore, we hypothesized that plasma glutamine and arginine concentrations do not provide the explanation of the beneficial effect of enteral feeding on the intestinal anastomosis or infectious complications.
No conflict of interest.

2158 ORAL

The impact of young age on survival in patients with metastatic colorectal cancer: Analysis from the ARCAD Clinical Trials Program

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Background: The median age of diagnosis of colorectal cancer (CRC) is 69 years. Patients younger than 50 years of age comprise 4.6% of the total incidence of CRC, but the incidence of CRC in the younger population is increasing. Only 5−7% of young-onset CRC cases are attributable to hereditary factors, and young patients with CRC present more commonly with stage III or IV disease. The purpose of this study is to assess whether age is prognostic for overall survival (OS) and progression-free survival (PFS) in patients with metastatic CRC. Previous investigations have treated age as dichotomized (e.g., <40 vs. >=40) and thus directly compared two groups representing broad pooled risk. Here, to obtain a better picture of the age-response relationship, we identify whether and how risk changes as a continuous (rather than categorized) function of age.
Materials and Methods: We analyzed data from the ARCAD Foundation CRC database which included 20,326 patients from 23 frontline phase III clinical trials, including trials with biologic agents. Endpoints included OS and PFS; primary covariates included age, sex, and performance status (PS). Cox proportional hazards models stratified by treatment arm within study were used to model primary age effects, as well as interactions with and/or adjustments for sex and PS. Patients without events by 1 year were right-censored. Non-linearity of age on the log relative hazard of PFS and OS was modeled using restricted cubic splines.
Results: 19,900 patients were evaluable for OS and PFS, of which 695 (3%) were younger than 40 years old. Age was prognostic for both OS ($p < 0.0001$) and PFS ($p < 0.0001$) with U-shaped risk for each endpoint; i.e., the highest risk of OS and PFS was evident in the youngest and oldest patients, while 57-year-olds and 61-year olds demonstrated the lowest risk of OS and PFS, respectively. Relative to these ages, the youngest CRC patients experienced 30% increased risk of death and 28% increased risk of progression or death (PFS) during the follow-up period. In contrast, the oldest CRC patients experienced a 72% increased risk of death and 19% increased risk of progression or death (PFS) in the follow-up period. Poor PS was significantly associated with decreased survival in younger patients but not older patients (interaction $p = 0.0001$). Sex was statistically but not clinically significant as an adjustment variable in these models.
Conclusions: Young age is associated with poorer OS and PFS in treated patients with metastatic CRC. Poor PS is also significantly associated with decreased survival in younger patients, though PS assessment may be subject to bias. Young patients with metastatic CRC represent a high-risk population for treatment failure and further studies identifying biological differences are warranted.
No conflict of interest.

2159 ORAL

Updated efficacy/safety findings from a randomized, phase 2 study of bevacizumab plus mFOLFOX6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer (OLIVIA study)

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Background: For patients with borderline resectable colorectal cancer liver-only metastases (CLMs), chemotherapy may downsize metastases and facilitate secondary resection. Intensified chemotherapy or the addition of a targeted agent may improve resection rates, but the optimal regimen remains undefined. OLIVIA aimed to determine if adding irinotecan to FOLFOX in combination with bevacizumab improved resection rates in patients with unresectable CLMs.
Material and Methods: OLIVIA was a multinational open-label phase 2 study in which patients with unresectable CLMs were randomized to bevacizumab (BEV) + mFOLFOX6 or FOLFOXIRI q2w. Unresectability was defined as ⩾1 of the following: no possibility of upfront R0/R1 resection of all hepatic lesions; <30% estimated residual liver after resection; or disease in contact with major vessels of the remnant liver. Resectability was assessed by interdisciplinary review. The primary endpoint was overall resection rate (R0/R1/R2). ClinicalTrials.gov identifier: NCT00778102.
Results: From 10/2008 to 12/2011, 80 patients were randomized to mFOLFOX6-BEV (n = 39) or FOLFOXIRI-BEV (n = 41). Patients were male (46% vs 71%), age ⩾60 y (36% vs 63%), with metastatic (82% vs 73%) or locoregional (18% vs 27%) disease in the mFOLFOX6-BEV and FOLFOXIRI-BEV arms, respectively. Efficacy outcomes are shown in the table. By 31 July 2012, 8 and 3 patients in the mFOLFOX6-BEV and FOLFOXIRI-BEV groups, respectively, had died. Follow-up is ongoing. Grade ⩾3 adverse events occurred in 84% and 95% of patients receiving mFOLFOX6-BEV and FOLFOXIRI-BEV, respectively, and included neutropenia (35% vs 48%; febrile, 8% vs 13%) and diarrhoea (14% vs 28%).

Table (abstract 2159).

Endpoint	mFOLFOX6-BEV (n = 39)	FOLFOXIRI-BEV (n = 41)	Difference	*P*
Resection R0/1/2 rate, % (95% CI)	48.7 (32.4–65.2)	61.0 (44.5–75.8)	12.3 (−11.0–35.5)	0.271
Histopathological response rate, n (%)*	7/14 (50)	10/20 (50)	0	1.0
Radiological response rate, % (95% CI)	61.5 (44.6–76.6)	80.5 (65.1–91.2)	18.9 (−2.1–40.0)	0.061
Median progression-free survival, mo (95% CI)†	12.0 (9.5–14.1)	18.8 (12.4–21.0)	–	0.0009
R0/R1	13.6 (9.8–15.9)	21.0 (16.0–31.8)	–	–
R2/other outcome	10.3 (7.4–12.4)	12.4 (8.5–19.6)	–	–

*Complete or major response (Blazer et al. JCO 2008); †Updated analysis (15 March 2013).

Conclusions: FOLFOXIRI-BEV was associated with higher resection and response rates and prolonged progression-free survival compared with mFOLFOX6-BEV in patients with initially unresectable CLMs. FOLFOXIRI-BEV should be evaluated further in this setting.

Conflict of interest: *Ownership: None. Advisory board: Hoffmann-La Roche − Adam, Bridgewater, Chau, Gruenberger. Board of directors: None. Corporate-sponsored research: None. Other substantive relationships: F. Hoffmann-La Roche − Lasserre and Loeffler are employees*

2160 ORAL

Prognostic impact of specific KRAS mutations in codon 12 and 13 in 2,165 BRAF-wildtype colon cancers: results from NCCTG (Alliance) trial N0147

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Background: Studies suggest that specific mutations in *KRAS* may differentially impact prognosis of colorectal cancer patients, but prior patient populations have been heterogeneous by disease stage and therapies received, and results have been inconsistent. We examined the prognostic impact of specific *KRAS* mutations in stage 3 colon cancer patients receiving FOLFOX alone or combined with cetuximab as adjuvant therapy in a phase 3 clinical trial. Analysis was focused on *BRAF*-wildtype tumors, given that $BRAF^{V600E}$ mutation was associated with poor prognosis in this cohort, and *BRAF* and *KRAS* mutations are mutually exclusive.

Material and Methods: *KRAS* mutations in codon 12 (6 mutations: G12A, G12R, G12D, G12C, G12S and G12V) and codon 13 (1 mutation: G13D) were examined in 2,165 colon adenocarcinomas found to carry wildtype *BRAF* from an adjuvant study, NCCTG N0147. *KRAS* was analyzed using the DxS mutation test kit (Manchester, UK) in a CLIA-certified laboratory. Given the lack of an interaction between *KRAS* status and treatment (P>.30), treatment arms were pooled for analysis. The primary endpoint, disease-free survival (DFS), was evaluated by hazard ratios (HR) using Cox models.

Results: Compared to patient tumors with wildtype copies of *KRAS* and *BRAF*, those with *KRAS* mutations in either codon 12 or 13 experienced significantly shorter DFS (Table). In multivariate analysis, 4 (G12R, G12D, G12S and G13D) of the 7 *KRAS* mutations, including those in codon 13, were significantly associated with shorter DFS as compared to *KRAS*-wildtype cancers (P < 0.5). Compared to *KRAS* wildtype, codon 12 and 13 mutations were each associated with right-sided (*v* left) tumor site (P < 0.001).

Conclusions: In a clinical trial population, we demonstrate for the first time that *KRAS* mutations in either codon 12 or 13 are associated with inferior disease-free survival in patients with stage 3 *BRAF*-wildtype colon cancer receiving FOLFOX as adjuvant therapy.

No conflict of interest.

2161 ORAL

Evaluation of PIK3CA mutation as a predictor of benefit from NSAID therapy in colorectal cancer

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Background: Aspirin and other NSAIDs protect against colorectal cancer (CRC) and are associated with reduced disease recurrence and improved outcome following primary treatment. However, toxicities of NSAIDs have limited their use as antineoplastic therapy. Recent data have suggested that the benefit of aspirin after CRC diagnosis is limited to patients with *PIK3CA*-mutant cancers. We sought to determine the predictive utility of *PIK3CA* mutation for benefit from both COX-2 inhibition and aspirin.

Material and Methods: We performed molecular analysis of tumours from 896 participants in VICTOR, a large randomized trial comparing rofecoxib with placebo following primary CRC resection. We compared relapse-free survival (RFS) and overall survival (OS) between rofecoxib therapy and placebo, and between the use and non-use of low-dose aspirin, according to tumour *PIK3CA* mutation status.

Results: We found no evidence of a greater benefit from rofecoxib treatment compared to placebo in patients whose tumour had *PIK3CA* mutation (multivariate adjusted hazard ratio [HR]; 1.2, 95% CI 0.53–2.72; $P = 0.66$; $P_{INTERACTION}=0.47$), compared with *PIK3CA* wild-type cancers (HR 0.87; 95% CI 0.64–1.16; $P = 0.34$). In contrast, regular aspirin use after CRC diagnosis was associated with a reduced rate of CRC recurrence in patients with *PIK3CA*-mutant cancers (HR 0.11; 95% CI 0.001 to 0.832; $P = 0.027$; $P_{INTERACTION}=0.024$), but not in cases lacking tumour *PIK3CA* mutation (HR 0.92; 95% CI 0.60–1.42; $P = 0.71$).

Conclusion: Although tumour *PIK3CA* mutation does not predict benefit from rofecoxib treatment, it merits further evaluation as a predictive biomarker for aspirin therapy. Our findings are concordant with recent data, and support the prospective investigation of adjuvant aspirin in *PIK3CA*-mutant CRC.

Conflict of interest: *Corporate-sponsored research: David J Kerr: Unrestricted educational grant from Merck to support VICTOR trial*

Table (abstract 2160).

KRAS status	# Patients	3-year DFS rate (95% CI)	Univariate			Multivariate[d]		
			HR	95% CI	P	HR	95% CI	P
Codon 12 mutation[a]	528 (24%)	68% (64%-72%)	1.46	1.23–1.74	<0.0001	1.44	1.20–1.73	.0001
Codon 13 mutation[b]	158 (7%)	65% (57%-73%	1.52	1.15–2.01	.0032	1.35	1.01–1.80	.047
Wildtype[c]	1479 (68%)	77% (75%-80%)	ref			ref		

[a] G12A, G12R, G12D, G12C, G12S, or G12V.
[b] G13D.
[c] Wildtype for *KRAS* and *BRAF*.
[d] Adjusted for age, gender, race, T stage, no. positive and examined nodes, grade, performance status, tumor site, mismatch repair status, treatment.

Poster Discussion Session and Poster Session
(Sun, 29 Sep)

Gastrointestinal Malignancies − Colorectal Cancer I

2162 POSTER DISCUSSION

Interim Analysis results of ABOVE phase II study with bevacizumab in patients with initially not resectable/borderline resectable colorectal liver-limited metastases

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Background: Bevacizumab (bev)-based therapy has demonstrated clinical efficacy for the neoadjuvant treatment of patients with CLLM. There are no data concerning the benefit of bev maintenance therapy after induction with bev-based therapy for patients who underwent R0 liver resection.
Methods: Untreated metastatic pts with histologically confirmed colorectal cancer with liver-limited mets were treated before surgery with the combination therapy mFOLFOX-6/bev for 5 cycle followed by one cycle of mFOLFOX6 alone (without bev). Postoperative chemotherapy + bev was restarted 5 weeks after surgery: patients were treated with the combination therapy mFOLFOX-6 + bevacizumab for additional 6 cycles. Immediately at the end of the post-operative phase, patients were treated with bev alone for 52 weeks (1 year). We report here an IA for the first 26 out of pre-planned 77 pts. Pts received oxaliplatin 85 mg/m^2 by intravenous infusion (i.v) on day1, i.v. LV 200 mg/m^2 on day 1, followed by 5-FU 2,400 mg/m^2, by continuous infusion over 46 hours + bev 5 mg/kg i.v on day 1 q2w. Eligibility criteria included adequate organ function and ECOG PS 0−1. All pts were candidates for neoadjuvant therapy and categorized according to the following surgical criteria: i) unresectable CLLM, ii) borderline resectable CLLM, where R0 surgery cannot be guaranteed iii) 'high risk' resectable CLLM based on number and mets size. Primary endpoint was ORR.
Results: According to ITT analysis, 26 out of 27 enrolled pts were assessable for ORR. Pts characteristics were: sex 18M/8F, median age 64.5 years [37−77], PS 0/1: 23/3. Site of primary tumor: rectum 2, colon 24. Synchronous/metachronous metastases: 24/2. Unresectable 14, borderline resectable 6, 'high risk' resectable 6. ORR was 16 responders (61.5%,all PR) and 10 non-responders [38.5%: 7 SD (26.9%) and 3 withdrawals], respectively. Fourteeen (53.8%) underwent R0 liver resection. Grade 3 related AEs (%) were: neutropenia 1 (3.8%) [and 2 G4 (7.6%)], myocardial infarction 1 (3.8%), fatigue 2 (7.6%), proteinuria 1 (3.8%), hypertransaminasemia 1 (3.8%).
Conclusions: IA results show high RR of mFOLFOX6/bev in CLLM treatment, resulting in high rate of R0 liver resection with good safety profile. Data should be confirmed and the role of bev maintenance elucidated with trial final results.
Conflict of interest: *Corporate-sponsored research: ROCHE*

2163 POSTER DISCUSSION

Endoscopy-based follow-up of clinical complete responders after chemoradiation for rectal cancer during a non-operative 'wait-and-see' policy

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Background: The standard treatment for locally advanced rectal cancer is chemoradiation (CRT) followed by surgery. In 15−25% of the patients CRT leads to a complete tumour response (CR), which has excellent long-term outcome. When accurately selected, these patients may also opt for a non-operative treatment ('wait-and-see'). Adequate monitoring then becomes crucial to ensure a persistent complete response and to detect any potential recurrence as early as possible. Aim of this prospective cohort study was to describe the rectal wall morphology on endoscopy during the follow-up of patients with a clinical complete response who are treated with a 'wait-and-see' policy.
Materials and Methods: 44 patients with a clinical suggestion of CR were included. The criteria for CR on endoscopy were [1] white scar with telangiectasia and/or [2] small superficial ulcer, strengthened by negative biopsies. Follow-up consisted of 3-monthly (first two years) to 6-monthly (>2 years) endoscopy, which served as the standard of reference, in addition to MRI, CEA, and CT of thorax&abdomen.
Results: Mean follow-up was 27 months (range 2−91). At the moment of inclusion endoscopy showed a white scar with telangiectasia in 38/44 patients, which persisted during follow-up. In 6/44 patients a small superficial ulcer was observed, which changed into a white scar with telangiectasia after three months for 4/6 patients. The remaining 2 developed a local recurrence within two years. For patient 1 the ulcer disappeared during follow-up but no typical white scar was observed. After 23 months a bulge was observed, which was proven to be recurrent adenocarcinoma by biopsy. For patient 2 the recurrence was already observed after three months, suggesting an incomplete response at the time of selection. Both patients were treated with salvage surgery.
Conclusion: In a 'wait-and-see' policy for patients with a complete response after chemoradiation for rectal cancer, endoscopy can be used as a standard of reference to monitor the local status. An endoscopic complete response is observed as a white scar with telangiectasia. A small superficial ulcer after chemoradiation deserves attention and close follow-up with short intervals.
No conflict of interest.

2164 POSTER DISCUSSION

Primary tumour lymph node status is associated with survival after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis

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Background: This study evaluated the association of primary tumour nodal status with outcome after CytoReductive Surgery (CRS) combined with Hyperthermic IntraPEritoneal Chemotherapy (HIPEC) for peritoneal metastases of colorectal origin in the Netherlands.
Patients and Methods: A multi-institutional database of patients treated by the Dutch CRS-HIPEC protocol for peritoneal carcinomatosis (PC) from colorectal cancer was established. Patient, tumour and treatment characteristics were prospectively obtained. The primary end point was overall survival (OS). Secondary end points were surgical outcome and disease-free survival (DFS).
Results: Of 660 patients treated for colorectal PC, extent of nodal involvement of the primary tumour was known in 557 patients. 365 patients (55%) had lymph node metastases at the time of the primary tumour.
Lymph node positivity was significantly associated with increased intraperitoneal tumorload ($P = 0.03$) at the time of CRS-HIPEC but not with completeness of macroscopic cytoreduction.
Median OS was 44 (95% confidence interval (CI): 30−58) months for node-negative patients and 28 (95% CI: 25−31) months for node-positive patients. 5-year OS rates differed significantly between node-negative and node-positive patients (41% versus 24%; $P = 0.001$). Median DFS was 20 (95% CI: 14−26) months for node-negatives and 14 (95% CI: 12−16) months for node-positives. 5-year DFS rates also differed significantly between node-negative and node-positive patients (26% versus 13%; $P = 0.003$). In multivariate analysis, lymph node positivity was shown to be an independent predictor of decreased OS (HR 1.5; 95% CI: 1.0−2.0; $P = 0.03$) and decreased DFS (HR 1.5; 95% CI: 1.1−2.0; $P = 0.01$).
Patterns of recurrence after CRS-HIPEC did not differ significantly between node-negatives and node-positives, with intraperitoneal recurrences occurring in 55% and 53%, respectively ($P > 0.05$).
Conclusion: This study shows that survival of patients with colorectal peritoneal carcinomatosis following CRS-HIPEC is significantly and independently determined by the nodal status of the primary tumour. Moreover, in patients with peritoneal carcinomatosis lymph node positivity does not lead to an increased tendency to develop systemic recurrences (as is the case in primary colorectal carcinoma); this would suggest that the biological behaviour of peritoneal metastases is significantly different from primary colorectal cancer.
No conflict of interest.

Table (abstract 2165).

Barrier	Solution
Mutation analysis and genetic counselling is not feasible in all colorectal cancer patients	Select patients based on IHC
Using IHC, most identified cases are sporadic and caused by methylation of *MLH1*	Perform *MLH1* promoter methylation analysis
Molecular screening does not identify mutations with retained protein expression, hereditary *MLH1* methylation or other hereditary syndromes	Molecular screening is a supplement to family history
Several Lynch Syndrome patients do not have a significant family history or are older than 50 years	
− Screening strategy has to be simple	Screen all patients independently of age or other criteria
Primary tumor is often not resected or not representative – stage IV – preoperative radiotherapy and/or chemotherapy	Encourage IHC on biopsies
Screening result should be ready along with the final diagnosis and staging	– Close collaboration between pathology and genetic laboratory – Fast methylation analysis
Interpretation of IHC and methylation is a specialist task	The pathologist should be the driving force and should interpret and report the results to the clinicians
In daily clinic deviations and exceptions from standard care are common	Develop guidelines, establish databases, perform quality control, and give feed-back

2165 POSTER DISCUSSION

Barriers to population based screening for Lynch Syndrome in colorectal cancer and how to overcome them

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Background: Lynch Syndrome is caused by germline mutation in the mismatch repair genes *MLH1*, *PMS2*, *MSH2*, or *MSH6*. Patients with Lynch Syndrome and their families must receive genetic counselling in order to identify all relatives at risk and to undergo surveillance for new cancers. We have established a true population based molecular screening for Lynch Syndrome in colorectal cancer patients and present here the challenges that must be met should the screening be efficient in daily clinic.
Materials and Methods: Patients diagnosed with colorectal cancer in a geographically defined area of 1,200,000 inhabitants were included during two years. Immunohistochemistry (IHC) was performed for pMLH1, pPMS2, pMSH2, and pMSH6 followed by *MLH1* promoter methylation analysis in cases with loss of pMLH1. Genetic counselling was indicated if any of the mismatch repair proteins were not expressed, but not if pMLH1 negative cases had *MHL1* methylation. Reminders were sent every 3−6 months if data was not reported to the national pathology database. 2,120 patients have been included and data is now available for 1932. Screening was positive in 54 patients.
Results: See the table.
Conclusion: Population based screening for possible Lynch Syndrome was positive in 54 of 1932 patients (2.8%). During the study, important barriers were identified and we suggest solutions that proved to work in daily clinic.
No conflict of interest.

2166 POSTER DISCUSSION

Updated results including quality of life of the phase III CAIRO3 study of the Dutch Colorectal Cancer Group (DCCG): Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC)

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Background: The optimal duration of chemotherapy and bevacizumab in mCRC is not well established. The CAIRO3 study investigated the efficacy of maintenance treatment with capecitabine plus bevacizumab versus observation in mCRC patients (pts) not progressing during induction treatment with capecitabine, oxaliplatin and bevacizumab (CAPOX-B).
Material and Methods: Previously untreated mCRC pts, PS 0−1, with stable disease or better after 6 cycles of CAPOX-B, not eligible for metastasectomy and eligible for future treatment with oxaliplatin, were randomized between observation (arm A) or maintenance treatment with capecitabine 625 mg/m^2 bid daily continuously and bevacizumab 7.5 mg/kg iv q 3 weeks (arm B). Upon first progression (PFS1), pts in both arms were treated with CAPOX-B until second progression (PFS2, primary endpoint). For pts not able to receive CAPOX-B upon PFS1, PFS2 was considered equal to PFS1. Secondary endpoints were overall survival (OS) and time to second progression (TTP2), which was defined as the time to progression or death on any treatment following PFS1. All endpoints were calculated from the time of randomization. This trial is registered with ClinicalTrials.gov with the number NCT00442637.
Results: A total of 558 pts were randomized. Median follow-up is 39 months. The median number of maintenance cycles in arm B was 9 (range 1−54). The median PFS1 in arm A vs B was 4.1 vs 8.5 months (HR 0.44, 95% CI 0.37–0.53, $p < 0.0001$). Upon PFS1, 75% of pts received CAPOX-B in arm A and 47% in arm B. The median PFS2 was 10.5 vs 11.5 months (HR 0.81, 95% CI 0.67–0.98, $p = 0.03$). The median TTP2 and OS in arm A vs B were 14.1 vs 18.7 months (HR 0.67, 95% CI 0.56–0.82, $p < 0.0001$), and 18.0 vs 21.7 months (HR 0.87, 95% CI 0.71–1.06, $p = 0.16$), respectively. The overall quality of life (QoL) was not significantly different between the 2 treatment arms.
Conclusions: Maintenance treatment with capecitabine plus bevacizumab after 6 cycles CAPOX-B significantly prolonged PFS2. The small absolute difference in PFS2 may be due to the low percentage of pts in arm B that received CAPOX-B following PFS1. Maintenance treatment also significantly prolonged PFS1 and TTP2. The observed benefit in median OS was not statistically significant. Our data support the use of maintenance treatment with chemotherapy plus bevacizumab until progression or unacceptable toxicity. Subset analyses will be presented.
No conflict of interest.

2167 POSTER DISCUSSION

The SOFT study: A randomized phase III trial of S-1/oxaliplatin (SOX) plus bevacizumab versus 5-FU/l-LV/oxaliplatin (mFOLFOX6) plus bevacizmab in patients with metastatic colorectal cancer [SOFT Study Group]

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Background: Several studies of oxaliplatin plus S-1 combination therapy (SOX) conducted in Asia have shown promising efficacy and safety for metastatic colorectal cancer (mCRC), suggesting the potential to replace mFOLFOX6. The SOFT study (JapicCTI-090699) is a randomized

phase III trial designed to evaluate non-inferiority of SOX plus bevacizmab (SOX+Bev) to mFOLFOX6 plus bevacizmab (mFOLFOX6+Bev) for patients (pts) with mCRC.
Methods: Chemotherapy-naive pts with mCRC, an ECOG PS of 0−1, and adequate organ functions were randomly assigned to receive either mFOLFOX6+Bev (5 mg/kg of bevacizumab, followed by 200 mg/m^2 of *l*-leucovorin given simultaneously with 85 mg/m^2 of oxaliplatin, followed by a 400 mg/m^2 bolus of 5-FU on day 1 and then 2,400 mg/m^2 of 5-FU over 46 h, every 2 weeks) or SOX+Bev (7.5 mg/kg of bevacizumab, 130 mg/m^2 of oxaliplatin on day 1, and 40−60 mg of S-1 twice daily for 2 weeks, followed by a 1-week rest). The primary endpoint was PFS. A sample size of 225 pts per group was estimated to be necessary based on a median PFS of 10.0 months in each group and an 80% power to demonstrate non-inferiority of SOX+Bev with a 2.5-month margin (hazard ratio, HR = 1.33) and a 2-sided alpha of 0.05.
Results: A total of 512 pts were enrolled from February 2009 to March 2011. Data were analyzed after confirming >388 events as planned. Demographic factors were well balanced. The median PFS was 11.5 months (95% CI: 10.7–13.2) for mFOLFOX6+Bev and 11.7 months (95% CI: 10.7–12.9) for SOX+Bev. The adjusted HR for PFS was 1.043 (95% CI: 0.860–1.266), and the p value for non-inferiority was 0.0139. RR was 62.7% for mFOLFOX6+Bev and 61.5% for SOX+Bev. A waterfall plot analysis to investigate tumor shrinkage of target lesions disclosed that the response rates of target lesions at 8 weeks and 16 weeks and the maximum tumor response rate were 42.9%, 63.5% and 71.7% for mFOLFOX6+Bev and 40.3%, 58.8% and 72.3% for SOX+Bev, respectively. Grade >3 adverse events (%) with mFOLFOX6+Bev/SOX+Bev were leukopenia (8.4/2.4), neutropenia (33.7/8.8), anorexia (1.2/5.2) and diarrhea (2.8/9.2).
Conclusions: Consistent with the primary and secondary endpoints, the findings of a waterfall plot analysis support our conclusion that SOX+Bev was evaluated to be non-inferior to mFOLFOX6+Bev and could be one of the 1st line chemotherapies for mCRC pts.
Conflict of interest: *Advisory board: Taiho Pharmaceutical,Chugai Pharmaceutical,Yakult Honsha. Corporate-sponsored research: Taiho Pharmaceutical*

2168 POSTER DISCUSSION

Updated survival analysis of EXPERT-C, a randomized phase II trial of neoadjuvant capecitabine and oxaliplatin (CAPOX) and chemoradiotherapy (CRT) with or without cetuximab in MRI-defined high risk rectal cancer patients

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Background: EXPERT-C was a multicentre, randomised phase II trial of neoadjuvant CAPOX and CRT ± cetuximab in patients with MRI defined high-risk rectal cancer patients. We have shown previously that the addition of cetuximab did not result in a significant improvement in complete response (CR) and progression-free survival (PFS). However, in the initial analysis, a statistically significant overall survival (OS) benefit was observed in the group of KRAS/BRAF wild type (WT) patients. Here, we report the survival outcomes with extended follow-up.
Material and Methods: Between October 2005 and July 2008, 164 eligible patients were randomly assigned to 4 cycles of CAPOX followed by capecitabine CRT, surgery, and 4 cycles of adjuvant CAPOX (n = 81) or the same regimen plus weekly cetuximab (CAPOX-C, n = 83). The primary endpoint was CR in KRAS/BRAF WT patients (n = 90). PFS and OS in KRAS/BRAF WT and overall populations were secondary endpoints and estimated by using the Kaplan–Meier method.
Results: After a median follow-up of 63.1 months (95% CI: 61.0–65.3) 52 events were observed, 28 in the CAPOX arm and 24 in the CAPOX-C arm. In the KRAS/BRAF WT group, the 5-year PFS rates were 67.8% (95% CI: 53.9–81.7) and 80.0% (95% CI: 68.2–91.8) for CAPOX and CAPOX-C, respectively (p = 0.21). No difference in local and distant relapse rates between the two arms was found. The 5-year OS rates were 72.3% (95% CI: 59.0–85.6) and 84.3% (95% CI: 73.5–95.1) (p = 0.20). In the entire population, the 5-year PFS rates were 64.8% (95% CI: 54.2–75.4) and 72.0% (95% CI: 62.2–81.8) for CAPOX and CAPOX-C, respectively (p = 0.36). The 5-year OS rates were 68.5% (95% CI: 58.3–78.7) and 77.8% (95% CI: 68.8–86.8) (p = 0.13). Irrespective of the treatment received, pathologic CR (pCR) was associated with a significant improvement in relapse-free survival (92.6% vs 73.7%, p = 0.04) and OS (96.3% vs 77.3%, p = 0.02).
Conclusions: Neoadjuvant chemotherapy before standard CRT was associated with promising long-term outcomes in high-risk rectal cancer patients. Based on the absence of improvement in any of the study endpoints, cetuximab did not appear to be the optimal companion targeted agent to further increase the efficacy of this strategy. pCR was demonstrated to be a reliable surrogate end point for rectal cancer trials even in the context of intensified pre-operative regimens including induction chemotherapy.
Conflict of interest: *Ownership: None. Advisory board: David Cunningham, Roche (C), Roche (U), Merck (C), Sanofi-aventis (C). Josep Tabernero, Amgen (C), Roche (C), Sanofi-aventis (C), Merck (C). Andres Cervantes, Merck Serono (C). Ian Chau, Merck Serono (U), Roche (C), Sanofi-aventis (C). Other substantive relationships: Research funding: David Cunningham, Merck, Amgen. Ian Chau, Merck, Roche. Expert Testimony: David Cunningham, Amgen. Honoraria: David Cunningham, Roche, Merck,Sanofi-aventis. Andres Cervantes, Merck Serono, Roche Ian Chau, Roche, Sanofi-aventis*

2169 POSTER DISCUSSION

Feasibility results from a multi institutional randomized phase II study for patients with rectal cancer at risks for systemic disease: The KIR study

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Background: Patients (pts) with rectal cancer at high risks for metastases are well identified at presentation with magnetic resonance imaging (MRI) using circumferential radial margins (CRM), features of extra mural venous invasion (EMVI) or qualitative nodal morphological changes (N+). In North America, the standard of care for locally advanced rectal cancer is neoadjuvant chemo-radiation therapy (CRT) prior to total mesorectal surgery (TME) followed by adjuvant chemotherapy(CT). This results in a median time of 4.5−5.5 months from the start of local therapy to the start of systemic treatment. The present study is proposing to evaluate a modified strategy to shorten the local disease treatment time to 2.5−3.5 months to allow for optimization of CT with FOLFOX chemotherapy (CT) given either in neoadjuvant or adjuvant setting.
Material and Methods: The primary endpoint is patient compliance to CT. Based on a reported compliance rate to adjuvant CT of 60 % after neoadjuvant radiation, a sample size of 180 pts was determined to allow the detection of an 85% compliance rate using one-sided binomial test and a significance level of 5% with a power of 90%. The pts were randomized using a 2:1 ratio. Image guided high dose rate endorectal brachytherapy (HDREBT) was used to deliver 26 Gy in 4 fractions either after 6 cycles of FOLFOX CT (arm A) and before TME or upfront to TME and 12 cycles of adjuvant FOLFOX (arm B).
Results: From 2010–2012, 70 out of the planned 180 pts were recruited with 47 pts treated in arm A and 23 pts in arm B. All pts underwent TME as planned. In arm A, MRI was repeated after CT in 37/41 pts that completed their treatment. The radiological rate of complete response, excellent response (>50%), partial response (⩽50%), minimal to no response and tumor progression were respectively: 8.1%, 37.8%, 27.3%, 13.5%, and13.5%. HDREBT was feasible in all pts but one pt. decided to have external beam RT. There was no significant difference in the rate of post-operative complications between the two arms and the preliminary results showed CT compliance rate of 94% for arm A compared to 50% in arm B.
Conclusion: The safety of this study design is confirmed and the study is now being activated across the province. This is also the first multi-institutional study using HDREBT as a neoadjuvant RT modality for rectal cancer, which confirms the feasibility and applicability of HDREBT in multi-centric trial.
Conflict of interest: *Ownership: Jewish General Hospital, McGill University. Advisory board: Institutional Review Board. Board of directors: Lady Davis Institute. Corporate-sponsored research: This study is supported by a Sanofi research grant*

2170 POSTER DISCUSSION

A comparison of the outcome of rectal cancer patients treated with high dose rate endorectal brachytherapy, short-course radiotherapy, or chemoradiation

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Background: Short course external beam radiotherapy decreases local recurrences in patients with rectal cancer. However, improvements should be weighed against treatment-related morbidity since there might be other preoperative options with fewer side effects, for example high dose rate endorectal brachytherapy (HDREBT). The current study compared overall survival, local recurrence and cancer specific mortality in rectal cancer patients treated with either preoperative short course radiotherapy or chemoradiotherapy (CRT) in The Netherlands and HDREBT in Canada.
Material and Methods: In total, 134 Dutch T3 rectal cancer patients treated with either preoperative 5x5 Gy radiotherapy (n = 52) or CRT (n = 82), and 141 T3 rectal cancer patients from Canada treated with preoperative HDREBT (26 Gy over 4 days) were included. Cox proportional hazard models were used to estimate hazard ratios along with 95% confidence intervals (CIs) adjusted for potential confounders. Primary endpoint was overall survival, secondary endpoints were local recurrence, regardless the status of systemic disease and cancer specific mortality.
Results: No differences in local recurrence and cancer specific mortality at five years were found between The Netherlands and Canada (5/134 versus 2/141, and 6/134 versus 4/141, respectively). A statistically significant reduction in the 5-year overall survival was observed with patients from Canada, compared to patients from The Netherlands, after adjustment for potential confounders (HR 0.42, 95% CIs 0.20–0.90, p = 0.03).
Conclusions: In the current study, no significant differences in local recurrence and cancer specific mortality were observed. Overall survival, on the other hand, was superior in Canada, possibly due to lower treatment-related toxicities. A previous study has shown that postoperative complications did not vary between short course radiotherapy and HDREBT. These findings could have profound clinical implications and should therefore be formally tested in a randomized controlled trial.
No conflict of interest.

2171 POSTER DISCUSSION

Stereotactic radiotherapy for oligometastatic cancer: a predictive model for survival

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Background: Stereotactic body radiotherapy (SBRT) is a safe and locally effective treatment for patients with inoperable oligometastases. The challenge remains identifying subsets of patients that benefit in terms of overall survival (OS).
Methods: Between 2005 and 2011, 309 patients with $\leqslant$5 metastases were treated by SBRT (n = 209) and/or by intracranial stereotactic radiosurgery (n = 107). We analyzed OS and performed a risk factor analysis.
Results: The median survival of all patients was 24 months. The 3-year, 4-year and 5-year OS rates were 32%, 25% and 19% respectively. The following 4 risk factors were independently associated with impaired OS: non-adenocarcinoma histology (p < 0.01), intra-cranial metastases (p < 0.01), synchronous metastatic disease (p < 0.01) and male gender (p = 0.02). Patients with 0, 1 and 2 risk factors displayed a median survival (95% CI) of 40 (24−63), 29 (23−35) and 23 (16−29) months respectively and are defined as patients with good prognosis. Patients with 3 and 4 risk factors had a median survival of 9 (6−11) and 4(1−7) months only and are defined as bad prognostic patients.
Conclusions: We identified subsets of oligometastatic cancer patients with good prognosis after stereotactic radiotherapy. These patients are candidates for inclusion in prospective randomized trials for defining the role of SBRT in the management of oligometastases.
No conflict of interest.

2172 POSTER DISCUSSION

Urinary dysfunction after mesorectal excision with and without lateral lymph node dissection for clinical stage II or stage III lower rectal cancer (JCOG0212)

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Background: Postoperative urinary dysfunction is recognized as a major complication of rectal cancer surgery. A randomized controlled trial was performed at 33 major hospitals in Japan to confirm the non-inferiority of mesorectal excision (ME) in relapse-free survival compared to ME with lateral lymph node dissection (LLND) (JCOG0212). The primary analysis is planned for 2015. Urinary dysfunction after surgery was investigated as secondary endpoint in this study.
Methods: Eligibility criteria included histologically proven rectal cancer of clinical stage II/III, with the main lesion located in the rectum with the lower margin below the peritoneal reflex, no lateral pelvic lymph node enlargement, PS of 0 or 1, patient age 20−75 years, and no past history of chemotherapy, pelvic surgery or radiation. After surgeons had confirmed R0 resection by ME, patients were randomized intraoperatively to ME alone or ME with LLND. Pelvic autonomic nerves were preserved as much as possible in both arms. The residual urine volume was measured 3 times as a general rule during postoperative 10−14 days in this protocol. Urinary dysfunction was defined that there was residual urine of 50 ml or more even once. Missing measurements of urine volume were counted as dysfunction. Risk factors, including LLND, demographics, tumor location, type of surgery, operative time and blood loss, were investigated by univariable and multivariable analysis.
Results: Urinary dysfunction in the ME alone group and the ME with LLND group were observed in 57.7% (202/350 pts; 95% CI, 52.4–63.0%; 76 pts with missing data) and 59.0% (207/351 pts; 95% CI, 53.6–64.2%; 74 pts with missing data), respectively (P = 0.76). In the univaliable analysis, tumor center located below the peritoneal reflection (P = 0.01) and blood loss $\geqslant$500 mL (P = 0.004) were increased risk of urinary dysfunction. In multivariable regression analysis, only blood loss remained associated with urinary dysfunction (relative risk 1.25, P = 0.04).
Conclusion: The ME alone did not show significant decrease of urinary dysfunction. Urinary dysfunction was associated with tumor location and blood loss.
No conflict of interest.

2173 POSTER DISCUSSION

Sexual dysfunction after rectal cancer surgery − the results from a prospective randomized trial comparing mesorectal excision with and without lateral lymph node dissection for clinical stage II or stage III lower rectal cancer: Japan Clinical Oncology Group Study JCOG0212

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Background: Sexual dysfunction is one of potential complications of rectal cancer surgery. Generally, the proportion of the sexual dysfunction after mesorectal excision (ME) with lateral lymph node dissection (LLND) is deemed higher than ME alone. A randomized controlled trial was performed at 33 major hospitals in Japan to confirm the non-inferiority of ME in relapse-free survival compared to ME with LLND (JCOG0212). General postoperative complications were reported previously (Fujita et al., Lancet Oncol 2012). The primary analysis is planned for 2015. Sexual dysfunction after surgery was investigated as a secondary endpoint in this study.
Material and Methods: Patients (Pts) with clinical stage II/III lower rectal cancer were randomized intra-operatively to ME alone or ME with LLND both preserving all autonomic nerves. Questions on sexual function

were asked for men before surgery and 1 year after surgery, using the Japanese version of the abridged five-item version of the International Index of Erectile Function (IIEF-5). Sexual dysfunction was defined as IIEF-5 score of 21 or less, because no ED score is defined as 22−25 in IIEF-5. Proportion of sexual dysfunction was defined as pts having sexual dysfunction after surgery among no ED pts before surgery. Pts, whose sexual function was not evaluated postoperatively because of their death or other reasons, were included in the numerator of sexual dysfunction. For no ED or mild ED (IIEF-5 score: 17−21) pts before surgery, we analyzed the impact of LLND, age, tumor location, surgery type, operative time and blood loss on erectile function by IIEF-5 score difference between pre- and post-surgery.

Results: A total of 701 pts were randomized and 472 male pts were included in the present analysis. Among them, preoperative questionnaire were collected in 413 pts (87.5%). Both preoperative and postoperative questionnaires were collected in 343 patients (72.7%). Proportion of sexual dysfunction in the ME with LLND group and the ME alone group were observed in 79.3% (23/29; 95% CI, 60.3–92.0%; 5 pts were not evaluated after surgery) and 68.0% (17/25; 95% CI, 46.5–85.1%; 4 pts were not evaluated after surgery), respectively (P = 0.37). Postoperative score was decreased compared to preoperative score in both ME with LLND group (median (range); pre, 20 (17−25) vs. post, 13 (1−25); *P* <0.0001) and ME alone group (pre, 20 (17−25) vs. post, 16 (1−25); *P* <0.0001). Score difference was not statistically higher in ME with LLND group than in ME alone group (P = 0.10). In score difference, only age 56 or older was a risk factor for sexual dysfunction after surgery in multivariate analysis (P = 0.024).

Conclusion: LLND did not increase sexual dysfunction after rectal cancer surgery. Sexual dysfunction was associated with age.

No conflict of interest.

Poster Discussion Session (Mon, 30 Sep) and Poster Session (Sun, 29 Sep)
Gastrointestinal Malignancies − Colorectal Cancer II

2174 POSTER DISCUSSION

Bowel function 14 years after sphincter-preserving total mesorectal excision for rectal cancer: Report of a multicentre randomised trial

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Background: Bowel dysfunction is an important adverse outcome of sphincter-preserving surgery for rectal cancer, and the accuracy of its assessment is determined by the evaluation instrument and setting. Consequently, we investigated very long-term bowel function after sphincter-preserving treatment for rectal cancer using a standardised scoring system, and examined the association of bowel dysfunction with health-related quality of life (HRQL), in the setting of a randomised trial.

Material and Methods: In the TME trial (1996–1999), 1530 Dutch patients with resectable rectal cancer received total mesorectal excision (TME) and were randomly assigned to 5x5 Gy preoperative short-course radiotherapy (PRT). In 2012, a questionnaire was sent to all surviving non-stoma patients (n = 297), comprising the Low Anterior Resection Syndrome Score (LARS score), the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30) and Colorectal Module (EORTC QLQ-CR29). The LARS score has been validated extensively, and the score range is split into 'No LARS', 'Minor LARS', and 'Major LARS' categories in ascending severity of bowel dysfunction. Potential risk factors for Major LARS were tested by logistic regression. HRQL was compared between LARS score categories. To correct for multiple testing, statistical significance was set at p < 0.01. Ethics approval was obtained and patients gave informed consent.

Results: A response rate of 81% was achieved, with 242 patients participating (49% PRT+TME, 51% TME, patient characteristics comparable). The median time since treatment was 14.6 years (range 12.6–16.6) and the median age at follow-up was 75 years (range 39−95). Nearly half (46%) of all patients experienced Major LARS. PRT (odds ratio 2.6) and age ⩽75 at follow-up (odds ratio 2.3) increased the risk of Major LARS. In contrast, gender, distance of tumour from anal verge, time since treatment, and comorbid diabetes did not alter the risk of Major LARS. Patients with Major LARS were worse off in most of the HRQL domains measured by the EORTC QLQ-C30 and the EORTC QLQ-CR29.

Table: Selected HRQL results

	Mean score Major LARS	Mean score Minor/No LARS	p
Global health status*	73.4	80.3	<0.01
Role functioning*	79.0	85.5	<0.01
Emotional functioning*	81.8	87.5	<0.01
Cognitive functioning*	80.9	87.7	<0.01
Social functioning*	83.3	91.2	<0.01
Fatigue†	27.0	18.6	<0.01
Constipation†	20.8	12.1	<0.01
Diarrhoea†	24.8	4.6	<0.01
Stool frequency†	34.1	13.8	<0.01
Flatulence†	46.3	23.2	<0.01
Faecal incontinence†	27.5	7.6	<0.01

*Higher score = better HRQL; †Higher score = worse HRQL.

Conclusions: A substantial proportion of patients endure severe long-term bowel dysfunction after sphincter-preserving TME. Although surgery is probably the main contributing factor to Major LARS, PRT and age ⩽75 pose additional risks. Major LARS is associated with reduced HRQL. Patients should be well informed of these late complications prior to treatment.

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No conflict of interest.

2175 POSTER DISCUSSION

Two-stage hepatectomy for non resectable colorectal cancer liver metastases: Results of the first prospective multicenter study

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Background: Two-stage hepatectomy (TSH) may achieve long-term survival in selected patients whose liver metastases cannot be removed in a single procedure. There are encouraging preliminary results from retrospective, single-center studies, but this approach has not previously been prospectively assessed in a multicenter trial.

Material and Methods: In the SEPRA-C2T study (clinicaltrial.gov NCT01262417) undertaken between July 2008 and March 2010, a prospective cohort of patients with non resectable colorectal liver metastases (CRCm) who were candidates for TSH were enrolled from 8 French centers. Data were obtained on preoperative treatment, the nature of the first and second hepatectomies, and short and long term outcome.

Results: 54 patients, aged 60±9 years, had an initial hepatectomy. 93% of non resectable CRCm were synchronous (number 6.2±4, maximum diameter 5.4±2.8 cm). All patients had had induction chemotherapy (9±4 cycles). First hepatectomy was mostly minor and associated with ablation in 46% of patients and primary tumor resection in 57%. 56% of patients had portal vein embolization. There were no deaths. 44% of patients had at least 1 postoperative complication, severe in 11% (bilioma requiring percutaneous radiological drainage in 4 patients and intensive care unit hospitalization in 2 patients − after reoperation for a colorectal anastomosis fistula in 1 case and after cardiac failure in the other). Median hospital stay after first hepatectomy was 13 days (4−64). 41 patients (76%) had the second hepatectomy after a median interval of 2.5 months (0.9−9) and 2 cycles of chemotherapy (1−13). The second hepatectomy was a major resection in 76% of patients. There were no postoperative deaths. 32% of patients had at least one complication, severe in 10%. 2 biliomas required percutaneous drainage and there were 2 reoperations, for a postoperative occlusion and an intra-abdominal abscess. Median hospital stay was 10 days (5−28). At median follow-up of 45 months, 4 year overall survival is 62% and 4 year progression free survival 17% (intent to treat analysis).

Conclusions: This is the first prospective, multicenter study to confirm the feasibility of TSH in patients with initially non-resectable CRCm. It provides encouraging evidence of long term survival.
This trial was funded by the French NCI (under PHRC grant 2007-A00987−46).
No conflict of interest.

2176 POSTER DISCUSSION

Anastomotic leakage following low anterior resection in the Netherlands: Analyses from the Dutch Surgical Colorectal Audit (DSCA)

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Background: Anastomotic leakage (AL) is a severe complication following a low anterior resection (LAR) for rectal cancer. In the current study we analyzed the incidence of AL and its mortality following a LAR, using data from the Dutch Surgical Colorectal Audit (DSCA). Finally, we tried to indentify risk factors for AL.
Methods: All patients in the Netherlands who underwent a LAR with the construction of a primary anastomosis between January 2009 and January 2013, registered in the DSCA, were included in this study. Univariate and multivariate analyses were performed to indentify the risk factors of 'mild' AL (not requiring surgical intervention) and 'severe' AL (requiring surgical intervention).
Results: A total of 4170 patients underwent a LAR with a primary anastomosis. In 409 cases (9.8%) AL was reported of whom 256 (62.6%) had 'severe' AL. The overall 30-day mortality rate was 1.5% (n = 64). In 20 patients (5% of those with AL) AL was the cause of death in 14 patients suffering from 'severe' AL compared to 6 suffering from 'mild' AL ($p < 0.001$). Multivariate analysis showed that patients in whom a diverting ileostoma was constructed (n = 2752) had a decreased risk of developing 'severe' AL (OR=0.26; CI 0.20–0.35) while more 'mild' AL was observed in this group (OR=1.69; CI 1.06–2.68). A laparoscopic procedure showed significantly less 'mild' AL (OR=0.66; CI 0.46–0.94) and a trend towards less 'severe' AL (OR = 0.85; CI 0.65–1.11). Male gender was a risk factor for developing 'severe' AL (OR=1.71; CI 1.27–2.30) and patients who received neo-adjuvant radiotherapy or chemo-radiation showed a higher risk of developing 'mild' AL (OR = 2.60; CI 1.22–5.52 and OR = 2.38; CI 1.08–5.24). Patients who had an anastomosis constructed less than 7 cm from the anal ring developed significantly more 'severe' AL (OR = 1.84; CI 1.34–2.51).
Conclusion: The data from the DSCA show that AL following a LAR occurs in 9.8% of the patients. In the majority of cases AL is 'severe', requiring surgical intervention. The mortality rate of AL is 5%. The increased risk to develop 'mild' AL after the construction of a diverting ileostoma is most likely caused by patient selection in a way that those prone to develop AL receive an ileostoma, decreasing the risk of a 'severe' AL. Patients selected for laparoscopic surgery have a lower chance to develop AL while male gender, neo-adjuvant therapies and a distal anastomosis increase this risk.
No conflict of interest.

2177 POSTER DISCUSSION

Failure-to-rescue after colorectal cancer surgery and the association with three structural hospital factors

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Objective: To evaluate the association between structural hospital characteristics and failure-to-rescue after colorectal cancer surgery.
Background: There is a growing body of evidence suggesting a large hospital variation concerning mortality rates in patients with a severe complication (failure-to-rescue) in colorectal cancer surgery. Which structural hospital factors are associated with better failure-to-rescue rates remains largely unclear.
Methods: All patients undergoing colorectal cancer surgery and registered in the Dutch Surgical Colorectal Audit (DSCA) from 2009 through 2011 by 92 Dutch hospitals were analysed. Univariate and multivariate logistic regression models including casemix, hospital volume, teaching status and different levels of ICU facilities were used to analyse risk-adjusted FTR rates.
Results: 25591 patients from 92 hospitals were included. The failure-to-rescue rate ranged between 0 and 39%. In univariate analysis, FTR rates were lower in patients operated in high hospital volume hospitals (13% in hospitals operating >200 patients/year versus 18% in hospitals performing $\leqslant$200 colorectal resections/year), teaching status (12% in academic hospitals, versus 17% in teaching hospitals and 21% in non-teaching hospitals) and high level of ICU facilities (16% in highest level 3 versus 21% in lowest level 1 ICU hospitals). Only the higher levels of ICU facilities (2 or 3 compared to level 1) were independently associated with lower failure-to-rescue rates (OR 0.72 (95% CI 0.65–0.88) in multivariate analysis.
Discussion: Hospital type and annual hospital volume were not independently associated with failure-to-rescue rates in colorectal cancer surgery. Instead, the lowest level of ICU facilities was independently associated with higher rates. This suggests that a more advanced ICU may be an important factor that contributes to better failure-to-rescue rates, although individual hospitals perform well with lower ICU levels.
No conflict of interest.

2178 POSTER DISCUSSION

Chemotherapy plus cetuximab as conversion therapy for patients with initially unresectable colorectal cancer liver metastases

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Background: ~85% of patients (pts) with metastatic colorectal cancer (mCRC) present with liver disease that is initially unresectable. First-line chemotherapy (CT) can render such lesions resectable in certain pts, providing the best chance of long-term survival and in some cases even cure. The aim of this review was to evaluate the data from published studies in mCRC to assess whether addition of cetuximab to first-line CT increased the conversion rate of *KRAS* wild-type (wt), liver-limited metastatic disease from initially unresectable to resectable.
Material and Methods: Electronic searches of literature databases were carried out to identify publications describing resection rates for pts with *KRAS* wt mCRC receiving CT ± cetuximab. Results were checked for relevance regarding the inclusion of data related to liver-limited disease (LLD).
Results: Excluding reviews and case reports, 17 publications were identified that described the results of 14 different studies or observational cohorts. Of these, four randomized controlled trials reported resection rates for LLD in pts with *KRAS* wt mCRC in CT + cetuximab compared with CT alone treatment groups (Table). In three of these trials, R0 resection rates were markedly higher in the CT + cetuximab group for pts with *KRAS* wt tumors. In the fourth study (COIN), resection rates were similar between treatment groups, although data were not reported for oral and infusional fluoropyrimidine subgroups. Only one trial, carried out in Chinese pts, was specifically designed to assess the rate of resectability of *KRAS* wt synchronous LLD. In this, the R0 resection rate in the CT + cetuximab group was significantly higher than in the CT alone group (25.7% vs 7.4%; $p = 0.004$). PFS and OS were also longer in pts in the CT + cetuximab group (HR 0.60, $p = 0.004$ and HR 0.54, $p = 0.013$, respectively).
Conclusions: Data from randomized trials in mCRC confirm that the addition of cetuximab to first-line infusional 5-fluoropyrimidine-based CT regimens improves the rate of R0 resection of initially unresectable *KRAS* wt LLD and prolongs PFS and OS when compared with the corresponding CT regimen alone.
Conflict of interest: *Ownership: Merck KGaA (RE, employment and stock ownership). Advisory board: Merck KGaA, Roche/Genentech, Lilly, Sanofi-Aventis (GF),Merck Serono (CB). Corporate-sponsored research: Merck Serono (EVC, CB), Merck KGaA (GF). Other substantive relationships: Honoraria:Merck KGaA, Roche/Genentech, Lilly, Sanofi-Aventis (GF)*

Parameter	CRYSTAL		OPUS		NCT01564810[a]		COIN	
	FOLFIRI + cetuximab n = 68	FOLFIRI n = 72	FOLFOX4 + cetuximab n = 25	FOLFOX4 n = 23	CT + cetuximab n = 70	CT n = 68	CT + cetuximab n = 87	CT n = 91
Response								
Rate, %	70.6	44.4	76.0	39.1	57.1	29.4		
Odds ratio	3.40		4.57					
p-value	<0.001		0.016		0.001			
Resection								
R0 rate, %	13.2	5.6	16.0	4.3	25.7	7.4	14.9	13.2
Odds ratio	2.58		4.00		4.37			
p-value	0.125		0.21		0.004		0.74	

[a] Chinese study.

2179 POSTER DISCUSSION

ONCO-Predict-II: A deep sequencing test predicting outcome in patients with colorectal cancer of stage II based on mutations signatures in driver genes

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Background: Approximately 20% of patients (pts) with colorectal cancer of stage II will progress within 2−3 years after surgery while 80% of patients are cured by surgical resection. Assignment of patients with colorectal cancer of UICC stage II to adjuvant chemotherapy remains controversial. Pathological parameters (pT4, L+, V+) are poor predictors of the recurrence risk. Several RNA expression signatures (Oncotype Dx Colon Cancer Assay, ColonPrint, Predictor C) have been develeped, but their clinical performance is limited.
Methods: Patients with colorectal cancer of UICC stage II were selected from the observational prospective, multicenter MSKK study. Since 2005 more than 7.200 patients with colorectal cancer of all four UICC stages have been recruited by investigtors of 40 hospitals in Germany. Deep sequencing of 37 well known cancer genes using Illumina technology (MiSeq) was employed using a custom cancer panel of 120 amlicons. Only high quality missense and nonsense mutations were used for further analysis. Boolean Algebra was used to analyse the mutations, to generate truth values for each of the cancer genes and to connect cancer genes with Boolean functions including conjunction (AND), negation of conjunction (NAND), disjunction (OR), negation of disjunction (NOR), equivalence (EQV), exclusive disjunction (XOR), material implication (IMP) negation of material implication (NIMP).
Results: Altogether 173 pts fulfilled all the inclusion criteria, 61 females, 112 males, 87 were younger than 68 yrs, 86 were older, 31 pts had a rectum tumor, 142 a colon tumor. pT3 tumors were diagnosed in 153 pts, and pT4 tumors in 20 pts. L+ was seen in 37 tumors, V+ in 13 tumors. 41 pts received adjuvant therapy. 94 pts were progression free at 3 years, 12 were diagnsoed with local recurrence, 27 with secondary malignancy, and 40 pts were diagnosed with metastatic disease at 3 years. 497 missense and nonsense mutations were identified in approx. 13 driver genes. We then used these missense and nonsense variations in a double nested bootstrap to predict progression of disease events in a prospective fashion and to receive second order unbiased estimates of the performance characteristics.
From missense and nonsense mutations in 13 driver genes we found TP53 to have the largest impact followed by BRAF. The Boolean function !TP53 Eqv !BRAF reads as follows: 'pts who have neither missense or nonsense mutations in TP53 and BRAF, or pts who have missense and nonsense mutations in TP53 and BRAF have the highest likelihood of developing metastatic disease'. !TP53 EQV !BRAF has a sensitivity of 0.74, a specificity of 0.65, a positive predictive value of 0.48, a negative predictive value of 0.86 and an area under the receiver operating curve (AROC) of 0.69. A second signature !TP53 EQv !BRAF OR SMAD4 OR ATM OR KRAS leads to an increase of the sensitivity to 0.89, however on the expense of the specificity of 0.39.
Conclusion: Here we show that the aggregation of somatic mutations in well known cancer genes using Boolean algebra leads to signatures with clinical utility in UICC stage II colorectal cancer that outperform clinical marker. Our signature based on deep sequencing of FFPE tissue is more robust than any of the RNA expression signatures.
Conflict of interest: *Ownership: Signature Diagnostics AG. Other substantive relationships: employment, stock ownership*

2180 POSTER DISCUSSION

Assessing tumor response beyond RECIST criteria: early tumor shrinkage (ETS) and deepness of response (DpR) in phase III TRIBE trial by the GONO group

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Background: TRIBE trial demonstrated that first-line FOLFOXIRI plus bevacizumab (bev) provides a significant improvement in PFS and objective response rate (ORR), compared to FOLFIRI plus bev. Recent experiences evidenced that both the ETS and the DpR may implement the RECIST assessment of tumor response and correlate with survival.
Material and Methods: ETS was defined as the relative change in the sum of the longest diameters of RECIST target lesions at week 8 compared to baseline. A 20% decrease was adopted as cut-off value to discriminate early responders and non responders. DpR was defined as the relative change in the sum of the longest diameters of RECIST target lesions at the nadir in the absence of new lesions or progression of non-target lesions. compared to baseline. The median value was adopted as cut-off.
Results: Out of 508 randomized patients, 443 patients were evaluable for ETS. 142 (64%) out of 221 patients in the FOLFOXIRI plus bev arm achieved early response, compared to 114 (51%) out of 222 patients in the FOLFIRI plus bev arm ($p = 0.006$). A mean ETS of 30.2% was reported in the experimental arm compared to 21.4% in the control arm ($p = 0.0001$). In the global population, early responders achieved significantly longer PFS (median PFS: 12.7 months vs 10 months, HR: 0.66 [0.52–0.80], $p < 0.0001$). A significant correlation of ETS as a continuous variable with PFS was also observed (HR: 0.982 [0.977–0.987], $p < 0.0001$). 484 patients were evaluable for DpR. A mean DpR of 41.1% was reported in the FOLFOXIRI plus bev arm compared to 32.9% in the FOLFIRI plus bev arm ($p = 0.003$). Median time to DpR was 4.3 and 3.9 months in the experimental and control arm, respectively. In the global population, patients achieving a DpR higher than the median value achieved significantly longer PFS (median PFS: 13.1 months vs 9.3 months, HR: 0.61 [0.49–0.73], $p < 0.0001$). A significant correlation of DpR as a continuous variable with PFS was observed (HR: 0.983 [0.979–0.986], $p < 0.0001$).
Conclusions: FOLFOXIRI plus bev allows to achieve a better rate of early response and an higher extent of DpR compared to FOLFIRI plus bev. As previously suggested, both ETS and DpR are significantly related to PFS. Correlations with OS will be presented.
No conflict of interest.

2181 POSTER DISCUSSION

Towards the molecular structure of colorectal liver metastasis: ultra-deep sequencing of matched pairs of resected liver mets and primary tumors in 94 patients with metastatic colorectal cancer

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Background: In colorectal cancer (CRC) metastasis occurs predominantly in the liver. Patients (pts) die from metastasis and not from the primary tumor. While exome sequencing data from more than 200 patients with CRC are in the public domain little is known about the somatic mutation structure of liver metastasis. We attempted ultra-deep sequencing of resected liver metastases and their matched primary CRC tumors in 94 pts with metastatic colorectal cancer in order to identify molecular differences between liver mets and primary tumors.
Materials and Methods: Pts with metastatic CRC ($N = 1400$) originated from our prospective, multicenter MSKK study with 40 hospitals in Germany. We identified 233 pts (16%) with liver mets tissue in our MSKK tumor bank. After pathological review 178 pts had matched pairs of liver mets tissue and primary tumor tissue of sufficient size and quality and were accepted for the study. Macro-dissection was performed for all liver mets and primary tumor tissue. Specimens were only accepted for further

analysis if they had more than 15% tumor content. DNA was isolated and quality controlled for size using a LINE RT-PCR assay. Ultra-deep sequencing was performed on a MiSeq sequencer (Illumina) using a custom panel of 37 driver genes (represented in 120 amplicons) known to be mutated in CRC.
Results: We sequenced liver mets and matched primary tumor tissus of 94 pts with metastatic CRC. Sequence data of both FFPE (liver mets) and fresh frozen tissue (matched primary tumor) was of high quality allowing reliable mutation detection in all 94 matched pairs (188 mets/primary specimens). The average coverage was 5.000fold per base pair. Among the 94 pairs we identified significant differences in the mutation pattern between primary tumor and liver metastasis in 22 pts (22.3%). In 10 pts the liver mets displayed one or several actionable mutations that were not present in the primary tumor. In a further 7 pts, the primary tumor showed actionable mutations which did not exist in the matched liver mets. In three pts we found new actionable mutations in the liver mets but also mutations in the primary tumor which were not found in the mets: case 1: PIK3CA E545K in liver mets, TP53 C275F in primary, case 2: KIT M541L, APC Q1378X, and TP53 R196X in liver mets, TP53 R175H in primary, case 3: SMAD4 S343L and APC P1453L in liver mets, KRAS G12A in primary. In one case with two liver mets we found differences between the two mets and the primary specimen (mets 2: KRAS G13D und TP53 R175H; mets 1: KRAS G13D and TP53 E286K; primary tumor: KRAS G13D and TP53 E286K.
Conclusion: Deep sequencing of 36 driver genes revealed significant differences in the somatic mutation pattern in 22% of patients with liver mets and matched primary tumors. For these patients knowledge of the additional mutations in the liver mets might change the therapy. In the majority of cases other molecular features like copy number variations or mutations outside the known colorectal cancer driver genes might be responsible for altered signaling in liver mets with respect to their parent tumors.
Conflict of interest: *Ownership: Signature Diagnostics AG. Other substantive relationships: employment, ownership of stock.*

2182 POSTER DISCUSSION

Somatic variations in onco-genes relate to time-to-progression and survival in patients with colorectal cancer UICC stage III undergoing standard-chemotherapy

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Background: In colorectal cancer UICC-stage III current guidelines recommend chemotherapy for all patients (pts). Yet, many factors like co-morbidity, clinical performance, age, patient and family preferences influence decision making regarding chemotherapy. We investigated whether somatic variations in well-known onco-genes in the tumor might relate to time-to-progression (TTP) and overall survival (OS).
Materials and Methods: From the multi-center, prospective, diagnostic study 'Molecular Signatures in Colorectal Cancer' we selected pts using the inclusion criteria: 1) clinical UICC stage III, 2) no neo-adjuvant therapy, 3) R0 resection, 4) chemotherapy with either 5-Fluoruracil(5-FU) (5-FU+/− Leucovorin or Capecitabine) or 5-FU plus Oxaliplatin, 5) minimum observation time 2 years since diagnosis, 6) tumor specimen (fresh-frozen or FFPE) passing pathological quality control available, 7) new generation sequencing using Illumina technology (37 genes, 120 amplicons, average coverage per base >2000) of extracted DNA successful. We then used missense and nonsense variations in a double nested bootstrap to predict progression of disease events in a prospective fashion and to receive second order unbiased estimates of the performance characteristics. Lastly, we checked whether these predictions hold retrospectively within prognostic subgroups using survival analysis, in particular the log-rank test.
Results: Altogether 218 pts (111 female, 107 male), median age of 67 years (range 26−86 years) fulfilled all inclusion criteria. Baseline and tumor characteristics were typical for UICC stage III patients; 95 pts received 5-FU-based therapy and 123 FOLFOX/CAPOX therapy. Only 6 pts with rectum tumors received FOLFOX/CAPOX. The genes with 5 or more missense/nonsense variations were [gene symbol (Count)]: TP53 (158), APC (91), KRAS (88), KDR (74), PIK3CA (36), KIT (30), BRAF (26), SMAD4 (23), FBXW7 (21), MET (19), ATM (14), NRAS (8), JAK3 (7), and PTEN (5). A prediction scheme based on SMAD4, FBXW7, JAK3, APC, ATM, and BRAF missense variations achieves significant progression-free and overall survival discrimination in all clinical subgroups. Log-rank test p-values for overall survival time difference were: colon (0.00221), rectum (0.02156), UICC stage IIIB (0.00094), UICC stage IIIC (0.01192), N1 (0.00306), N2 (0.04424).
Conclusions: Our results show that UICC-stage III patients can be stratified into those likely to progress and those at low risk for progression of disease event. Since these data were generated in a multi-center prospective study recruiting more than 7000 patients, we expect that the results will be generalizable.
Conflict of interest: *Ownership: Signature Diagnostics AG. Board of directors: Signature Diagnostics AG*

2183 POSTER DISCUSSION

COX-2 expression influences the prognostic effect of aspirin use after diagnosis in colon cancer patients

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Background: Previous studies showed that aspirin use after diagnosis was associated with a survival advantage in colon cancer patients. Use of other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) is however not associated with a worse survival. The reasons for this phenomenon remain unclear, but might be related to selective inhibition of cyclooxygenase-2 (COX-2). Approximately 70% of all colon cancers express COX-2, which is related to tumorigenesis and might therefore influence the effect of aspirin and NSAID on prognosis.
Material and Methods: The study population consisted of 999 patients diagnosed with colon cancer, registered in the Eindhoven Cancer Registry (ECR) between 1998 and 2007, linked to dispensings of aspirin and NSAIDs registered in the community pharmacy database of the PHARMO record linkage system. A tissue micro array (TMA) was constructed. TMA slides were immunohistochemically stained for COX-2 expression and scored for intensity of the staining. Survival was analyzed with user status as a time-dependent covariate. Multivariate Poisson regression survival models were used to study the effect of aspirin on Overall Survival (OS) and Distant Recurrence Free Survival (DRFS) and were further stratified for COX-2 expression.
Results: Aspirin use after diagnosis was associated with a better OS (HR 0.48, CI 0.22–1.03, $p = 0.05$). NSAID use was associated with a worse survival (HR 1.62, CI 1.18–2.23, $p = 0.004$). 61 patients (44.9%) with aspirin or NSAID use after diagnosis showed weak COX-2 tumor staining and 75 patients (55.1%) showed strong COX-2 staining. Interestingly, after stratification for COX-2 expression, only frequent aspirin use ($\geqslant$5 prescriptions) remained significantly associated with a better OS and DRFS in patients with strong expression of COX-2 (adjusted HR 0.32, CI 0.11–0.97, $p = 0.04$ and adjusted HR 0.32, CI 0.11–0.97, $p = 0.04$). This effect on OS was larger in older colon cancer patients (adjusted HR 0.05, CI 0.01–0.46, $p = 0.008$). After stratification for COX-2 expression, patients with NSAID use showed a worse OS in patients with both high and low expression of COX-2.
Conclusions: Frequent aspirin use is associated with a better OS and DRFS in patients with high COX-2 expression in their tumor sections, especially in older colon cancer patients. COX-2 might therefore play an important role in the effect of aspirin. Currently, COX-1 and PIK3CA are investigated for their role in this phenomenon.
No conflict of interest.

2184 POSTER DISCUSSION

Prospective multi-center study of the impact of Oncotype® DX Colon Cancer Assay results on treatment recommendations in stage II colon cancer patients

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Background: The Onco*type* DX Colon Cancer Recurrence Score® assay is a clinically-validated predictor of recurrence risk in stage II colon cancer patients. This prospective study evaluated the impact of Recurrence Score results on physician recommendations regarding adjuvant chemotherapy in T3, Mismatch Repair-proficient (MMR-P) stage II colon cancer patients.
Patients and Methods: Stage IIA colon cancer patients were enrolled in 17 centers. Patient tumour specimens were assessed by the Recurrence Score test (quantitative RT-PCR) and MMR (IHC). For each patient, the physician's recommended post-operative treatment plan of observation, fluoropyrimidine monotherapy, or combination therapy with oxaliplatin was recorded before and after the Recurrence Score and MMR results were provided.
Results: Of 221 enrolled patients, 141 patients had T3 MMR-P tumours and were eligible for the primary analysis. Treatment recommendations changed for 63 (45%, 95% CI 36%-53%) of these 141 T3 MMR-P patients, with intensity decreasing for 47 (33%) and increasing for 16 (11%). Recommendations for chemotherapy decreased from 73 (52%) to 42 (30%) patients, following review of Recurrence Score results by physician and patient. Increased treatment intensity was more often observed at higher Recurrence Score values and decreased intensity at lower values ($p = 0.011$).
Conclusion: Compared to traditional clinicopathological assessment, incorporation of the Recurrence Score result into clinical decision-making was associated with treatment recommendation changes for 45% of T3 MMR-P stage II colon cancer patients in this prospective multi-center study. Use of the Recurrence Score assay may lead to overall reduction in adjuvant chemotherapy use in this subgroup of stage II colon cancer patients.
Conflict of interest: *Other substantive relationships: Margarita Lopatin-Lead Program Biostatician, Genomic Health, Inc, also has stock ownership. Calcin Chao-Senior Director, Medical Affairs, Genomic Health Inc, also has stock owndership.*

Poster Session (Sun, 29 Sep)
Gastrointestinal Malignancies − Colorectal Cancer

2185 POSTER

Tissue proteinase levels and 10 year survival in colorectal cancer

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Background: Proteinases and their inhibitors are involved in tumour invasion and metastasis. The levels of matrix metalloproteinase (MMP) and plasminogen activator (PA) system components were determined in paired colorectal tumour and normal tissue samples and correlated with the tumour pathology and ten year survival.
Material and Methods: MMP and PAS expression was determined in 101 paired tissue samples from colorectal cancer patients by ELISAs; MMPs-1, 2, −3 and −9 and the tissue inhibitors, TIMPs −1 and −2, urokinase and tissue type PA (uPA and tPA), the PA inhibitors, PAI-1 and −2 and the receptor for uPA, uPAR. Tissue levels were correlated with tumour pathology; Dukes stage, differentiation, tumour depth, vascular and lymphatic invasion ($P<0.05$, Spearman's correlation) and ten year survival analysis was performed ($p < 0.05$ Kaplan Meier). The study had ethics approval.
Results: The levels of all studied MMPs, uPA, uPAR, TIMP-1 and PAIs were significantly greater in colorectal tumour tissue than normal mucosa ($P<0.05$ Mann Whitney) e.g. PAI-1: tumour, median 14.9(range, 0.2–80.2)ng/mg total protein; normal, 2.1(0.1–65.0). However tPA levels were significantly greater in normal mucosa.
Tumour levels of MMPs, uPA, uPAR and PAI-1 significantly correlated with Dukes' stage e.g. MMP-1: Adenoma, 0.9(0.2−6.8); Dukes A, 4.7(0.1–23.0); Dukes B, 11.9(0.6–86.9); Dukes D, 16.3(0.3–30.8). PAI-1 and uPA tumour levels also significantly correlated with lymphatic invasion, TIMP-1 and PAI-1 with tumour depth and PAI-2 with vascular invasion.
The proportion of active MMP-2 and MMP-9 in tumour tissue significantly correlated to both disease free and overall ten year survival, with patients with higher levels of these factors having poorer survival.
Conclusions: Tumour levels of proteinases and inhibitors from both the MMP and PA proteinase systems correlated with tumour pathology. However, only active MMP-2 and MMP-9 levels correlated with disease-free and overall ten year survival.
No conflict of interest.

2186 POSTER

Biomarkers of resistance to anti-EGFR in wild type KRAS/BRAF colorectal cancer cell lines

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Background: Treatment of metastatic colorectal cancer (mCRC) with targeted therapies such as monoclonal antibody (mAb) inhibiting the epidermal growth factor receptor (EGFR) offer promise in improving patient outcomes. However, a high proportion of CRC patients who receive mAb show resistance to such therapy. Biomarkers such as mutant KRAS, BRAF and NRAS predict resistance to anti-EGFR therapy in only a proportion of patients and we hypothesise that other biomarkers for resistance to EGFR-targeted therapies exist. We aimed to identify resistant and sensitive wild type (WT) KRAS/BRAF CRC cell lines to anti-EGFR treatment, to identify candidate biomarkers in resistant CRC cell lines, to validate these findings using qRT-PCR and to use siRNA to knockdown one or more of these biomarkers overexpressed in the resistant cell lines. We hypothesise that knockdown of such biomarkers in the resistant cell lines will restore sensitivity.
Materials and Methods: Six WT KRAS/BRAF CRC cell lines were tested for resistance/sensitivity to anti-EGFR treatment and proliferation determined using the Promega CellTiter 96® AQueous Assay kit, with proliferation rate >50% deemed resistant and <50% deemed sensitive (Jhawer *et al.* 2008). Biomarker expression in the cell lines was determined using Qiagen RT-Profiler Array Human EGF/PDGF pathway kit and validated using qRT-PCR. siRNA was performed to knockdown HBEGF in the resistant cell line SNUC1. siRNA concentration was optimised using 10 nm/well, 50 nm/well and 100 nm/well, and transfection reagent was used at 0.2 μL/well, 0.5 μL/well and 1 μL/well concentrations. qRTPCR was performed to confirm knockdown and determine optimum concentrations for both reagents.
Results: SW48, COLO-320DM and SNU-C1 were resistant to anti-EGFR treatment, with 59.1%, 68.25% and 83.8% proliferation respectively while LIM1215, CaCo2 and SW948 were sensitive to the treatment with 18.6%, 41.9% and 36.8% proliferation respectively ($P = 0.0003$). Following RT-Profiler Array, 3 upregulated genes were chosen as candidate biomarkers of resistance based on a number of criteria; number of occurrences in all combinations of resistance vs sensitive cell lines, fold change more than 3 and statistical significance and this correlated with qRT-PCR results. EGR1 (early growth response protein 1) was upregulated in the resistant cell line SW48 by 28-fold, AKT3 (protein kinase B gamma) was upregulated in COLO-320DM by 31.3-fold and HBEGF (heparin-binding epidermal growth factor-like growth factor) was upregulated in SNUC1 by 22.6-fold. siRNA knockdown of HBEGF by 73% was achieved in SNUC1 (by qRT-PCR), at 10 nm/well for siRNA and 0.2 μL/well transfection reagent, compared to the negative control sequence (7%) used in the same conditions.
Conclusion: Three biomarkers up-regulated in the resistant cell lines have been identified and these may have a role in causing resistance to anti-EGFR treatment. They may emerge as biomarkers of resistance and be predictive of patients' response to anti-EGFR therapy.
No conflict of interest.

2187 POSTER

miR-126 and miR-20b are under-expressed in colorectal tumors

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Background: MicroRNAs (miRNAs), member of a family of short nucleotide non-coding RNAs, play important roles in cell proliferation, differentiation, apoptosis, and development. MiR-126 regulates angiogenic

signaling and vascular integrity, and suppresses the neoplastic cell growth by targeting PI3K signaling in colon cancers. MiR-20b regulates VEGF expression mediated by HIF-1α, and affects cell proliferation. The aim of this study is to clarify significance of miR-126 and miR-20b in colorectal carcinogenesis.
Materials: Colorectal tumors and corresponding normal tissues obtained after informed consent from 2008 to 2011. In all, 58 FAP tumors, 16 Lynch syndrome tumors, and 62 sporadic colorectal tumors, including 38 MSS tumors, and 23 MSI-H tumors, were analyzed for miRNA expression in this study.
Results: Expression levels of miR-126 and miR-20b in colorectal tumors were lower than those in normal mucosa. Frequency of miR-126 down-regulation was 100.0% in FAP adenoma, 87.5% in FAP intramucosal carcinoma, 88.9% in invasive carcinoma, 86.7% in Lynch syndrome, 70.0% in MSS tumor, and 75.0% in MSI-H tumor, respectively. Frequency of miR-20b down-regulation was 64.0% in FAP adenoma, 50.0% in FAP intramucosal carcinoma, 73.3% in invasive carcinoma, 62.5% in Lynch syndrome, 79.5% in MSS tumor, and 91.3% in MSI-H tumor, respectively.
Conclusion: The under-expression of miR-126 and miR-20b were observed in various types of colorectal cancer, and the current study supports that the under-expressions of miR-126 and miR-20b occur in the early event of colorectal carcinogenesis.
No conflict of interest.

2188 POSTER

Dual blockade of IGF-IR and EGFR sensitizes colorectal cancer cells to 5-FU-based radiochemotherapy in vitro and in vivo

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Background: Receptor tyrosine kinases (RTKs) are known to be key players in the development of colorectal cancer (CRC). We hypothesize that the simultaneous inhibition of the RTKs insulin-like growth factor receptor (IGF-IR) and epidermal growth factor receptor (EGFR) increases efficiency of the 5-Fluorouracil-based radiochemotherapy (RCT) of CRC in non-responder patients.
Methods: Colony formation assays and xenograft models were used to study sensitization and therapy effects after RCT in combination with the inhibition of IGF-IR (AEW-541) and EGFR (erlotinib) *in vitro* and *in vivo*. To identify the molecular mechanisms of the success of the additional RTK inhibition western blot, immunofluorescence, live/dead and caspase activation assays were performed to unravel DNA damage repair and induction of apoptosis; cell cycle distribution was analysed by flow cytometry. Furthermore, proximity ligation assays were applied to study interaction of IGF-IR and EGFR during RCT treatment.
Results: Simultaneous inhibition of IGF-IR and EGFR results in a sensitization of CRC cells (DLD-1, SW837 and Caco-2) to RCT regardless of their responder state to RCT. In addition, dual blockade of both receptors in CRC cells enhanced the therapy success in the SW837 xenograft model. To identify the molecular mechanisms underlying this sensitization of CRC cells we analysed the DNA repair mechanisms, apoptosis and cell cycle distribution. Phospho-H2AX staining as a marker for double strand breaks revealed impairment of DNA repair in single inhibitor treatments 24 h after RCT and even more pronounced effects were observed when both receptors were inhibited simultaneously. Moreover, DLD-1 cells showed a cell cycle arrest in G2, mediated by cyclin B1, whereas induction of apoptosis was observed in SW837 and Caco-2 cells. Furthermore, we could show using proximity ligation and co-immunoprecipitation assays that IGF-IR and EGFR form heterodimers in CRC cells in a ligand-dependent manner. During RCT this heterodimerization of IGF-IR and EGFR is disturbed.
Conclusion: Taken together, these results indicate a role of RTKs EGFR and IGF-IR in sensitization of CRC cells to RCT. Dual inhibition of both RTKs EGFR and IGF-IR might represent a promising new approach for patients with rectal cancer not responding to a combined RCT.
No conflict of interest.

2189 POSTER

KRAS G13D mutations associated with sensitivity to cetuximab or panitumumab treatment in colorectal cancer cell lines

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Background: The treatment of metastatic colorectal cancer (mCRC) has improved over recent years, with targeted therapies providing additional benefit. One such target that has emerged for mCRC treatment is the epidermal growth factor receptor (EGFR). It is well accepted that a mutation in codon 12 or 13 in *KRAS,* downstream of the EGFR, evokes constitutive activation of the RAS/RAF/MAPK signalling pathway, and that this correlates with resistance to anti-EGFR monoclonal antibody therapies. However, a retrospective study reported that a proportion of patients with KRAS G13D mutation respond better to cetuximab (Cmab) compared to patients with other KRAS mutation. A similar analysis for panitumumab (Pmab) was not as conclusive. We aimed to determine the sensitivity of colorectal cancer cell lines to Cmab or Pmab treatment, and investigate the correlation of the KRAS mutational status of the colorectal cancer cell lines to the responsiveness to Cmab or Pmab.
Materials and Methods: To determine the responsiveness of CRC cell lines to Cmab or Pmab, proliferation assays were conducted using the MTS colorimetric assay with the Promega CellTiter 96® AQueous Assay kit.
Results: Following treatment with Cmab or Pmab at the optimum concentration of 8 μg, SW480 with KRAS G12V mutation had the highest proliferation rate for Cmab at 72.3% and for Pmab at 71.4%, showing resistance to both treatments. LIM1215, a KRAS WT and BRAF WT cell line, had the lowest proliferation rate for Cmab at 29.3% and Pmab at 29%, showing greatest sensitivity to both treatments. HCT-116, LoVo and T84, all with KRAS G13D mutation and BRAF WT showed intermediate sensitivity to Cmab and Pmab. In the Cmab treatment group, HCT-116 showed highest sensitivity at 44.5% proliferation, followed by T84 at 55.2% and LoVo at 60.6%. In the Pmab treatment group, LoVo showed highest sensitivity at 40.4% proliferation, followed by T84 at 45.4% and HCT-116 at 48.3%. However, there was no significant difference noted overall between sensitivity of KRAS G13D mutated cell lines to Pmab vs Cmab (44.7% vs 53.7%), differing from that reported in the clinic.
Conclusion: The specific KRAS mutation determines the responsiveness to anti-EGFR monoclonal antibody treatment and confirms clinical observations for Cmab, but the difference of efficacy between Pmab and Cmab was not confirmed.
Conflict of interest: *Advisory board: Merck and Amgen*

2190 POSTER

Protein kinase CK2 enhances colorectal cancer malignancy by upregulating the expression of cyclooxygenase-2 through the canonical Wnt signaling pathway

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Background: Protein kinase CK2 is abnormally elevated in a wide variety of cancers. The concept that cancer cells are become 'addicted to CK2' in order to create a cellular environment favorable to neoplasia has recently emerged. Regarding to this, CK2 promotes an elevated activity of β-catenin at the canonical Wnt signaling pathway. Aberrant activation of this pathway leads to an increased expression of genes, including survivin and cyclooxygenase-2 (COX-2), which are linked to cancer development and progression. Also, COX-2's metabolite prostaglandin E2 (PGE2) has been demonstrated to be involved in progression and metastasis of colon and breast cancers. However, if CK2 regulates the COX-2-dependent production of PGE2 and this is functionally related with colon cancer cell viability and invasion has not been studied.
Methods: Changes in COX-2, β-catenin and survivin expression were analyzed by RT-PCR and western blot in colon (HT29-ATCC, HT29-US, DLD-1) and breast (ZR-75) cancer cells. CK2 activity was specifically inibited with TBB or DMAT, while COX-2 activity was inhibited with SC-791 or celecoxib. Proliferation and apoptosis were determined by the MTS® and Caspase-Glo® assays, respectively. Cell invasion was evaluated with

a matrigel-based assay®. The effects of PGE2 on proliferation, apoptosis and cell invasion were investigated.
Results: Elevated COX-2 expression and activity were detected in colon and breast cancer cells. Inhibition of both CK2 and COX-2 significantly down-regulated cell viability, as observed by decreased proliferation and increased apoptosis. CK2 inhibition also correlated with decreased mRNA and protein levels of COX-2. However, supply of PGE2 did revert the CK2's inhibitor-induced loss of COX-2 expression, augmenting proliferation and invasiveness, as well as decreasing apoptosis.
Conclusions: Our results identify the CK2/COX-2/PGE2 axis like relevant for colon and breast cancer malignancy. Moreover, they point to CK2 as a potentially interesting pharmacological target in colon and breast cancer treatment. Supported by grants from ICGEB (CRP/CHI10−01) and FONDECYT (11070116, 1120132).
No conflict of interest.

2191 POSTER

Simvastatin induces KRAS translocation in KRAS mutant colorectal cancer cells and may influence the susceptibility to anti-EGFR therapy

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Background: *KRAS* mutation status in colorectal cancer is leading for the use of EGFR antibodies, such as cetuximab. KRAS is activated by post-translational modification (prenylation) by binding C15 and C17 fatty acid chains. As a consequence KRAS becomes more lipophilic and associates with the membrane to exert its function. Statins inhibit the synthesis of these C15 and C17 chains. Statins may therefore have the potential to influence the KRAS mutant phenotype. Previous experiments have shown that *KRAS* mutant cells could be sensitized to anti-EGFR therapy using simvastatin.
This study sought to determine the mechanism of sensitisation by simvastatin in *KRAS* mutant CRC cells. We hypothesise that by inhibiting the prenylation, KRAS will not associate with the inner-membrane and KRAS will be less active, making *KRAS* mutant cells more susceptible to anti-EGFR therapy.
Material and Methods: LoVo (*KRAS mutant* G13D) and SW48 (*KRAS* wildtype) CRC cells were seeded in NuncTM glass 8-chamber slides at density of 20,000 cells/well and cultured for 24 hours. After 24 hours, medium was replaced with medium with or without simvastatin (2μM) and cultured for another 24 hours. Cells were fixated with 2% PFA, permeabilized using 0.1% Saponin + 2% PFA, incubated with KRAS mouse anti-human antibody and incubated with Alexa 488 goat anti-mouse antibody. Vectashield-Dapi was used to stain the nucleus.
Results: Confocal microscopy showed that KRAS is associated with the membrane in both wildtype and mutant CRC cells. In wildtype *KRAS* cells, we observed that KRAS is also localized in the cytoplasm. After incubation with simvastatin, in *KRAS* mutant Lovo cells, KRAS translocates from the membrane to the cytoplasm.
Conclusions: Simvastatin induces translocation of KRAS from the membrane to the cytoplasm in *KRAS* mutant cells and therefore may sensitize *KRAS* mutant CRC cells to anti-EGFR therapy.
No conflict of interest.

2192 POSTER

Blockade of PDGFR family together with SRC leads to diminished proliferation of CRC cells

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Background: Among the family of receptor tyrosine kinases (RTKs) the platelet-derived growth factor receptor (PDGFR) has attracted increasing attention as potential target of anti-tumor therapy in colorectal cancer (CRC).
Methods and Results: Varying expression of the PDGFRβ was demonstrated in CRC cell lines. SW480 cells showing the highest PDGFRβ expression were used for receptor down-regulation by siRNA and by the pharmacological inhibitor of PDGFRβ Ki11502. Blockade of PDGFRβ using both approaches led to a moderate inhibition of cell proliferation and diminished the PDGF-BB-induced phosphorylation of the downstream signaling pathway AKT. Surprisingly, incubation with Ki11502 resulted in an arrest of SW480 cells in the G2 phase of the cell cycle, whereas the siRNA approach did not. To address this difference, we analyzed proliferation and cell cycle distribution in DLD-1 and Caco-2 cells either with down-regulated PDGFRβ expression or after Ki11502 treatment. Whereas DLD-1 cells (high c-KIT expression) showed a strong decrease of proliferation after treatment with Ki11502, this effect was not observed in the siRNA approach. Caco-2 cells (no c-KIT expression) did not respond at all. Hence, we reduced expression of c-KIT in SW480 and DLD-1 cells, but proliferation studies could not prove the involvement of c-KIT inactivation during Ki11502 treatment.
To identify the underlying cause of effectiveness of Ki11502 in CRC cell lines we applied a RTK activation antibody array on SW480 cells treated with siRNAs against c-KIT, PDGFRβ or both and two concentrations of Ki11502. This analysis revealed that SRC kinase is inactivated after Ki11502 treatment, but not after the siRNA approach. Further studies using the SRC-specific inhibitor PP2 showed that SRC inhibition upon treatment with the inhibitor Ki11502 is responsible for the observed effects of Ki11502 in SW480 CRC cells.
Conclusion: In summary our results demonstrate, that inhibition of PDGFRβ alone using siRNA has only moderate cellular effects in CRC cell lines, instead, multi-target inhibition of PDGFRβ, c-KIT and SRC, e.g. using Ki11502, represent a promising therapeutic intervention for the treatment of CRC.
No conflict of interest.

2194 POSTER

Kiss-1 suppresses the motility of colorectal cancer cells via the ERK pathway and aberrant expression of Kiss-1 and its receptor (Kiss-1R) in patients with colorectal cancer

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Background: The metastatic process involves impairment of cell-cell adhesion in neoplastic epithelia, invasion into adjacent tissues and dissemination of cancer cells through the lymphatic and haematogenous routes. During the process, metastasis suppressor genes play pivotal roles. However, classical metastasis suppressor genes are limited in both numbers and to the knowledge of their mode of actions. Kiss-1 and its receptor (Kiss-1R) have been suggested as a novel pair of metastasis suppressors in several human solid tumours. However, the role of Kiss-1 and Kiss-1R in colorectal cancer remains largely unknown. Therefore, the aim of this study was to investigate the role and signal transduction of Kiss-1 and its receptor in colorectal cancer.
Material and Methods: Colorectal cancer cell lines (HT115, HRT18, RKO and Caco-2) were screened for the mRNA expression levels of Kiss-1 and Kiss-1R using PCR analysis. Sublines of cancer cells with differential expression of Kiss-1 and Kiss-1R were created, using ribozyme transgenes to respectively knock down the expression of Kiss-1 and Kiss-1R. The influence of Kiss-1 and Kiss-1R on the biological functions of cancer cells was evaluated using *in vitro* function assays and ECIS assay. A cohort of human colorectal cancer tissues (n = 171) were investigated Kiss-1 and Kiss-1R expression. The expression levels of both molecules were correlated with the clinical and pathological and outcome results of the patients.
Results: Over-expression of Kiss-1 suppressed the *in vitro* invasion and migration of colorectal cancer cells. Exogenous Kiss-1 (Kisspeptin-10) decreased cellular migration of colorectal cancer cells, an action required ERK signalling as shown in an ECIS based cellular model. In human colorectal cancer tissues, levels of message expression of Kiss-1 had a negative correlation with Dukes staging, TNM staging, tumour size and lymph node involvement. Kiss-1R expression was significantly decreased in tumour tissues compared with adjacent normal tissues ($p<0.00001$). In contrast, the increased expression of Kiss-1R had positive correlation with colorectal incidence ($p = 0.0207$). In addition, it was observed that patients with high level of Kiss-1R had significantly shorter overall and disease free survival time than those with low level was observed ($p = 0.011$ and $p = 0.033$, respectively).
Conclusions: It is concluded that Kiss-1 plays a pivotal tumour suppressor role in colorectal cancer through the inhibiting of the motility of colorectal cancer cells, a process requiring the participation of the ERK pathway. Together with the aberrant expression of Kiss-1 and Kiss-1R in patients with colorectal cancer, it is suggested that the Kiss-1 complex is a potential tumour suppressor with prognostic value in patients with colorectal cancer.
No conflict of interest.

2195 POSTER

Genetic variants in DNA repair genes and survival in colorectal cancer patients treated with oxaliplatin combination chemotherapy

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Background: Oxaliplatin has become one of the main chemotherapeutic agents for the treatment of colorectal cancer (CRC). The platinum agent causes DNA adducts and crosslinks, which forces the (tumor) cell to go into apoptosis. The Nucleotide Excision Repair (NER) pathway and the Double Strand Break Repair (DSBR) pathway are involved in the repair of damage caused by oxaliplatin treatment. Genetic variants in these genes may therefore influence survival in CRC patients. Only a limited number of genetic variants in these genes have been investigated so far and therefore we assessed the association between 321 genetic variants in 52 genes of the NER and DSBR pathways and overall survival (OS) in CRC patients who received oxaliplatin chemotherapy and assessed differential effects compared to patients with other chemotherapeutics.
Material and Methods: We included 620 CRC patients diagnosed between 01.01.2003 and 31.12.2007 and recruited in a German population-based study (DACHS), who received adjuvant chemotherapy (223 patients with oxaliplatin treatment) and had complete follow-up for 3 to 5 years. Detailed epidemiological, clinical and therapy data were collected using questionnaires and clinical/pathological records. Genotyping was conducted using the Illumina GoldenGate assay. Genetic main effect analysis was performed using component-wise Cox regression models, adjusting for age, sex, UICC stage, cancer site and BMI. The Benjamini & Hochberg False Discovery Rate (FDR) was used to correct for multiple comparisons. Effect modification by oxaliplatin treatment was assessed using a multiplicative interaction term.
Results: Median follow-up time in patients receiving oxaliplatin was 3.0 years after which 107 patients were deceased. In patients who received oxaliplatin, 15 SNPs were nominally significantly associated with overall survival (OS). Six SNPs in 6 genes showed some evidence of differential association with OS according to oxaliplatin treatment (nominal p for heterogeneity <0.01). Of these SNPs, only rs11574214 in the Werner syndrome ATP-dependent helicase (*WRN)* gene showed to be a marginally predictive marker for outcome after oxaliplatin treatment after correction for multiple testing (adjusted p for heterogeneity =0.07).
Conclusion: Our data suggest that genetic variants in the *WRN* gene may be predictive markers for oxaliplatin treatment; however, more research is warranted to confirm these results.
No conflict of interest.

2196 POSTER

Elevated frequency but decreased absolute count of regulatory T lymphocytes in rectal cancer patients undergoing therapy

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Introduction: T-regulatory cells (Tregs) are a specialized subpopulation of T cells that suppress the activation, expansion, and function of other T cells. Tregs inhibit and eradicate cytotoxic T-lymphocytes and T-helper lymphocytes. In colorectal cancer, they are up to 80% of the population of tumor-infiltrating lymphocytes and their number in tumor has been reported to correlate with worse outcome.
Materials and Methods: Peripheral blood was sampled into K_3EDTA anticoagulant and CBC and Tregs were measured within 3 hours from blood withdrawal. Tregs were detected as CD3-FITC(+), CD127-PE(low/-), CD25-PC5(+) and CD4-PC7(+) cells using flow cytometry. Tregs were evaluated in samples from reference population (51 men, 51 women) and from patients with rectal tumors (102 men, 43 women) as frequency (% from lymphocytes) and absolute count (cell/microL).
Results: In reference population, the median of absolute Treg count was 39.2 cells/microL (**interquartile range IR:** 28.8 to 53.5 cells/microL) and median of Treg frequence was 4.9% (**IR:** 3.9 to 6.4%). We have not observed either difference in Tregs level between men and women or age-dependence. In cancer patient group, median of absolute Treg count was 21.1 cells/microL (**IR:** 15.3 to 29.3 cells/microL) and median of Treg frequence was 6.3% (IR: 3.9 to 8.5%). Comparing both, absolute count and percentage, we found statistically significant difference between reference and cancer population. Interestingly however lower absolute Tregs and increased percentage of Tregs in rectal cancer patients. Higher proportion of Tregs is likely result of lower lymphocyte count in patients undergoing anticancer therapy (1.21 x 10^9/L vs 1.81 x 10^9/L in reference population).
Conclusion: The elevated levels of circulating Tregs have been reported as a negative prognostic factor for various cancers. Here we show that Treg absolute count and frequency are not interchangeable and that Treg count but not their frequency is stable within one cancer patients. In conclusion, we evaluated peripheral blood Tregs as a potential marker of disease and prognostic factor, which is relatively easy to measure, and discuss our findings.
Acknowledgement: The work was supported by EU funding for RECAMO (CZ CZ.1.05/2.1.00/03.0101).
No conflict of interest.

2197 POSTER

The gp130/Jak/Stat3 pathway is required for Wnt induced regeneration and tumorigenesis in the mouse intestine

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Background: The majority of sporadic and familial colorectal cancers (CRC) arise from mutations in the tumor suppressor gene *APC* leading to uncontrolled activation of the canonical WNT signalling pathway. Meanwhile, WNT mediated regulation of intestinal stem cells (ISCs) is critical for epithelial regeneration and homeostasis. Thus far, however, therapeutic targeting of the WNT pathway has proven difficult in human disease.
Material and Methods: We use mouse models of inherited and sporadic CRC to genetically and pharmacologically target the cytokine-dependent gp130/Jak/Stat3 pathway. Furthermore, we assay the growth of human CRC cell lines *in vitro* and *in vivo* under conditions that interfere with gp130/Jak/Stat3 signalling.
Results: We show that excessive gp130/Jak/Stat3 signalling promotes WNT-pathway dependent regeneration of the intestinal epithelium after injury and exacerbates intestinal tumorigenesis in mouse models of spontaneous or inherited CRC, and arising from mutant *APC*. Conversely, genetic restriction of the gp130/Jak/Stat3 pathway inhibits intestinal regeneration and suppresses tumor growth despite persistent excessive WNT signalling. Additionally, therapeutic administration of a small molecule Jak kinase inhibitor potently blocked *de novo* tumor formation and restricted the growth of already existing lesions in mouse models of spontaneous and inherited CRC. Moreover, this inhibitor also blocked the growth of human CRC cell lines with *APC* mutations in soft agar colony assays and as xenografts in nude mice, but had no effect on the growth of isogenic CRC cell counterparts that expressed wild type *APC*. These results suggest that gp130/Jak/Stat3 pathway is only rate limiting for the proliferative responses elicited during conditions of excessive WNT signalling. We identify Stat3-dependent Bmi1 induction and the resulting repression of p16 and p21 as the mechanism by which the gp130/Jak/Stat3 pathway modulates the cellular response to excessive WNT signalling.
Conclusions: We propose that the gp130/Jak/Stat3 pathway is rate-limiting selectively for the growth of *APC* mutant tumors, and this pathway therefore provides a readily exploitable target for the therapeutic treatment of CRC.
No conflict of interest.

2198 POSTER

Is there a synergistic effect between ascorbic acid and conventional chemotherapy in the treatment of colorectal carcinoma?

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Background: Colorectal cancer (CRC) is a major health problem with more than one million new cases diagnosed worldwide every year.

Ascorbic acid (AA), the reduced form of vitamin C works as a pro-oxidant at pharmacological concentrations, promoting the formation of reactive oxygen species which can induce cancer cell death. It has been proved that AA doesn't protect cancer cells from chemotherapy but plays a protective role in normal cells. At the same time AA can enhance tumor growth inhibitory effect conferred by usual therapies regardless tumor type. Giving the positive feedback in turn of the use of AA with chemotherapy, the aim of this study is to evaluate the therapeutic potential of AA in combination with 5-Fluorouracil (5FU) in human CRC cell lines.
Methods: WiDr, C2BBe1 and LS1034 (multidrug resistant) cell lines were cultured in appropriate culture medium and incubated in absence and with different concentrations of AA and 5FU alone or in combination during different periods of time. The half maximal inhibitory concentration (IC50), as well as the interaction index were calculated after 48, 72 and 96 hours by sulphorhodamine B (SRB) assay. To evaluate cell survival clonogenic assays were done, the number of colonies was counted, being plate efficiency and survival factor determined. To evaluate cell viability and types of cell death, flow cytometry was performed, using annexin V and propidium iodide double staining.
Results: Results obtained with SRB showed an anti-proliferative effect induced by AA in all cell lines in a dose and cell line-dependent way (r^2>0.90). C2BBe1 cells revealed to be the most sensitive to AA (IC50=0.82mM) comparing to WiDr (IC50=5.9mM) and LS1034 cells (IC50=5.37mM). Clonogenic assays revealed that, as the concentration of AA increases, survival factor decreases. AA also induces a cytotoxic effect when present in higher concentrations. When in combination, we reached an addictive effect at 72 hours of incubation for C2BBe1 and LS1034 and a synergistic effect at 96 hours in all cell lines, more evident in LS1034. Clonogenic assays corroborate these results.
Conclusions: Our study allowed us to verify the existence of synergism between AA and 5FU as the combination of these drugs induced an anti-proliferative effect and a decrease in cell survival more relevant than that obtained with compounds alone that probably affect somehow LS1034 resistance. The data obtained could contribute to the development of a promising therapy in CRC with reduced doses of conventional chemotherapeutic drugs and consequently, a decrease in secondary effects.
No conflict of interest.

2199 POSTER

Ascorbic acid and colon carcinoma: correlation between uptake and cytotoxic effect

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Background: Ascorbic acid (AA), the reduced form of vitamin-C, has a double action: antioxidant and pro-oxidant. AA is a powerful antioxidant, since it can neutralize free radicals, constituting a powerful anticancer mechanism. As a pro-oxidant, AA promotes the formation of reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2), which endanger the cell viability. Another feature shown in tumor cells is the reduction of ROS-detoxification machinery, such as catalase, compared with normal cells. Thus, the increased production of H_2O_2 coupled with deficiency of catalase activity and presence of transition metals may result in the selective cytotoxicity of vitamin-C. The aim of this work is to correlate the metabolism of vitamin-C with the cytotoxic effect on colon carcinoma cells.
Material and Methods: The cell lines used were LS1034 and C2BBe1. Both cell lines were incubated in absence and with different concentrations of AA. The half maximal inhibitory response (IC50) was calculated after 24, 48, 72 and 96 hours by sulphorhodamine B (SRB) assay. To complement, clonogenic assays were performed to evaluate cell survival. To study the uptake of vitamin-C by the cells it was used a radionuclide (^{99m}Tc) to label the reduced form of vitamin-C obtaining ^{99m}Tc-AA, with a previously described method. The respective quality control was done by HPLC in order to determine the labeling efficiency. Cell suspensions were incubated with ^{99m}Tc-AA (25 μCi/ml) and uptake studies were conducted.
Results: Our results obtained with SRB showed that AA induces a decrease in cell proliferation in both cell lines, in a dose-dependent way (r^2>0.91). The clonogenic assays revealed that, as the concentration of AA increases, the survival factor decreases. These facts were much more evident in C2BBe1 cells (IC50<0.95mM) comparing to LS1034 cells (IC50>4.33mM). The percentage of uptake of ^{99m}Tc-AA is higher than the uptake of sodium pertechnetate ($^{99m}TcO_4Na$) in both cell lines. The radiolabeling efficiency was 97.5%±2.28%, determined by graphic integration and normalization of the peaks by HPLC. Preliminary results showed that ^{99m}Tc-AA uptake is higher in C2BBe1 (around 6%) and lower in LS1034 cells (not exceeding 1.06%).
Conclusions: Our study suggests that AA induces an anti-proliferative effect and decreases cell survival. The higher uptake and the higher sensitivity of C2BBe1 cells to AA, lead to a possible correlation between the cytotoxic effects and the uptake of AA by cells.
No conflict of interest.

2200 POSTER

Circulating tumor cells (CTCs) as a surrogate biomarker of DFS in patients (pts) with liver-only (L) metastases of colorectal cancer (LM-CRC)

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Background: The role of CTCs in pts with LM-CRC metastases has been little explored. The purpose of this study was to quantify CTCs during radical liver surgery (LS) in pts with LM-CRC and to demonstrate the role of CTCs in pts behavior.
Methods: 7.5 ml of blood were drawn in CellSave tubes. CTCs were enumerated before, just performed and 3 months after radical LS. CTCs were immunomagnetically separated and fluorescently labeled using the CellSearch System (Veridex/Immunicon Corp.).
Results: From February 2009 to March 2013 the samples of 48 pts were analyzed. Pts characteristics were as follows: median age was 64 (45−79) with 68% men. K-ras status was wild-type in 56%; 55% received neoadjuvant treatment, (95% with fluoropirimidines-based) and 70% received adjuvant treatment. Among 29 pts, best response rates were 69% PR and 31% SD. In 75% of cases, limited LS were done (R0:77%). Of the 25 pts analysed, pCR were observed in 2 (8%) with 11 other pts (44%) with major pathological response. With a median of follow-up of 26 months, progression disease occurred in 25 pts (46.3%), and 8 died (14.8%).
Median CTCs was 0 before (0−2: 82.5%; ⩾3: 17.5%) and just performed (0−2: 70.7%; ⩾3: 29.3%) increasing in 12% the group of CTCs ⩾3 after surgery. Median of DFS was 27 months (95% CI: 19.05–34.95), with DFS for pts with post-surgery CTCs 0−2 and CTCs ⩾3 group of 31 and 20 months, respectively (p = 0.038). There are no difference in overall survival in any group. In t he multivariate analysis post-surgery CTCs proves to be an independent predictor of outcome for DFS in our study (HR: 0.31, 95% CI: 0.10–0.96).
Conclusion: Based on our results, CTCs level analyzed just performed LS in pts with LM-CRC could be a useful independent predictor of DFS in this scenario, although more prospective studies are needed to confirm our results.
No conflict of interest.

2201 POSTER

Aflibercept inhibits tumor growth more effectively than bevacizumab in patient-derived xenograft (PDX) models of colorectal cancer

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Background: Aflibercept (afl) is a potent new multiple angiogenic factor trap that prevents not only VEGF-A but also VEGF-B and PlGF from activating their native receptors. Based on the overall survival benefit demonstrated in the phase 3 VELOUR trial, afl + FOLFIRI was approved for patients with metastatic colorectal cancer (mCRC) who had failed a prior oxaliplatin-containing regimen. In preclinical studies, afl inhibits VEGFR signaling more potently and blocks cell migration more effectively than bevacizumab (bev). Here, the efficacy of afl and bev were compared in 48 PDX CRC models. PDX models may better represent histology and genetic heterogeneity of human cancer than xenografts derived from cancer cell lines.

Methods: CRC adenocarcinoma tumors from primary or metastatic sites were engrafted and passaged subcutaneously (SC) into NMRI nude mice, creating 48 PDX models. Expression of mouse (m) and human (h) VEGF-A (mVEGF-A, hVEGF-A) and PlGF (mPlGF, hPlGF) in untreated tumors was measured by ELISA and Luminex. Tumor-bearing mice were dosed with afl, bev, or placebo (8 mice/treatment group/model) 2x/wk for 3 wks and SC tumor measurements recorded 2x/wk. Activity was expressed as the relative change in tumor volume between treatment (dT) and control (dC) at 3 wks. A dT/dC value of <10% (>90% inhibition) was scored as activity. Partial tumor regression was defined by $\geqslant$50% reduction in tumor size from baseline.
Results: Afl inhibited tumor growth in more PDX models than did bev (43/48 vs 7/48; Table). The 5 models insensitive to afl were also resistant to bev. Partial tumor regression occurred in 16/48 models treated with afl and in only 3/48 models treated with bev. Tumor levels of hVEGF-A (776–56,039 pg/mg total protein) were ~16- to 1,777-fold greater than mVEGF-A (8–159 pg/mg total protein) in PDX models. Tumor levels of mPlGF (104–1,837 pg/mg total protein) were higher than hPlGF (0–543 pg/mg total protein) in 47/48 models.

Table: Antitumor response to afl and bev in 48 PDX CRC models

	Afl	Bev
Tumor growth inhibition	43/48	7/48
Partial tumor regression	16/48	3/48

Conclusions: Afl demonstrated greater and more consistent antitumor activity than did bev in PDX models of metastatic and primary CRC. Tumor cells were the major source of VEGF, whereas PlGF was primarily produced by the tumor stroma. Tumor levels of hVEGF-A were much greater than mVEGF-A; thus, the inability of bev to bind to mVEGF-A does not explain the enhanced relative activity of afl.
Conflict of interest: *Ownership: Sanofi, Oncotest GmbH. Board of directors: Prof Heiner Fiebig. Corporate-sponsored research: Full time Sanofi Oncology employee. Other substantive relationships: Full time Sanofi Oncology employee*

2202 POSTER

Investigation of miR-504 expression in colorectal and breast cancer

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Background: MicroRNAs are a group of short non-coding RNAs which regulate gene expression at a post transcriptional level. The discovery that MicroRNAs(miRs) are differentially expressed in cancer has added a new dimension to investigation of novel diagnostic and therapeutic strategies for a number of cancers. miR-504 has recently been implicated in regulation of the *p53* tumour suppressor, which plays a central role in development of many cancers. However, miR-504 expression in patient samples has not previously been reported. This study aimed to investigate miR-504 expression at both the circulating and tissue level in patients with colorectal or breast cancer.
Materials and Methods: Following informed consent, tissue was harvested from patients with breast or colorectal cancer. RNA was extracted from colorectal tissue (n = 20 tumour, n = 13 tumour associated normal), breast tissue (n = 43 tumour, n = 20 normal), whole blood from patients with breast cancer (n = 20), blood from patients with colorectal cancer (n = 23) and blood from healthy controls (n = 23). RNA was reverse transcribed and relative levels of miR-504 in the tissue and circulation quantified by RQ-PCR.
Results: In breast tissue, significantly lower expression of miR-504 was observed in cancers (Mean$\pm$SEM; 1.766$\pm$0.096 $\log_{10}$ Relative Quantity (RQ)) in comparison with normal breast samples (2.935$\pm$0.202 $\log_{10}$RQ, p<0.001). Samples were further analysed according to patient clinico-pathological details. Within the breast cancer cohort, no significant difference was observed across epithelial subtype (p = 0.347), tumour grade (p = 0.38) or disease stage (p=0.20). In contrast to the differential expression observed in breast cancer, in colorectal cancer tissue no significant difference was observed (2.99$\pm$0.33 $\log_{10}$RQ) when compared with tumour associated normals (2.73$\pm$0.30 $\log_{10}$RQ). At a circulating level, no change in miR-504 expression was observed in colon cancer, breast cancer or healthy controls.
Conclusions: This is the first study to examine miR-504 expression in patient samples. The data herein shows miR-504 to be dysregulated in breast tumour tissue but not in colorectal cancer tissue. Combined with the absence of dysregulation in the circulation, this highlights the potential importance of miR-504 in the breast tumour microenvironment.
No conflict of interest.

2203 POSTER

From monoclonal tumor cell arises an identical colon adenocarcinoma?

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Background: The study aims to identify differences between left and right colon adenocarcinomas of identical clonal origin in orthotopic animal models of human cancer and contribute towards a better understanding of extracellular environment influence on MMP2, p53 and beta-Catenin expression as an important factor in the development of tumor phenotype characteristics.
Material and Methods: In the orthotopic model of right colon tumor the animals (a *Rat* without a thymus) were submitted to a cecostomy (n = 10), while for the left colon model a distal mucous fistula (n = 13) in the descending colon was used. Cultivated human colon adenocarcima cells (CCL-218) were inoculated into the sub-mucosa via the models' cecos-tomies and distal fistulas. Conventional e*x vivo* anatomic pathology studies (HE) were conducted, as well as gene expression analysis (RT-PCR) for beta-Catenin, p53, MMP2 and immunohistochemical examination for p53 and beta-Catenin expression. Statistical analysis adopted a significance value of 5% as the criterion for rejecting the hypothesis of nullity and was conducted using central tendency, variance analysis and the Livak delta-delta-CT methods for determining gene expression.
Results: In the left colon 100% of the tumors exhibited infiltrative ulceration while in the right colon tumor growth was predominantly exophytic (67%). Tumor growth in the left colon was undifferentiated (100%) and moderately differentiated in the right colon (83%). RT-PCR gene expression analysis revealed there was greater MMP2, p53 and beta-Catenin expression in right colon tumors compared to left colon tumors and the p53 and beta-Catenin expressions for those locations were confirmed by immunohistochemical means.
Conclusion: Human adenocarcinomas of the left and right colons developed in animal models have distinct characteristics even when their clonal origin is identical. Micro-environmental action modifies p53, beta-Catenin, and MMP2 expression in animal colon models leading to differentiated phenotype characteristics, even when their origin is monoclonal.
No conflict of interest.

2204 POSTER

Increased activation and migration potential of dendritic cell in patients with colorectal cancer − the implication and future of cancer immunotherapy

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Background: Dendritic cells (DC) are antigen presenting cells that migrate to lymphoid tissues to initiate a cytotoxic or tolerogenic immune response to tumour antigens. CD40 is a co-stimulatory molecule and a marker for DC activation. Increased expression of CD40 on DCs can be associated with maturation and enhanced cytokine production against tumour cells. Activation of DC is accompanied by up regulation of the lymph node migration marker C-chemokine receptor7 (CCR7). However, DC in cancer are unable to elicit effective immune responses against tumour cells. Previous studies on DC in colorectal cancer (CRC) were on cell lines and animal models. We aimed to determine the phenotype and activation status of systemic DC in CRC patients.
Materials and Methods: Peripheral blood mononuclear cells were obtained from CRC patients before any surgical intervention (n = 19). Blood from age and sex-matched healthy controls (n = 19) was also collected. DC identified as HLA-DR positive and lineage(anti-CD3, CD14, CD16, CD19, CD34 and CD56) negative cells. DC were further classified as CD11c+ myeloid (mDC) or CD11c- putative plasmacytoid. CD40, CD80, CD86 and CCR7 expression was determined on DC by flow-cytometry.
Results: In CRC the expression of CD40 was significantly higher on all DC (27.76% $\pm$2.790 vs 17.37%$\pm$ 3.306, p = 0.0215) compared to control. This increase was driven by the mDC subset, which was significantly increased in CRC (30.81%$\pm$4.480 vs 18.84%$\pm$2.391, p = 0.0240). There was also a increased CCR7 expression on all DC from CRC compared with control. This increase was a statistically significant on mDC in CRC

(33.33%±3.971) compared with control (15.15%±2.269), (p = 0.0003). There were no differences in CD80 and CD86 expression between groups.
Conclusion: DC in CRC patients are activated and their potential capacity to migrate to lymph nodes is increased. This increase in CCR7 expression suggests a role for DC in the metastasis of CRC. Our results are contrary to previous studies on monocyte-derived DC, which showed reduced CD40 expression. Hence, results should be interpreted with caution when using such cytokine stimulated DC as they do not resemble those normally present in blood.
Activated DC may stimulate either immunogenic or suppressive responses upon migration to lymph nodes. Therefore, further studies are warranted to investigate which immune response DC in CRC are inducing, which is an important step towards creating more suitable anti-tumour vaccines.
No conflict of interest.

2205 POSTER

rs28381943 and rs2032586 SNPs of ABCB1 gene may be the reason of mRNA stabilisation which may lead to gene overexpression in gastrointestinal cancers

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Background: One of the major mechanisms for drug resistance is associated with altered anticancer drug transport, mediated by human-adenosine triphosphate binding cassette (ABC) transporter superfamily proteins. The overexpression of MDR1 (Multi Drug Resistance 1) by multidrug-resistant cancer cells is a serious impediment to chemotherapy. In our study we have studied the possibility that the mechanism of MDR1 overexpression is caused by structural single-nucleotide polymorphisms (SNPs).
Materials and Methods: A total of 101 MDR1 cases and 100 controls were genotyped with SSP-PCR (Sequence Specific Primer). Gene expression was evaluated for 70 MDR1 cases and 54 controls by Real Time PCR. The correlation between the two groups was based on secondary structures of RNA were predicted by bioinformatics tool (Rn) (Vienna RNA Fold Server).
Results: The results of genotyping showed that among 3 studied SNPs, rs28381943 and rs2032586 have significant difference between MDR1 cases and control group but there were no differences in the two groups for C3435T. The results of Real Time PCR showed overexpression of ABCB1 when we compared our data with each of the genotypes in average mode. Prediction of secondary structures in the existence of 2 related SNPs (rs28381943 and rs2032586) showed that the amount of ΔG for original mRNA is higher than the amount of ΔG for the two mentioned SNPs.
Conclusions: We have observed that 2 of our studied SNPs (rs283821943 and rs2032586) may affect the overexpression of MDR1 gene, and the observed overexpression may be due to mRNA stability while this was not the case for C3435T.
No conflict of interest.

2206 POSTER

TRP genes family expression in colorectal cancer and its relationship with prognostic factors

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Background: Colorectal cancer (CC) is the most common cancer of the gastrointestinal tract. Different factors are effective in the development of CC. With the discovery of that TRP (transient receptor potential) genes family is an important component of calcium channel, about 30 members of the family of TRP ion channel in mammals have been determined up to the present. TRP channels are associated with many pathological conditions like cancer, neurodegenerative and cardiovascular diseases as well as the physiological significance of them. The aim of this study is to investigate TRPM, TRPV and TRPC gene expression levels in tumor tissues of CC patients and to analyze the relationship of expression in tumor tissue of colorectal cancer with other known prognostic factors.
Material and Methods: In this study, 93 CC patients whose follow-up and treatment realized in Medical Oncology Department of Gaziantep University Medical Faculty Hospital were analyzed retrospectively. Level of TRP gene expression in paraffin blocks of normal and cancerous colorectal tissue samples of 93 patients were studied at the level of mRNA with Real-time PCR.
Results: According to Real-time PCR results realized to determine levels of mRNAs obtained from normal and cancerous colorectal tissues of 37 female and 56 male patients diagnosed with colorectal cancer, expressions of TRPV3, TRPV4, TRPV5, TRPM4 and TRPC6 genes in tumor tissue were detected lower when compared to normal tissue (p < 0.05). When expression levels of other TRP genes in tissues were compared, any significant difference wasn't found (p > 0.05). There was no meaningful difference between prognostic factors and gene expressions of tumor tissues statistically (p > 0.05).
Conclusions: Expression of many proteins in cancer cells compared to normal cells increases or decreases. In CC, TRPV3, TRPV4, TRPV5, TRPM4 and TRPC6 genes of which expression in cancerous tissue decreases may be thought as potential genes contributing to tumorigenesis. To verify this hypothesis, it should be supported with further studies.
No conflict of interest.

2207 POSTER

MicroRNA-124 suppresses colorectal tumor progression via targeting KITENIN, a metastasis-enhancing protein

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Background: MicroRNAs (miRNAs) are increasingly implicated in modulating the progression of various cancers. Although there is emerging evidences that some miRNAs can function as oncogenes or tumour suppressors, the regulation of colorectal cancer (CRC) progression by miRNA is not fully understood. Several lines of reports demonstrated the potential tumor suppressor role of miR-124, however, it remains unclear which target genes are responsible for the role of miR-124 on progression of CRC and whether miR-124 plays a certain role in the suppression of colorectal tumorigenesis. KITENIN (KAI1 C-terminal interacting tetraspanin) acts as a major component of functional KITENIN complex promoting CRC cell invasiveness. We previously reported that KITENIN is highly expressed in sporadic human CRC tissues, however, the underlying regulation mechanisms of aberrant expression are not clearly understood.
Methods: We tried to identify which miRNAs modulate the expression of KITENIN, using luciferase assay and with computational prediction of miRNA targeting KITENIN.
Results: We here identified several miRNAs and one of them is miR-124. miR-124 negatively regulated KITENIN expression through binding to the 3'-untranslated region of KITENIN. We further examined whether increased expression of miR-124 affects colorectal tumor progression through targeting KITENIN. Forced expression of miR-124 was found to suppress the migration and invasiveness of various CRC cells. Overexpressed miR-124 also inhibited tumor growth in a mouse xenograft model.
Conclusions: These findings provide the experimental evidence to a possible therapeutic effect of miR-124 on suppressing colorectal tumor progression.
No conflict of interest.

2208 POSTER

mTOR activity and mTOR inhibitor sensitivity of colon carcinoma cells and their relation to mTOR complexes

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The constellation of features of PI3K/AKT/mTOR signalling − critical cellular functions (growth and survival), prevalent oncogenic genetic aberrations, consequent therapeutic resistance and its potential reversal − have made the inhibition of this pathway an attractive target for anticancer strategies. The activation of mTOR is associated with growth and progression of a number of cancers, including colorectal cancer. The active form of mTOR kinase exists in two funcionally different complexes (mTORC1 and mTORC2).
We investigated the effect of different mTOR inhibitors (mTORI) on several colon carcinoma cell lines in relation to mTOR complex activity. The in vitro effects on proliferation and apoptosis were monitored by Alamar blue assay and flow cytometry. The expression and activity of mTOR signaling related proteins were studied by immunocytochemistry using Duolink technique and Western-blotting. p-mTOR, p-S6, Raptor and Rictor expression was also analysed by immunohistochemistry (IHC) in more than 100 human

colon carcinoma samples in order to find correlation between clinical and experimental data.
mTOR activity, and C1 and C2 mTOR complex activity was altered in different colon carcinoma cells. mTOR inhibitor (rapamycin, PP-242, NVP-BEZ235) sensitivity correlated to the Rictor to Raptor ratio. Rapamycin alone was less effective in cells with high Rictor expression, as well as in combination with EGFR inhibitors (gefitinib, erbitux). More than 70% of human tumor samples displayed high mTOR activity. Rictor and Raptor IHC showed Rictor overexpression (element of mTORC2) in about 50%, and Raptor overexpression (mTORC1) in 13% of the cases; Rictor and Raptor expression was equal in the remainder of the cases. Low mTOR activity was related to good prognosis. Patients with high mTOR activity and Rictor overexpression had the worst prognosis during 5 year follow up. The majority of colorectal carcinomas have characteristic high mTOR activity, especially in patients with poor prognosis. Targeting mTOR activity may be an additional therapeutical option in these cases. Moreover, we suggest that the evaluation of mTORC1 and C2 related activity in colon carcinomas may help identify patients suitable for adequate mTORI therapy, who can expect longer survival or potential cure with conventional mTORI therapy, and warn if dual inhibitors are required in order to provide therapeutical benefit.
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No conflict of interest.

2209 POSTER

Activation and maturation status of dendritic cells is altered in post-operative colorectal cancer patients

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Background: Dendritic cells (DC) are antigen presenting cells that promote a cytotoxic or tolerogenic immune response against tumour antigens upon migration to lymph nodes. CD40 is a co-stimulatory molecule and a marker for DC activation. Immunoglobulin-like transcript 3 (ILT3) is an inhibitory receptor expressed on DC and negatively regulates their activation. Activation of DC is accompanied by up regulation of the lymph node migration marker C-chemokine receptor7 (CCR7). Previous studies have shown that tumour cells and microenvironment have both direct and indirect effects on the ability for DC to promote cancer specific cytotoxic immune response. However, little is known about the activation and phenotype status of systemic DC in postoperative colorectal patients. We aimed to determine changes in systemic DC phenotype after a curative resection of CRC.
Material and Methods: Blood samples were obtained from 7 CRC patients pre-operatively and 4 to 6 weeks after operation, prior to chemo or radiotherapy. All patients had same tumour staging and no significant medical co-morbidity. Peripheral blood mononuclear cells were separated and DC identified as HLA-DR positive and lineage cocktail (anti-CD3, CD14, CD16, CD19, CD34 and CD56) negative cells. DC were further classified as CD11c+ myeloid (mDC) or CD11c- putative plasmacytoid (pDC). CD40, CCR-7 and ILT3 expression was determined on DC by flow cytometry. Results are the mean $\pm$SED. Paired student *t* test was used for comparison and $p < 0.05$ was considered as significant.
Results: CD40 expression was decreased on mDC and pDC post-operatively from $26.32\pm5.787\%$ to $14.88\pm6.024\%$ ($p = 0.0393$). ILT3 expression increased post-operatively from $45.32\pm9.621\%$ to $72.04\pm7.336\%$ ($p = 0.004$). There were no significant differences in CCR7 expression on DC between pre and post-operation.
Conclusion: We have demonstrated that removal of colorectal tumour alters the phenotype of DC resulting in systemic DC becoming less activated and more immature. Postoperative immunosuppression increases the recurrence and adversely affects the prognosis of cancer patients. Our findings suggest that these changes in CD40 and ILT3 expression may contribute to the general postoperative immunosuppression. Hence, immunotherapy targeting the activation of DC immediately after operation could be a potential tool in the treatment of colorectal cancer.
No conflict of interest.

2210 POSTER

Influence of sodium butyrate on 18F-FDG uptake in two colon cancer cell lines

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Background: Butyrate is a short chain fatty acid (SCFA) and it's produced by decomposition of dietary fiber by intestine's bacteria, being the main energy source of colonocytes. It is related with colon cancer mostly because of its capacity to inhibit histone deacetylases (HDAC), and inducing apoptosis and differentiation in contrast to normal cells. Some studies suggest that the Warburg effect may explain why the cancer cells use preferentially glucose rather than other energy sources, inducing butyrate accumulation in the tumor cells. Other studies also suggest that butyrate can be used by tumor cells as energy source when glucose levels are reduced. The aim of this study is to evaluate if butyrate interferes with uptake of the radiolabeled glucose analogue (^{18}F-FDG) and the increased glycolysis in colorectal cancer cells.
Methods: WiDr and C2BBe1 cell lines were cultured in DMEM with low glucose content (5mM). To perform the uptake studies, cells were incubated with or without butyrate, 3mM for WiDr cells and 15mM for C2BBe1 cells (values chosen taking into account the respective IC_{50}) during 1 and 4 hours, before the incubation with ^{18}F-FDG (25 μCi/ml). At 5, 30, 60, 90, and 120 minutes, duplicate samples of 200 μl of cell suspension were collected for eppendorfs with iced phosphate buffer solution (PBS). The samples were centrifuged at 10000rpm for 60 seconds, separating the pellet from the supernatant. In order to calculate the ^{18}F-FDG uptake percentage, radioactivity of both fractions was measured in a well-type gamma counter, in counts per minute (CPM).
Results: ^{18}F-FDG uptake is greater in WiDr cells than in C2BBe1 cells, being the uptake at 120 minutes of $6.91\%\pm0.15\%$ and $5.05\%\pm0.15\%$, respectively. In both cell lines, we observed that incubation with butyrate decreases the ^{18}F-FDG uptake. This difference was more pronounced in WiDr cell line however, in C2BBe1 cells there seems to be a trend for a decrease in tracer uptake with increasing exposure time to butyrate.
Conclusions: Our study suggests that butyrate can reduce the ^{18}F-FDG uptake and may interfere with the Warburg effect which influences the agressiveness of the tumor. This also suggests that butyrate can act in cancer cells in an advanced phase of development, and could contribute to the understanding of the importance of our diet in advanced tumor stages.
No conflict of interest.

2211 POSTER

Pharmacogenetic analysis of tegafur-uracil (UFT) plus leucovorin (LV) with preoperative chemoradiation for locally advanced rectal cancer (LARC)

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Background: Tegafur-uracil (UFT) is one of oral fluoropyrimidines and has shown its efficacy on colorectal cancer. Various doses (300–400 mg/m^2/day) of UFT have been tried for preoperative chemoradiation (preop CRT) of locally advanced rectal cancer (LARC). This study aims to evaluate efficacy of higher dose (400 mg/m^2) of UFT plus leucovorin (LV) with preop CRT and to explore the impact of germline polymorphisms concerning metabolism and transmembrane transport of tegafur on clinical outcome.
Materials and Methods: A total of 88 patients (pts) with MRI-defined cT3 or cT4 were enrolled to this phase II trial and were given UFT 400 mg/m^2/day and LV 90 mg/m^2/day for 5 days a week during preop CRT (50.4 Gy/28 fractions). Genomic DNA was extracted from peripheral blood, where genotyping was done for CYP2A6 (*4, *7, *9 and *10), OPRT G638C, and three genotypes of ABCB1 as C1236T, C3435T, and G2677T.
Results: One pt refused surgery after preop CRT and 87 who underwent curative surgery were analyzed for efficacy outcome; circumferential margin was positive ($\leqslant$1 mm) in 12 (13.8%) and pathologic complete response (pCR) was noted in 10 pts (11.5%). For all treated 88 pts, toxicities $\geqslant$ grade 2 included diarrhea (14, 15.9%), abdominal pain (9, 10.2%) anemia (9, 10.2%) neutropenia (6, 6.8%) and stomatitis (6, 6.8%). Pts with OPRT 638 CC genotype experienced significantly more frequent grade 2−3 diarrhea and any adverse events (AE) $\geqslant$ grade 3 when adjusted to age, sex, and performance status (table). There was a tendency of increasing pCR rate according to number of variant allele: GG genotype (2/41, 4.9%),

GC genotype (6/38, 15.8%) and CC genotype (2/8, 25%) (p for trend = 0.05). Polymorphisms in CYP2A6 and ABCB1 had no clinical correlation with outcome from UFT/LV-based preop CRT.

Conclusions: Preop CRT with UFT 400 mg/m^2/day with LV was feasible and safe. OPRT 638 CC genotype might be a candidate biomarker predicting toxicity and pathologic response in pts receiving UFT/LV-based preop CRT for LARC.

No conflict of interest.

Toxicity and genotype	Odds ratio	95% Confidence interval	P value
Diarrhea ⩾grade 2			
OPRT 638 GG (n = 41)	1		
OPRT 638 GC (n = 39)	1.96	0.42–9.06	0.389
OPRT 638 CC (n = 8)	10.76	1.50–77.40	0.018
Any AE ⩾ grade 3			
OPRT 638 GG (n = 41)	1		
OPRT 638 GC (n = 39)	0.97	0.28–3.40	0.962
OPRT 638 CC (n = 8)	10.20	1.44–72.13	0.020

2212 POSTER

Outcome in patients with locally recurrent rectal cancer after TME with and without neoadjuvant radiotherapy for the primary rectal tumor

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Background: The application of neoadjuvant radiotherapy (nRTx) for rectal cancer became widespread after the Dutch TME trial demonstrated that nRTx followed by total mesorectal excision (TME) reduces local recurrence rates. However, this widespread use of nRTx followed by TME introduced the problem of treating locally recurrent rectal cancer (LRRC) after nRTx and TME. Primary tumor resection by TME may lead to recurrences that are not limited to the anatomical compartment lined by the visceral rectal fascia and when neoadjuvant radiotherapy was administered for the primary tumor, the radiation dose for the treatment of LRRC is limited. These factors render radical resection of these local recurrences more demanding than resection in patients who did not receive nRTx or TME for their primary tumor. However, few data exist on the outcome of the surgical treatment of this specific 'type' of LRRC and the influence of nRTx for the primary tumor on the outcome is unclear.

Methods: All patients treated for LRRC between January 1996 and July 2012 were retrospectively analyzed. The outcome of the surgical treatment of LRRC in patients who received nRTx and TME for the primary tumor was compared with the outcome of patients who had TME without nRTx for the primary tumor.

Results: During this period, 139 patients underwent surgery for LRRC; 93 of these patients underwent curative resection of LRRC after TME for the primary tumor. Twenty-eight patients received nRTx for the primary tumor, while 65 patients did not receive nRTx for the primary tumor. Both groups were comparable with respect to the baseline and demographic characteristics. There were no significant differences in the number of incomplete resections or peri-operative morbidities. Although, there tend to be more R1-resections in patients treated with nRTx for the primary tumor (64% versus 46%, p = 0.11). There was no significant difference in 5-year overall survival (43% vs. 28%, p = 0.81), recurrence-free survival (48% vs. 55%, p = 0.50) and disease-free survival (40% vs. 27%, p = 0.59). A significant difference in distant metastasis-free survival was found in favor of patients who received nRTx for the primary tumor (66 vs. 39%, p = 0.05).

Conclusion: Surgical treatment of resectable LRRC after nRTx and TME for the primary tumor is feasible and can result in sustained local control and overall survival. Patients who received nRTx for the primary tumor do not have a poorer outcome than patients who did not.

No conflict of interest.

2213 POSTER

Patterns of recurrence following complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer

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Background: Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has an established role in the multidisciplinary treatment of metastasized colorectal cancer. In selected patients long term survival is achieved in 40%. Nonetheless, many patients suffer from recurrence after CRS+HIPEC. The aim of the study was to describe the recurrence pattern following CRS+HIPEC, including anatomical location, treatment and outcome.

Methods: A prospective database of all patients treated with CRS+HIPEC between April 2005 and March 2013 was retrospectively analyzed with special interest in the following parameters: disease recurrence and location, interval between HIPEC and recurrence, treatment, and survival. Survival and the prognostic value of several clinical and histopathological parameters was calculated using Kaplan–Meier method and Cox Regression.

Results: In total 139 patients with colorectal cancer (no PMP or appendiceal cancer) and peritoneal carcinomatosis were treated with complete CRS (i.e., no residual macroscopic disease) and HIPEC. After a median follow-up of 21.4 months, 74 patients (53%) had reported recurrence. The median interval between HIPEC and recurrence was 12.4 months (range 3−54). 33 patients (45%) developed isolated peritoneal recurrence, 20 patients (27%) isolated distant metastases and 21 patients (28%) peritoneal recurrence combined with distant metastases. Of these patients 26 were treated surgically with curative intent. Pulmonary metastasectomy was performed in 7/10 patients with isolated pulmonary recurrence, partial liver resection in 5/9 patients with isolated liver recurrence, repeat cytoreductive surgery with or without HIPEC in 14/33 patients with isolated peritoneal recurrence, and in one patient with distant and peritoneal recurrence a pulmonary metastasectomy and a repeat CRS+HIPEC procedure was performed. The overall survival was significantly longer in patients with resection of recurrence vs. no resection with a median overall survival of 11 months vs. 43 months after diagnosis of disease recurrence (P<0.001). Additionally, a longer interval between HIPEC and recurrence was significantly related to a improved overall survival after disease recurrence (P<0.001). Other clinical and histological parameters were not significantly related to survival.

Conclusion: Disease recurrence after cytoreductive surgery and HIPEC is common, however, surgery in a selected patient group may be beneficial and result in long-term survival.

No conflict of interest.

2214 POSTER

Clinical complete response after neoadjuvant chemoradiotherapy (nCRT) of rectal cancer: A key end point to increase conservative treatment − findings from the ACCORD12 randomized trial

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Background: During the ACCORD12 randomized trial, a specific evaluation of the clinical tumor response of the rectal cancer following nCRT was performed before surgery. The correlation of this end point with patient characteristics and treatment outcomes is reported.

Material and Method: Between 2005 and 2008 a randomized trial comparing 2 different regimens of nCRT (cap45: capecitabine + 45 Gy/5w vs capox50: capecitabine + 50 Gy/5w + oxaliplatine) included 598 patients. A careful evaluation of the clinical response of the tumor was planned 5 weeks after the end of CRT just before surgery. Rectoscopy and digital rectal examination (DRE) was used to establish a specific score of clinical response adapted from the RECIST criteria: Clinical complete response: no visible or palpable tumor, supple rectal wall (cCR); partial response (PR), stable disease (ST), progressive disease (PROG). This score was correlated with patients characteristics, type of surgery, pathological response and 3-year clinical outcome.

	cCR (16 pts)	PR (137 pts)	ST + PG (48 pts)
Sphincter. Saving Surgery	13* (87 %)	105 (76 %)	33 (68 %)
yp CR (pTo)	11 (73 %)	21 (15 %)	6 (12 %)
CRM R1	0 (0 %)	4 (3 %)	4 (9 %)
DFS 3 y	87.5%	77.6%	65%

*11 Ant. Resection; 2 local excision; + one patient watch and wait only.

Results: Clinical response was evaluable in 201 patients. Score was as follow: cCR: 8%, PR: 68%, ST + PROG: 24%, PROG: 4%. There was a trend toward more cCR in the capox 50 arm (9.3% vs 6.7%). When analysed for the whole cohort of 201 patients, cCR was associated with early T stage (T2: 28% vs T3−4: 6%). cCR was associated with sphincter saving surgery, ypCR, CRM R1, disease free survival (table). In 3 patients with cCR a rectal preservation was possible (2 local exicision-one watch and wait strategy) with the 3 patients alive and well between 3 and 5 years follow up.

Conclusion: cCR appears as a very important end point after neoadjuvant treatment of rectal cancer. It is correlated with increased pCR, negative CRM, 3 year DFS and it is probably influencing the chance of a sphincter saving procedure. Rectoscopy and DRE should be performed after neoadjuvant CRT to evaluate the tumor response and adapt the surgical technique.
No conflict of interest.

2215 POSTER

What about the young rectal cancer patient?

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Background: Multiple studies have shown a rising incidence of young patients with rectal cancer. These patients often present with more advanced stage of disease and different tumor characteristics, resulting in possibly worse oncological outcome. However, studies with an interest in tumor characteristics and outcome of young rectal cancer patients are scarce.
Methods: For this study population based data of the Netherlands Cancer Registry (NCR) were used. Patients with rectal or rectosigmoid cancer diagnosed between 1989 until 2009 were included. Younger patients (⩽40 years) were compared to middle aged patients (41−70 years) with respect to tumor characteristics, treatment and outcome. Patients older than 70 years were excluded from this analysis.
Results: A total of 37,639 patients were included (⩽40 years n = 1146). The young presented more often with pT4 stage (6.0% vs. 5.1%), and less often pT3 (46.3% vs. 47.2%) and pT1−2 stage (30.9% vs. 33.9%) compared to middle aged patients (p = 0.04). Younger patients presented more often with pN1 (23.3% vs. 16.9%) and pN2 stage (22.1% and 11.8% p < 0.001) and more often with metastatic disease at presentation (22.8% vs. 19.2% p = 0.003). Tumour histology of younger patients was less often an adenocarcinoma (82.1 vs. 88.0%) but more frequently mucinous type carcinomas (10.4% vs. 8.8%), signetcell carcinomas (2.5% vs. 0.6%) and carcinoid tumors (2.5% vs. 0.3) (p < 0.001). In the young the histopathological grade of differentiation was more often poorly differentiated (G3) but less often moderately differentiated (G2) (p = 0.001). The young were more often treated with radiotherapy (51.7% vs. 38.4% p = 0.028) or chemotherapy (48.5% vs. 24.7% p < 0.001) but received less curative rectal surgery (77.0% vs. 82.7% p < 0.001). The overall 5-year survival rate was better for younger patients (57% vs. 53% p < 0.001) and survival of both young and middle-aged patients improved significantly over time. Also stage-specific survival was better for younger patients, except for stage IV rectal cancer.
Conclusions: This study shows that the overall survival of younger patients is the same as in older patients and have improved over time, despite the fact that younger patients present with more aggressive tumors and higher disease state. The standard treatment for younger patients seems therefore appropriate. As earlier detection might be more effective than more aggressive treatment, we have to focus on improving awareness amongst (primary) health-care providers.
No conflict of interest.

2216 POSTER

Overall survival, resection of liver metastases and response to treatment in patients with initially unresectable colorectal liver metastases and following treatment with FOLFOX/cetuximab or FOLFIRI/cetuximab (CELIM-study)

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Background: Initially unresectable CRC liver metastases can potentially be resected following active medical treatment. Cetuximab plus chemotherapy has been shown to increase the rates of tumor response and resection of liver metastases (Van Cutsem et al., JCO 2011).
Methods: Patients (pts) with technically non-resectable and/or with >4 liver metastases were randomized to receive FOLFOX/cetuximab (arm A) or FOLFIRI/cetuximab (arm B). Resectability was evaluated every 2 months. Liver resection was offered to those patients who became resectable. K-ras and b-raf status were evaluated retrospectively. A blinded surgical review was performed to analyze resectability according to imaging criteria. Data on tumor response and resection were reported earlier (Folprecht et al, Lancet Oncol 2010, NCT00153998). Overall and progression free survival were analyzed in December 2012.
Results: Between Dec 2004 and March 2008, 56 pts were randomized to arm A, 55 to arm B. For the current analysis, 109 pts were evaluable for overall survival (OS), and 106 patients for PFS. The median OS was 35.7 [95% CI: 27.2–44.2] months (arm A: 35.8 [28.1–43.6], arm B: 29.0 [16.0–41.9], HR 1.03 [0.66–1.61], p = 0.9). The median PFS was 10.8 [9.3–12.2] months (Arm A: 11.2 [7.2–15.3], Arm B: 10.5 [8.9–12.2], HR 1.18 [0.79–1.74], p = 0.4). Patients with R0 resection had a better OS (median: 53.9 [35.9–71.9] vs. 27.3 [21.1–33.4] mo, p = 0.002) and PFS (median 15.4 [11.4–19.5] vs. 8.9 [6.7–11.1] mo, p < 0.001) than patients without R0 resection. The trend to a longer OS with R0 resection was confirmed in the subgroup of patients who achieved a PR/CR (median 54.6 [29.2–79.9] vs. 41.6 [31.0–52.3], n.s.). The 5 year survival in all R0 resected patients is 46.2%.
Resectability according to the surgical imaging review after treatment (HR 0.50 [0.29–0.85]) had a significant influence on overall survival, in contrast to baseline imaging (HR 0.77 [0.42–1.41]). In a multivariate analysis, k-ras status at baseline, response to treatment and R status were significant factors for overall survival.
Conclusions: This study confirmed a favourable long term survival of selected patients with initially 'non-resectable' CRC liver metastases treated in a multidisciplinary approach and the influence of both, efficacy of systemic treatment and resection of liver metastases.
Conflict of interest: *Ownership: None. Advisory board: Roche/Genentech, Merck, Amgen, Sanofi-Aventis, Lilly, Bayer, Bristol-Myers Squibb, Pfizer. Board of directors: None. Corporate-sponsored research: This study was supported by Merck, Pfizer and Sanofi-Aventis. Other substantive relationships: Speaker honoraries from Roche/Genentech, Merck, Amgen, Sanofi-Aventis, Lilly, Bayer, Bristol-Myers Squibb, Pfizer*

2217 POSTER

Prognosis and value of adjuvant chemotherapy in stage III mucinous colorectal carcinoma

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Background: Colorectal mucinous adenocarcinoma (MC) is reported in 10−15% of cases with colorectal cancer and has been associated with impaired prognosis compared to non-mucinous adenocarcinoma (NMC). Response to palliative chemotherapy is poor in advanced disease, but the benefit of adjuvant chemotherapeutic treatment has never been assessed in large patient groups. This study analyses overall survival of mucinous colorectal cancer patients and efficacy of adjuvant chemotherapy in terms of survival in patients following radical resection for mucinous colon cancer.
Patients and Methods: This population-based study involved 27,251 unselected patients diagnosed with colorectal carcinoma between 1990 and 2010. Clinicopathologic data was recorded prospectively and included additional variables concerning comorbidity and socio-economic status. A meta-analysis of published data for MC patients treated with palliative and adjuvant chemotherapy was conducted.
Results: MCs were found in 12.3% (N = 3,052) of colorectal tumours with a different distribution compared to NMC, with only 24.4% located in the rectum and 54.3% in the proximal colon (P<0.0001). NMCs were more often classified as stage I disease (P<0.0001). After adjustments for covariates, mucinous histology was associated with a higher risk of death only when located in the rectum (HR 1.28; 95% CI 1.17–1.40). Multivariate regression analysis showed a similar response to adjuvant chemotherapy for stage III MC and NMC patients. A meta-analysis demonstrated a poorer response to chemotherapy in the palliative setting (HR 1.67; 95% CI 1.39–2.00), but not in the adjuvant setting.
Conclusions: Based on its histological appearance and its clinico-pathologic features MC may be considered a distinct entity with a

predominant right sided location. Mucinous histology has no impact on prognosis, except when the tumour is located in the rectum. Despite lower response to palliative chemotherapy in MC, there is no difference in the efficacy of chemotherapy between MC and NMC in the adjuvant setting. Therefore, current adjuvant treatment recommendations should not take histology into account.
No conflict of interest.

2218 POSTER

Accurate identification of complete responders after CRT for rectal cancer with endoscopy and MRI

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Background: Chemoradiotherapy (CRT) for rectal cancer leads to complete tumour response (CR) in up to 15−25%. Accurate identification of a CR is necessary when less invasive treatment is considered (i.e. local excision or wait-and-see policy). Standard imaging consisting of T2-weighted (T2W) MRI and endoscopic ultrasound (EUS) cannot accurately identify a CR. Aim was to evaluate the accuracy of [1] endoscopy and [2] MRI including diffusion weighted imaging (DWI) for identification of a CR and compare it to standard MRI.
Materials and Methods: 49 patients who underwent CRT followed by response evaluation (standard MRI including DWI and endoscopy) 8 weeks after completion of CRT, were retrospectively included. One experienced reader scored [1] the standard T2W images followed by [2] the MR images including DWI. A second reader scored the endoscopy images. Readers were blinded for histology and each other's results. Scoring was performed with a confidence level score (0=definitely residual tumour, 4=definitely CR) and results were compared with histology (CR vs non-CR).
Results: Of the 49 patients, 31 had residual tumour and 18 had a CR. The AUCs for standard MRI, standard MRI + DWI, and endoscopy were 0.71, 0.78, and 0.88 respectively. Corresponding sensitivities and specificities were 39% and 87% for T2W-MRI, 39% and 93% for T2W+DWI, and 67% and 97% for endoscopy. When a combination of standard MRI + DWI with endoscopy was used the highest accuracy was reached: 0.91.
Conclusion: Endoscopy is more accurate in identifying a CR after CRT than standard MRI (+/−DWI). With a higher sensitivity, endoscopy corrects for understaging of a CR with MRI. MRI remains crucial to evaluate the presence of any extramural residual tumour and/or involved nodes. A combination of endoscopy and MRI+DWI is therefore recommendable to identify patients with a CR after CRT, making less invasive treatments after CRT feasible.
No conflict of interest.

2219 POSTER

Predictors of response and prognosis in patients with rectal adenocarcinoma who received preoperative chemoradiotherapy [CRT]: Biopsy specimens obtained one week after starting CRT are reliable factors

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Background: Preoperative chemoradiotherapy (CRT) for locally advanced rectal adenocarcinoma significantly reduced local recurrence. Patients with a marked histological response to CRT have been reported to reveal good oncologic outcomes. We tested the hypothesis that biopsy specimens obtained soon after the start of CRT can be used as predictive factors.
Subjects and Methods: The study group comprised 119 patients with cT3/T4, Nx, M0 or cT2, N+, M0 adenocarcinoma of the middle or lower rectum who received preoperative CRT from 2000 through 2012. Preoperative radiotherapy in a dose of 40 to 45 Gy was combined with oral uracil/tegafur (UFT) or S-1 chemotherapy. Surgery was performed 6 to 8 weeks after the completion of radiotherapy. We evaluated histologic findings on hematoxylin and eosin(H-E) staining and immunohistochemical expressions of Ki67, p53, p21, and apoptosis in biopsy specimens obtained one week after starting CRT. These findings were contrasted with the histologic response, the degree of tumor shrinkage and prognosis. Tumor Regression Grade 1 and 2 were defined as marked histologic regression.
Results: Twenty-one patients (17.6%) had a pathological complete response. The rates of histologic marked regression were as follows: 64% in patients with moderate changes and 20% in those with mild changes on H-E stained biopsy specimens; 61% in apoptosis-positive patients and 34% in apoptosis-negative patients; and 52% in p21-positive patients and 27% in p21-negative patients. Histologic marked regression rates were significantly higher in positive cases ($p < 0.01$, $p < 0.01$, and $p < 0.01$, respectively).
Tumor shrinkage rates from MRI volumetry were 77± 15% in patients with moderate changes on H-E stained specimens and 67±18% in those with mild changes. ($p < 0.01$) Tumor shrinkage rates were significantly larger in patients with apoptosis positive and with p21 positive expression as compared to those with apoptosis negative and with p21 negative expression, respectively.($p < 0.01$, $p = 0.05$) In 89 patients who received surgery until March 2011 (median follow-up, 44 months), the rates of recurrence-free survival and overall survival at 5 years were 83% and 98% in patients with moderate changes on H-E stained specimens, respectively, as compared with 62% and 85% in patients with mild changes. Patients with moderate changes on H-E stained specimens had better recurrence-free and overall survivals than those with mild changes ($p = 0.04$ and $p = 0.04$, respectively).
Conclusions: In patients with locally advanced rectal adenocarcinoma, histological changes on H-E stained biopsy specimens obtained one week after starting CRT are reliable predictors of response, equivalent to apoptosis and p21 expression on immunohistochemical staining. Histologic changes on H-E stained specimens are related to recurrence-free and overall survivals.
No conflict of interest.

2220 POSTER

Impact of neoadjuvant chemoradiotherapy on long-term results and sphincter sparing rate in distal rectal carcer patients

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Background: Tumor downstaging influenced by preoperative chemoradiotherapy (CRT) might result in higher sphincter preservation rate for low rectal cancer (LRC).
Material and Methods: Between 2006 and 2009, 321 patients with T3−4N0−2 or T2N0−2 adenocarcinoma located in low rectum (below 6 cm), enrolled into the study. 176 received preoperative CRT with total dose 50 Gy, Cisplatin, 5-FU followed by surgery after 5−6 weeks and 145 underwent surgery alone. Chemotherapy scheme was as follows: 5 days prolonged iv infusion 5-FU 350 mg/m^2, next 3 days − Cisplatin 30 mg iv single dose, concurrently with external beam radiation: single dose 4 Gy and followed by dynamic fractionation − daily dose 2.5 Gy divided in 2 fractions up to total dose of 50 Gy. Surgery was performed 5−6 weeks after completion of CRT. All patients had adjuvant chemotherapy (Xelox).
Results: Tumor downstaging was revealed in 66.4% of irradiated patients. Complete and near complete tumor regression according Mandard classification registered in 35.4% (11.4% and 24%, respectively). Average distance from anal verge to tumor increased from 5.0±2.3 up to 5.7±2.1 cm for all RC and from 3.8 to 4.4±1.1 cm for LRC due to regression.
There was increase of sphincter-saving surgery (SSS) rate (57.6% vs 13.2%, $p < 0.0001$) including partial sphincter resection for LRC after CRT compare to surgery. Distal margin was negative in all cases. Postoperative complications developed in 27.6% of irradiated patients and 20.1% after surgery alone ($p > 0.05$). With follow-up median 26 months (3−72) local recurrences developed in 2.4% and 11.4% ($p = 0.0031$), metastases − in 12.2% and 12.1% ($p = 1.0$) and 5-years disease free survival rate was − 75.8% and 57.6% in CRT and surgery ($p = 0.09$) groups, respectively.
Conclusion: Preoperative CRT results in increase of SSS rate for LRC and reduction of local recurrence.
No conflict of interest.

2221 POSTER

Nutrient patterns: a first application to colorectal cancer in the EPIC Study

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Background: Potential benefits of a diet are likely to be due to a combination of nutrients rather than nutrients in isolation. The aim of this study was to investigate associations between nutrient patterns and risk of colon and rectal cancers within a prospective cohort study.
Material and Methods: The present analysis includes 477,312 subjects (~70% women) aged between 25 and 70 years who were recruited between 1992 and 2000 in 23 centers from 10 European countries

participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. The intakes of 23 nutrients were estimated from country-specific baseline dietary questionnaires using the harmonized EPIC Nutrient DataBase (ENDB). Nutrient patterns were derived from Principle Component Analysis (PCA) of log-transformed nutrient densities (excluding alcohol) across all centers adjusting for non-alcohol energy intake. The relationship between each of the retained nutrient patterns (PC scores) and cancer risk was examined for colon and rectal cancers combined and separately, and also by sex. The hazard ratios to develop colon or rectal cancer (and associated 95% CI) were calculated for each PC score using Cox proportional hazard regression and adjusting for a number of relevant confounders.
Results: The first 4 nutrient patterns identified were retained. They explained 67% of the total variance and reflected the following nutrient patterns: (PC1) Animal vs. plant nutrients; (PC2) Vitamins and minerals; (PC3) Non-dairy-vitamin D; and (PC4) Dairy and soy driven nutrients. After adjustments, the HR (per SD of the population) of the association between colorectal cancer and PC2 was 0.92 for men (95% CI: 0.86, 0.98) and 0.95 for women (95% CI: 0.91, 1.00). The HR for PC4 were 0.94 (95% CI: 0.84, 1.04) for men and 0.91 (95% CI: 0.83, 0.99) for women. Similar inverse associations were found with colon cancer, but not with rectal cancer. PC1 and PC3 were not associated with risk of colon or rectal cancer.
Conclusions: A nutrient pattern high in vitamins and minerals appears to be associated with a decreased risk of colorectal cancer in men, while in women similar associations were found for a pattern driven by dairy and soy. Sub-group analyses by anatomical sub-site showed the associations to be driven by the colon.
Acknowledgements: We acknowledge the contribution of all EPIC colleagues to the study and funding by the EC, the Fondation de France and other national funding organizations.
No conflict of interest.

2222 POSTER

Diminishing differences in treatment between colorectal cancer patients with and without diabetes: A population-based study

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Background: Cancer patients with diabetes are less likely to be treated according to guidelines. We assessed changes in patient-, tumour-, and treatment- related variables in colorectal cancer patients with and without diabetes, thereby evaluating the implementation of national treatment guidelines.
Methods: All 17,170 cases of primary colorectal cancer between 1995 and 2010 in the South-Eastern Netherlands were included. The Cochrane-Armitage test and logistic regression analysis were used to analyse trends.
Results: 11,893 patients were diagnosed with colon cancer and 5,277 with rectal cancer, of whom 1,711 (14%) and 609 (12%), respectively, had diabetes at the time of cancer diagnosis. Colorectal cancer patients with diabetes compared to those without were about 5 years older and more often diagnosed with proximal colon tumours (60% vs. 54%, $p < 0.0001$). Chemotherapy administration significantly increased in stage III colon cancer patients with and without diabetes (from 17% in 1995–1998 to 52% in 2007–2010, 36% to 64%, respectively, $p < 0.0001$). However, even in the most recent period and after adjusting for the co-variables age, gender, year of diagnosis, and specific comorbidities, stage III colon cancer patients with diabetes received adjuvant chemotherapy less frequently than those without (OR: 0.8 (95% CI 0.6−1.0) $p = 0.04$). The proportion of stage II/III rectal cancer patients with and without diabetes who underwent radiotherapy was similar in recent years (91% vs. 87%). Furthermore, stage IV rectal cancer patients with diabetes received chemotherapy less frequently and received radiotherapy more often compared to patients without diabetes.
Conclusions: Although colorectal cancer patients with diabetes receive chemotherapy less often, differences in treatment between colorectal cancer patients with and without diabetes are decreasing. A growing knowledge of colorectal cancer care is probably shifting the approach in diabetic individuals towards more aggressive treatment. In future studies, we will investigate the influence of this more aggressive treatment on outcomes in colorectal cancer patients with diabetes.
No conflict of interest.

2223 POSTER

Phase I/II study of capecitabine, oxaliplatin, irinotecan and cetuximab (COI-E regimen) as perioperative treatment of high-risk or borderline resectable colorectal cancer liver metastases (CLM)

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Background: Perioperative treatment of CLM may increase R0 resection, convert borderline resectable disease to curative surgery and improve survival.
Materials and Methods: This phase I/II study aimed to determine the safety and activity of capecitabine, oxaliplatin and irinotecan plus cetuximab (COI-E regimen) as perioperative treatment in pts with contraindication for upfront resection of CLM. Six pts received as first dose level: irinotecan (180 mg/mq) and cetuximab (500 mg/mq) on day 1, oxaliplatin (85 mg/m^2) on day 2 and capecitabine (1000 mg/m^2 orally twice daily) on days 2−6; four biweekly cycles were administered both pre- and post-operatively. Since this was the recommended phase II dose (RP2D), 30 additional pts were enrolled from November 2008. In June 2009, the protocol was amended to enrol only KRAS exons 2−4 wild type. Main inclusion criteria: primary tumour resected; no extraepatic disease; borderline liver resectability with portal vein embolization or two stage epatectomy, involvement of >1 hepatic vein or >4 liver segments; and/or at least one adverse prognostic factor: >4 metastases; CEA >200; synchronous metastases. Primary endpoint: response rate (RR); secondary: R0 resection; safety; pathological response; relapse-free survival (RFS) and overall survival (OS).
Results: The RP2D was identified at the first level, due to occurring of G3 diarrhoea in 1/6 pts. Overall, 36 pts enrolled and 35 evaluable for response. RR was 86% (all PR), with 4 (11%) SD and 1 (3%) PD. Surgery with curative intent was performed in 33 pts (3 awaiting surgery) and R0 resection was achieved in 26 (79%), in addition with radiofrequency ablation in 2. Pts characteristics: M/F: 23/13, median age 58 yrs (range 35−72), synchronous CLM 28/36 (78%), number of CLM 1/2−4/>4 in 15 (42%)/14 (39%)/7 (19%), KRAS mutation 8/36 (22%), N+ hilar nodes 1/33 (3%), N+ at primary 25/36 (69%), CEA >200 2/36 (6%), extrahepatic disease 5/33 (15%: 2 extraregional nodes, 2 peritoneal carcinosis, 1 second primary). At a median follow up of 40 months, median RFS was 12.3 mos. OS and safety data will be presented at the Meeting.
Conclusions: Biweekly COI-E is feasible and active. The regimen is well suited for liver downstaging in KRAS wild type CLM before curative surgery.
No conflict of interest.

2224 POSTER

Similar survival outcome of locally advanced proximal and distal rectal cancer for patients treated in a specialized cancer center

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Background: Distal rectal cancer (DRC) that requires an abdominoperineal resection (APR), remained largely out of focus in the implementation of total mesorectal excision (TME) which improved outcome for patients with rectal cancer. DRC still has a worse prognosis compared to proximal rectal cancer (PRC), due to a high percentage of positive circumferential resection margins (CRM), resulting in a higher local recurrence rate and worse survival outcome. In this study we investigate whether the outcome of DRC can be brought to a similar level as PRC when the treatment is performed in a specialized cancer center.
Materials and Methods: Patients with advanced (T3 and T4) primary PRC and DRC treated between 1−1–2005 and 31−12–2010 in the Netherlands Cancer Institute, were analyzed for CRM involvement and survival outcome. A tumor located 5 cm or less from the anal verge was considered to be DRC, whereas higher situated tumors were considered to be PRC. Patients received preoperative (chemo)radiotherapy, except those who previously had radiotherapy of the pelvis, and had surgery. Data were collected on operative details, histological results, postoperative morbidity and mortality and long-term outcomes. Determinants of recurrence and survival were

examined using Kaplan–Meier survival curves and Cox regression analysis. Patients with distant metastasis at time of surgery were excluded from analysis for disease free survival.
Results: 102 patients with advanced PRC and 92 patients with advanced DRC were included. Median follow-up time was 37 months. After surgery CRM involvement was observed in 14/93 (15.1%) of the patients with PRC and in 16/87 (18.4%) of the patients with DRC (P = 0.501). The 3- and 5-year overall survival rates were 71% and 68% for PRC versus 78% and 67% for DRC (P = 0.600), the 3- and 5-year disease free survival rates were 70% and 57% for PRC and 67% and 55% for DRC (P = 0.426). Both the univariate and multivariate regression analyses on overall survival showed no difference between proximal and distal rectal cancer (P = 0.600 and P = 0.344).
Conclusion: Treatment in a specialized cancer center can reduce CRM involvement and recurrence rates for advanced distal rectal cancer, with improvement of survival outcomes similar to that of advanced proximal rectal cancer.
No conflict of interest.

2225 POSTER

The level of carcinoembryonic antigen (CEA) influences the pathological complete response after preoperative chemoradiotherapy in locally advanced rectal cancer

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Background: The ACE level after treatment is independent adverse factor in advanced colorectal cancer. We investigated the meaning of ACE as a predictor of pathologic complete response in patients with rectal cancer who receive preoperative chemoradiotherapy.
Material and Methods: In this retrospective analysis of patients treated from May 2005 to October 2012, included 253 patients with locally advanced rectal cancer with a mean age of 55 years (range 18−90), 57% male and 43% female, located in lower third in 58% (n = 147) medium 31% (n = 78) and superior in 11% (n = 27), with a medium length of 6 cm tumor. ACE level was determined in 237 and were <10 ng/dl in 154 cases (65%) and >10 ng/dl in 83 cases (35%). All patients received preoperative treatment with concomitant chemoradiotherapy and subsequently measured with endoscopy and biopsy followed by radical surgery (in 53%).
Results: The results are presented in the table.

	ACE 0−10 ng/dl	ACE >10 ng/dl
Number	154	83
Radical surgery	82 (53%)	44 (53%)
Pathologic complete response (with radical surgery)	23/82 (28%)	7/44 (16%)
Palliative surgical	6 (4%)	9 (11%)
Progression at QT-RT	11 (7%)	10 (12%)
No acept radical treatment, post-QT-RT*	45 (29%)	17 (20%)
Complete response with biopsy, without radical surgery*	39/45 (87%)	11/17 (65%)

Conclusions: In patients with rectal cancer who receive neoadjuvant concomitant QT-RT, ACE level pretreatment above 10 ng/ml may be a predictor of pathologic complete response. However, it requires a long-term monitoring and multivariate analysis.
No conflict of interest.

2226 POSTER

Long term outcome of pathological complete response patients after neoadiuvant therapy for locally advanced rectal cancer: Monoistitutional prospetictive trial

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Background: In the European randomized trials of neoadjuvant CRT the rate of complete response ranged from 11−16% and was significantly greater that for neoadjuvant radiotherapy alone. A favorable prognosis was observed for complete pathologic response after preoperative therapy in patients with locally advanced rectal cancer. The aim of our analysis was verify whether yPCR predicts a favorable outcome.
Patients and Methods: 370 patients with locally advanced low and mid rectal cancer underwent neoadjuvant chemoradiation at the Surgical Department of University Vita-Salute San Raffaele of Milan from January 1998 to December 2011. All patients were identified from our prospective Rectal Database. Eligibility criteria included locally advanced rectal cancer with no evidence of distant metastases at the time of the diagnosis and evidence of ypCR after the neoadjuvant treatment. All patients received the same neoadjuvant treatment with 5-FU and Oxaliplatin. After a median interval of 10 weeks after complatation of neoadjuvant treatment patients underwent a radical resection according to the principles of TME. Standard pathological tumour staging of resected specimen was performed according the AJCC Cancer staging Manual (7th edition) The pCR was defined by no evidence of viable tumour cell on pathologic analysis. Local recurrence was defined as clinical, radiological or pathological evidence of tumour in any other site. The time to last follow up, local recurrence, or death was measured from the time of radical resection. Statistical analysis was performed using SPSS (version 15.0; SPSS Inc Chicago, IL) Recurrence free survival and overall survival were estimated using the Kaplan Meier method, and differences between survival curves were determinated by using the long rank test. A P value of <0.05 was considered statistically significant.
Results: 61 patients had a complete response and 107 patients were not responders. Sphincher preserervation, anteroposterior resection and endoscopic surgery were performed in 57 patients (97.2%). five patients with complete no had surgical procedure. Mean number of examinated lymphnodes was 11.83±8.7. Median follow up was 60 months. In pCR patients no locoregional recurrence occured and distant metastase occured in 4 patients (6.5%). In the no responder group we found 21 (12.7%) local recurrence and 62 (57.9%) patients developped distant metastases The pCR group 5-years overall and disease free survival were 96.6% and 91.4% rispectively.
Conclusions: The improved patological outcome in patients with rectal cancer who achieve a pCR appears related to their significantly decreased rate of distant failure when compared with no down staging patients. To further improve the oncological outcomes and sphincter preservation rates in patients with locally advanced rectal cancer, the molecular mechanism governing the rectal cancer response to preoperative CRT need to be explored.
No conflict of interest.

2227 POSTER

Bevacizumab related complications in rectal cancer patients after neoadjuvant chemoradiotherapy and surgery

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Background: Bevacizumab was the first angiogenesis inhibitor approved for the first-line treatment of metastatic colorectal cancer in combination with intravenous fluorouracil-based chemotherapy. Clinical trial data have indicated that bevacizumab can induce complications. However, published informations regarding the safety of this treatment, especially for patients with rectal cancer already treated by radiotherapy and surgery are still limited.
Methods and Materials: We performed a retrospective evaluation of bevacizumab-associated adverse events from our institutional database. Medical records of these patients were examined for reports of clinicopathological factors, treatment and the safety profile, particularly the targeted adverse events such as proteinuria, bowel perforation, hypertension, fistlae, thromboembolism and bleeding.
Results: Records of patients treated for metastatic rectal cancer from january 2009 to December 2012 were reviewed. One hundred and six patients were identified with a median age of 61 years (range 25−85). Forty six patients (43%) had synchronous metastatis at initial diagnosis. Eighty patients (75%) received preoperative radiochemotherapy, 67 (63%) were operated after neo-adjuvant treatment. Ninety six patients (90%) were treated for metastatic or locally advanced disease with 5-FU, leucovorin regimen associated to irinotecan (FOLFIRI) or oxaliplatin (FOLFOX). Bevacizumab was associated to chemotherapy in 60 patients (62%). On average, bevacizumab was initiated 8 months after the initial operation; complications occurred 12 months after starting bevacizumab. The most common bevacizumab-related toxicity was fistulae formation in 9 patients (15%) followed by venous thromboembolic (VTE) events in 6 patients (10%). Fistulae were most commonly recto-vesical or recto-vaginal and were managed surgically in 61% of patients. No fistulae occurred in patients treated with chemotherapy alone.
Conclusions: Treatment with bevacizumab does not significantly increase thromboembolic toxicity compared to standard salvage chemotherapy. However, anti-angiogenic effect of bevacizumab may potentialise fistulae

occurrence in patients with rectal cancer already treated by chemoradiotherapy and surgery.
No conflict of interest.

2228 POSTER

Hyperthermic intraperitoneal chemotherapy during primary tumor resection in colorectal cancer limits extent of bowel resection compared to a two-stage treatment

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Introduction: Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is increasingly applied as a standard treatment in patients with synchronous peritoneal carcinomatosis (PC) from colorectal cancer (CRC). Synchronous PC is often diagnosed at laparoscopy or laparotomy scheduled to resect the primary tumor. CRS and HIPEC is a complex multimodality procedure, which is generally performed in specialized referral centers after prior resection. This study compares the clinical outcome of CRS and HIPEC procedures in CRC patients with synchronous PC in whom the primary tumor was previously resected to patients in which the primary tumor was resected in the same procedure as the CRS and HIPEC.
Methods: In total 72 patients (44 males; median age 60 years) with synchronous PC from CRC who underwent CRS and HIPEC between march 2005 and January 2012 were analyzed. Relevant clinicopathologic data were retrospectively retrieved from a prospective database with special interest in bowel continuity, ostomy formation and postoperative complications.
Results: In twenty patients (27.8%) the primary tumor was resected at the HIPEC procedure; fifteen of these patients had non-resective prior surgery, e.g. formation of a deviating ostomy. In the other 52 patients (72.2%) the primary tumor was resected prior to the CRS+HIPEC, with the creation of 37 anastomoses (71.1%). During CRS and HIPEC 22 (59.5%) of these anastomoses were resected. In 12 (54.5%) histopathological assessment of the anastomoses revealed malignancy. The median duration between the first operation and HIPEC procedure was 37 days (range 8−85) in patients with non-resective preceding surgery, which was significantly shorter ($P<0.001$) compared to patients whom already underwent a resection; median 93 days (range 42–175). Complication rates and long-term results were not statistically different between both groups. Anastomotic leakage rates seemed higher in patients with a resection of a previous anastomosis compared to the rest of the patients (31.8% vs. 14.7%). Twenty patients ended with a colostomy after CRS and HIPEC, 10 of these patients had complete bowel continuity after previous resection.
Conclusion: Referral before resecting the primary tumor may prevent extended bowel resections and permanent colostomy. Therefore, it is important to consider CRS and HIPEC in patients with synchronous PC from CRC.
No conflict of interest.

2229 POSTER

Synchronised chemoradiation and systemic chemotherapy for patients presenting with simultaneously primary and metastatic rectal cancer

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Background: Chemotherapy used during chemoradiation is adequate for radiosensitisation but suboptimal for systemic control. The aim of this study was to evaluate tolerability, and local and systemic benefits of a new treatment regimen delivering intensive chemotherapy and radical radiotherapy in a synchronised manner to achieve optimum systemic and local control concurrently.
Materials and Methods: This study reviewed our experience in treating patients presenting with untreated simultaneous symptomatic primary and metastatic rectal cancer. The protocol regimen was 12 weeks long. FOLFOX chemotherapy (oxaliplatin 100 mg/m^2 day 1, leucovorin 200 mg/m^2 day 1, 5-FU 400 mg/m^2 bolus day 1, then continuous infusion 2.4 g/m^2 over 46 hours) was given in week 1, 6, and 11. Pelvic radiotherapy (25.2 Gy in 3 weeks in 1.8 Gy/fr with concurrent oxaliplatin 85 mg/m^2 day 1 and 5-FU continuous infusion 200 mg/m^2/day) was given in week 3−5, and week 8−10. In total, patients received, in 12 weeks, 3 courses of FOLFOX and pelvic radiation 50.4 Gy with concurrent oxaplatin and 5-FU.
Results: Thirty-eight patients were treated in this study. The mean age was 63 (range 33−84) years. 63% were male. Liver, lung, extrapelvic nodes and other metastases were present in 74%, 26%, 13% and 11% of patients, respectively. 37% of patients had more than one site of metastatic disease. Thirty-five patients (92%) completed the 12-week treatment regimen. 95% patients received the planned radiation dose. 92% of patients receiving at least 75% of the oxaliplatin dose; 95% receiving $\geqslant$75% 5-FU. Worst-grade neutropenia were G1 21%, G2 13%, G3 29%, and G4 18%. PET metabolic response (CR+PR) rate was available for 34 patients. Metabolic CR+PR rate for rectal primary was 100%. Overall metabolic CR+PR rate for metastatic disease was 76% (CR 44%). Median survival was 21.5 months. For surviving patients (n = 15), median follow-up was 30 (range 18−57) months. Five patients had resection of primary and liver metastases: 4 remaining alive at the time of this analysis.
There were 11 patients $\geqslant$70 and 27 patients <70 years old: radiation completion rates 91% and 96% respectively; 82% and 96% of patients received $\geqslant$75% of the planned oxaliplatin dose respectively; 91% and 96% of patients received $\geqslant$75% of the planned 5-FU dose respectively.
Conclusions: This regimen provides good local treatment without compromising systemic therapy in patients presenting with rectal cancer and synchronous metastasis. Toxicity and efficacy compare favorably with other regimens. Although oxaliplatin dose reduction is more common in over 70 years group, overall tolerability in elderly patient is satisfactory. This strategy is the subject of an ongoing phase II clinical trial (CHROME B) with the addition of bevacizumab.
No conflict of interest.

2230 POSTER

CRAB trial: Long-term results from a prospective phase II study evaluating neoadjuvant capecitabine, radiotherapy (RT) and revacizumab in locally advanced rectal cancer

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Background: This study evaluated the impact of addition of bevacizumab to concurrent capecitabine based chemoradiotherapy (CRT) in locally advanced rectal cancer (LARC) on pathological complete response (pCR) as primary endpoint and on local control and survival parameters as secondary endpoints.
Methods: Enrolled patients (pts) with MRI-confirmed stage II/III rectal cancer were treated with an infusion of Bev (5 mg/kg) 2 weeks prior to neoadjuvant CRT, followed by Bev 5 mg/m^2 on week 3, 5, 7 and capecitabine 825 mg/m^2 bid including weekends during RT. RT was administered at 50.4 Gy (25$\times$1.8 Gy with boost 3$\times$1.8 Gy, 3D conformal technique), starting on week 3. Total mesorectal excision was scheduled 6−8 weeks after completion of CRT. Four to six cycles of adjuvant capecitabine chemotherapy were recommanded.
Results: Sixty pts were eligible for analysis. Median age was 60 (range: 31−79) years, 64% of pts were male. Twelve pts (20%) presented with stage II and all other with stage III of disease. In 28 patients (46.6%) the tumour invaded the mesorectal fascia. Radical resection was achieved in 58 pts (96.6%). TRG 4 (pCR) was recorded in 5 pts (13.3%) and TRG 3 in 6 pts (15%). Fifty patients (83.3%) received capecitabine postoperatively. Perioperative adverse events (within 30 days after surgery) were recorded in thirty-eight pts (62.3%): delayed wound healing (n = 18, 30%), infection/abscess (n = 12, 20%) and anastomotic leak (n = 7, 11.7%). Six pts required surgical reintervention for leak (n = 3), abdominal abscess (N = 2) and pnevmothorax (n = 1). With longer follow-up, the rate of adverse events was 41.6% (n = 25) and most commonly due to delayed wound healing (n = 9, 15%), followed by rectovaginal or uretro perineal fistula (n = 4, 6.7%), anastomotic leak (n = 2, 3.3%) and intestinal necrosis (n = 2, 3.3%). Six pts (10.0%) required re-operation. Median follow-up was 38 months (8−49). The 3-y overall survuval, recurrence-free survival, disease-free survival and local control were 80.9%, 80.7%, 74.1% and 94.4%, respectively.
Conclusions: This updated long-term analysis indicated that combination neoadjuvant CRT with bevacizumab in LARC resulted in good pathological responses, impressive rate of radical resections and excellent local control. Other long-term efficacy results are promising, safety profile is manageable, but with caution to higher incidence of post-operative complications.
No conflict of interest.

2231 POSTER

Preoperative neutrophil to lymphocyte ratio independently predicts failure to proceed with adjuvant chemotherapy in stage III colorectal cancer

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Background: The role of adjuvant chemotherapy [AC] is established in stage III colorectal cancer but a significant proportion do not proceed with therapy after colorectal resection. Preoperative neutrophil to lymphocyte ratio (NLR) has been found to be an independent negative prognostic outcome marker in patients with colorectal cancer (CRC). In an era of increasingly personalised cancer treatment, we assessed whether NLR might determine the likelihood of proceeding with adjuvant therapy.
Materials and Methods: All patients diagnosed with stage III CRC undergoing curative elective resection from 2006 to 2011 were assessed from a prospective database. Demographics, operative factors and postoperative outcomes were recorded. Data fields were complete for all patients in the study. Univariate analysis determined predictors of failure to initiate AC that were then submitted to multivariate analysis to determine independent predictors. Factors including sex, age, operation type (laparoscopic versus open), 30-day major morbidity [Clavien-Dindo (CD)$\geqslant$3], Enhanced Recovery protocol, TNM stage, ratio of positive lymph nodes, vascular invasion, tumour site, Charlson morbidity score, preoperative albumin and preoperative NLR were assessed. Emergency presentations and operations were excluded.
Results: 271 patients were analysed. Median age of 68.5 years [IQR, 57.25–77.00]. 177 patients (57%) were male. Multivariate regression analysis identified NLR>3 (OR 0.42, (95% CI 0.23–0.78) P = 0.006) and age $\geqslant$65 years (OR 0.13, (95% CI 0.06–0.26); P<0.001) as independent prognostic factors for failure to proceed with AC. NLR>3.0 was significantly associated with age, higher T and N stage and a low pre-operative albumin level.
Conclusions: In this prospective cohort study, preoperative NLR>3.0 and age were independent predictors of failure to proceed to adjuvant chemotherapy: NLR>3.0 was related to >50% reduction in the likelihood of starting therapy. Preoperative NLR may assist clinicians where individual risks need to be considered before initiating adjuvant therapy, particularly in older patients.
No conflict of interest.

2232 POSTER

Neoadjuvant treatment responses as a tumor necrosis grade for patients with rectal cancer

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Background: Neoadjuvant chemoradiotherapy for rectal cancer results in prevention of local recurrence and may achieve sphincter conserving surgery. Association between pathologic response evaluated after radical tumor resection and patient prognosis was well established. The object of this study was to assess the association between the degree of tumor necrosis after chemoradiotherapy and oncologic outcomes.
Patients and Methods: In all, 225 patients with locally advanced rectal cancer (stage II and III by endorectal ultrasonography, CT and MRI) had 50.4 Gy over 5.5 weeks, plus 5-fluorouracil and leucovorin and surgery was performed at 7 to 10 weeks after completion of all therapies. Pathologic tissue necrosis after chemoradiotherapy was reviewed and scored as follows: Grade 0, no response; Grade 1, necrosis or disappearance of tumor cells less than 2/3; Grade 2, necrosis or disappearance of tumor cells more than 2/3; and Grade 3, no viable cells (ypCR). Correlation analysis was performed using Pearson's Chi square or Fisher's exact test, as appropriate. Recurrence-free survival and overall survival were calculated using the Kaplan–Meier method.
Results: This study included cStage II (101 patients) and cStage III (124 patients) rectal cancer patients, and down stage rate was 57.3% and pCR was 16.9%. The pathologic tumor response (pStage 0 v I v II v III) was associated with 5-year RFS (97.4% v 81.5% v 76.6% v 50.0%; p < 0.001). The tumor necrosis (Grade 0 & 1 v 2 v 3) was associated with 5-year RFS (64.4% v 76.8 v 97.4%; p = 0.002).
Conclusions: The tumor necrosis to neoadjuvant chemoradiotherapy is a surrogate marker for recurrence and oncologic outcomes in rectal cancer patients treated with 5 flurouracil and leucovorin neo-adjuvant chemoradiotherapy.
No conflict of interest.

2233 POSTER

Synergistic antitumor interaction between valproic acid, capecitabine and radiotherapy in breast and colorectal cancer cells

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Background: Capecitabine is a pro-drug designed to take advantage of the increased levels of thymidine phosphorylase (TP), a key enzyme for its conversion to 5-florouracil (5- FU), observed in tumors as opposed to normal tissues, potentially allowing for selective cytotoxicity. We have recently demonstrated that the histone deacetylase-inhibitor (HDAC-i) vorinostat induces synergistic antitumour effects in combination with capecitabine by up-regulating, in *vitro* and *in vivo*, in colorectal cancer cells but not in *ex vivo* treated peripheral blood lymphocytes, the mRNA and protein expression of TP (Di Gennaro, Brit J Cancer 2010). Multiple HDACis have been shown to modulate radiosensitivity in preclinical models including valproic acid (VPA). HDACi vorinostat has been recently safely combined with short-term pelvic palliative radiotherapy in gastrointestinal neoplasms including rectal cancers. Based on these data we studied the effects of capecitabine metabolite 5′-deoxy-5-fluorouridine (5′-DFUR) and VPA in combination with radiotherapy in colorectal and breast cancer cells.
Methods: We evaluated the antiproliferative/cytotoxic effects of 5′-DFUR, VPA and/or radiotherapy by sulforhodamine B colorimetric and clonogenic assays. Drugs synergistic interaction was determined by calcusyn software based on Chou and Talalay method. protein, Western blotting analysis of γH2AX and caspase-3 measured DNA damage and apoptosis, respectively. TP knockdown was performed using TP-shRNA.
Results: We demonstrated synergistic/additive antiproliferative and proapoptotic effects of 5′-DFUR in combination with several HDACi, including VPA, in both breast and colorectal cancer cells. TP knockdown experiments confirmed the crucial role of TP protein modulation in the synergism observed. Interestingly, TP protein induction was achieved also at low doses of VPA corresponding to a plasma level between 50 and 100 μg/ml, easily reached in patients treated with common anticonvulsant doses. Radiotherapy further potentiated the antiproliferative effects, DNA damage and apoptosis, induced by 5′-DFUR/VPA combination.
Conclusions: On these bases we recently launched a phase I/II clinical study (V-ShoRT-R3 trial) to explore whether the addition of both VPA and capecitabine to short-course radiotherapy before optimal radical surgery, might increase the pathologic complete tumor regression rate in low-moderate risk rectal cancer patients (EudraCT Number: 2012–002831−28).
No conflict of interest.

2234 POSTER

Pathologic response after long-course or hypo fractionated preoperative radiotherapy in combination with capecitabine versus 5-fluorouracil leucovorin in locally advanced rectal cancer: A retrospective review National Cancer Institute Mexico

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Background: Chemoradiotherapy neoadjuvant is standard treatment in Locally Advanced Rectal Cancer (LARC). Two schemes of preoperative radiotherapy are possible: long course (45–50.4 Gy/25fr) and short course (25 Gy/5fr) both are effective in tumor control; different chemotherapeutic agents concomitant improving local control. The aim of the review is to assess tumoral response in patients who underwent preoperative radiotherapy according two different protocols: long course of 45 Gy/25 fractions and hypofractionated (45 Gy/15fr) concomitant with capecitabine or 5-fluorouracil (5-FU) leucovorin.
Material and Methods: A total of 135 patients with LARC, who received treatment preoperative between 2005 and 2011, were analyzed and performed pathological response. 75 patients were treated with hypofractionated 45 Gy in 15 fractions for fifteen days and 60 received conventional radiotherapy (45 Gy/25fr), simultaneous treatment with 5-FU, leucovorin intravenous or capecitabine 850 mg/m^2 twice a day for fourteen days. Pathological Complete Response (pCR) including downstaging tumour (T)/nodal (N) after surgery.
Results: One hundred and thirty-five patients were identified, with a mean age 53 years, 58 female and 77 men. 25 (19%) patients underwent

colostomy by stenosis over 90%. 64 (47.5%) patients were treated with 5-FU and 71 (52.5%) with capecitabine, four cycles of chemotherapy was mean of treatment. The tumoral pathological complete response was observed in 31 (22.9%) of all patients, 14% vs 9% of the patients treated with hypofractionated and conventionally radiotherapy, the difference was not significant (p = 0.46). A pCR was shown in 13 patients of 5-FU with hypofractionated radiotherapy and 2 patients who received conventional radiotherapy. In the capecitabine group 6 of 31 patients with hypofractionated and 10 of long course (45 Gy/25fr) had a pCR. There was no significant difference in of pathologic complete response between patients who received capecitabine vs 5-FU (pCR: 12.8% vs. 11.1%; p = 0.87).

Conclusions: Preoperative short term radiotherapy and long courses provide local control in rectal cancer, with this retrospective results are according to literature than short-course irradiation appears to be a useful alternative to long-course. These regimes of radiotherapy and chemotherapy with oral or intravenous fluoropyrimidine show effect in the pathological tumor response. However, a prospective study is needed to obtain data on survival and relapse in our population.

No conflict of interest.

2235 POSTER

A prognostic value for lymph node harvest in patients with colorectal cancer?

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The prognosis of patients with colorectal cancer has been associated with the number of lymph nodes that is harvested for pathological staging. The general concept is that the accuray of nodal staging improves with increased lymph node harvest, which might influence oncological outcome. In this study we analyzed if the correlation between lymph node harvest and prognosis is confounded by lymph node size. Additionally we studied the contribution of very small lymph nodes to staging of patients with colon cancer.

Stage I/II colon cancer patients who underwent elective surgery between November 2005 and July 2009 were included from a prospective database from the Gelre Hospital, Apeldoorn, the Netherlands. Lymph node size was determined by long axis measurements on H&E stained slides. We used the Pearson test for the correlation between lymph node size and harvest. To calculate the odds ratio (OR; 95% CI) of metastatic involvement, five categories (<3 mm, 3−6 mm, 6−10 mm, 10−15 mm and >15 mm) were defined. The most common lymph node sizes were used to determine the reference value for logistic regression analyses.

We included 96 stage I/II (pN0) and 55 stage III (pN+) patients in this study. In the N0 patients, a total of 1485 lymph nodes was harvested (measurements were obtained for 92.9%). For N+ patients, a total of 763 lymph nodes was harvested (measurements were obtained for 90.2%). The majority of lymph node diameters ranged between 3 and 6 mm (61.7%). The mean lymph node count for N0 patients who developed recurrent disease was lower than in patients without any recurrence (13 vs. 16 respectively; ns). Concordantly, the mean lymph node size in patients who developed a recurrence was significantly lower than those without recurrence (3.5 mm vs. 4.2 mm respectively, p = 0.008). The Pearson test showed a significant correlation of 0.314 between lymph node size and lymph node count (p = 0.003).

Of all measured lymph nodes (n = 2043), 99 nodes contained a metastatic lesion. Compared to the reference category (3−6 mm) the odds of metastatic involvement was significantly lower for lymph nodes <3 mm (OR 0.5; 0.3−0.9), similar for lymph nodes of 6−10 mm (OR 1.5; 0.9−2.5) and significantly increased for lymph nodes of 10−15 mm or larger (OR 3.6; 1.5−8.1 and OR = 6.7; 2.5–17.8, respectively). Metastatic involvement in lymph nodes smaller than 3 mm was found in 9 (6.0%) patients, but was responsible for nodal upstaging in only two patients.

An increase in lymph node harvest does not necessarily result in more accurate staging. The success of lymph node harvest in patients with colorectal cancer with a favourable prognosis might merely be a result of the increased lymph node size. Moreover our study suggests that detection of very small lymph nodes is not likely to result in better staging. Not only the number of lymph nodes is important for staging, but selection of the relevant lymph nodes might be important for accuracy as well.

No conflict of interest.

2236 POSTER

Pathological complete response in colorectal cancer (CRC) patients with liver metastasis after preoperative chemotherapy

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Background: CRC is the second most common malignancy in Spain. Almost 50% of patients develop metastases, and the common sites of metastases are liver and lung. Advances in multimodal treatment have led to prolongation of survival in patients after resection of colorectal liver metastasis. The aim of this study was to evaluate the prognostic factor of pathological complete response in CRC patients with liver metastasis after preoperative chemotherapy.

Material and Methods: Between 2004–2010, 226 patients (pts) with CRC and liver limited disease were diagnosed in our institution. All patients were evaluated by multidisciplinary team and patients were subdivided in three groups according with recommendations from European Colorectal Metastases Treatment Group (Nordlinger, et al. Annals of Oncology 2009): a) Resectable liver metastases, b) Potentially resectable liver metastases, c) Unresectable and never likely to be resectable liver metastases. Pts classified as b were evaluated after neoadjuvant chemotherapy and those who achieved radiological response were proposed for surgery. We analyzed clinical characteristics of patients who achieved pathological complete response after neoadjuvant chemotherapy.

Results: Of 226 patients with CRC and liver metastases, 54 were clasificated as b (potencially resectable liver metastases), 31 were operated and seven achieved complete pathological response.5 pts (71%) are alive, after mean of follow up 4.8 years range 5.22 (3−8.2). Four pts are disease free and one patient develop liver recurrence.Two pts have died, one after disease recurrence and one after upper gastrointestinal bleeding.

Conclusions: This study has shown a good survival benefit in stage IV CRC when pathological complete response is achieved after preoperative chemotherapy.

No conflict of interest.

2237 POSTER

A retrospective study analysing the significance of a microscopically positive resection margin in the curative intent treatment of rectal adenocarcinoma

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Background: A positive microscopic margin (R1) after resection of rectal cancer is still challenging and management depends on prior radiotherapy and further possibility of surgery. There is no general consensus on the definition of R1 in rectal adenocarcinoma, no standard approach has been validated and data on these cases is scarce.

Material and Methods: We have reviewed all pathology data concerning resected specimens from patients with rectal or recto-sigmoid adenocarcinoma operated with curative intent at the Institute of Oncology 'Prof. Dr. Ion Chiricuta', Cluj, Romania between 2000–2011 (763 patients in 12 years) and pathology files of patients addressed from other institutions for adjuvant treatment (318 patients). We have included specimens obtained through anterior resection, Hartmann's procedure and abdomino-perineal resection, but have excluded transanal excision results and situations when R2/R1 was obtained at first intervention, but R0 was achieved after re-resection (56 patients). We have identified and analyzed a number of 30 R1-patients.

Results: With surgery only local relapse (LR) followed resection inevitably. Interestingly, when neoadjuvant chemoradiation was used, only 14.3% of patients presented LR after 2 years of minimum follow-up despite of an R1-resection. If radiotherapy was given (in conventional doses) after surgery, only 50% of patients were LR free at 2 years, or in other words only half were compensated for R1. Comparison of other risk factors with R0 cases is in progress.

Conclusions: R1 after primary surgery must be compensated by either re-resection or if not possible, by adjuvant chemoradiation; higher radiotherapy doses should be tested in a prospective study. Because it seems that R1 is difficult to compensate with adjuvant treatment, a good quality total

mesorectal excision (TME) should be always aimed for and the use of neoadjuvant chemoradiation should be employed whenever possible. In the case of R1 after neoadjuvant chemoradiation it is difficult to decide further treatment, because a large percentage of cases won't relapse despite a positive margin, probably due to the fact, that a minimum of 1 mm margin, although it is considered positive in the TNM staging system, would be safe in most cases or the cancer cells in question are not viable. A subclassification of R1 should be always reported.

Conflict of interest: *Other substantive relationships: This study was accomplished with the sponsorship of the European Social Found through the POSDRU project no. 107/1.5/S/78702.*

2238 POSTER

The influence of the treatment response on the impact of resection margin status after preoperative chemoradiotherapy in rectal cancer

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Background: Circumferential resection margin (CRM) and distal resection margin (DRM) have different impact on clinical outcomes after preoperative chemoradiotherapy (CRT) followed by surgery. Effect and adequate length of resection margin as well as impact of treatment response after preoperative CRT was evaluated.

Material and Methods: Total of 403 patients with locally advanced rectal cancer underwent preoperative CRT followed by total mesorectal excision between January 2004 and December 2010. After applying the criterion of margin less than 0.5 cm for CRM or less than 1 cm for DRM, 158 cases were included as a study cohort. All patients underwent conventionally fractionated radiation with radiation dose over 50 Gy and concurrent chemotherapy with 5-FU or capecitabine. Postoperative chemotherapy was administered to 146 patients (92.4%). Median follow-up duration was 44.9 months.

Results: The 5-year overall survival (OS), disease-free survival (DFS), locoregional relapse-free survival (LRFS), and distant metastasis-free survival (DMFS) were 83.3%, 75.6%, 86.3%, and 77.4% respectively. CRM of 1.5 mm and DRM of 7 mm were cutting points showing maximal difference using a maximally selected rank method. In univariate analysis, the shorter CRM was significantly related with worse clinical outcomes, whereas DRM was not. In multivariate analysis, CRM of 1.5 mm, ypT, ypN, and perineural invasion were prognosticators for all studied endpoints. CRM was not a significant prognostic factor for good responders, defined as patients with near total regression or T down-staging, which was found in 16.5% and 40.5% of the patients, respectively. However, poor responders demonstrated a significant difference according to the CRM status.

Conclusions: Close CRM, defined as 1.5 mm, was a significant prognosticator, but the impact was different for treatment response. Postoperative treatment strategy may be individualized based on this finding. However, findings from this study need to be validated with larger independent cohort.

No conflict of interest.

Table: Subgroup analysis according to response of preoperative treatment

	Good responders			Poor responders		
	CRM >1.5 mm 65 patients	CRM ⩽1.5 mm 10 patients	p†	CRM >1.5 mm 60 patients	CRM ⩽1.5 mm 23 patients	p†
5 yr OS	92.1	90.0	0.333	86.7	51.1	<0.001
5 yr DFS	86.4	90.9	0.989	77.8	34.2	<0.001
5 yr LRFS	93.4	100.0	0.529	87.0	59.9	0.001
5 yr DMFS	88.0	90.0	0.869	79.8	36.9	<0.001

*Values are percentages of patients; † log rank test. OS, overall survival; DFS, disease-free survival; LRFS, locoregional-free survival; DMFS, distant metastasis-free survival; CRM, circumferential resection margin.

2239 POSTER

Long term survival and prognostic factors in metastatic colorectal cancer patients treatment with preoperative transarterial chemoembolization (TACE)

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Background: Hepatic resection (HR) is a main treatment option in liver colorectal (CR) metastases patient. The role of neoadjuvant therapy hasn't been estimated yet. The purpose of the study was to evaluate the long term survival and prognostic factors in CR liver metastases patients with treatment included preoperative TACE with oxaliplatin following HR.

Material and Methods: Prospective nonrandomized trial, including 66 synchronous and metachronous CR liver metastases patients, has been completed. HR has been performed in the group 1 (n = 40, average age − 59, 25 men, 15 women). TACE with 50–100 mg oxaliplatin following HR in 4−6 weeks was carried out in group 2 (n = 10, 58, 2/8). TACE with 30−50 mg doxorubicin following HR in 4−6 weeks was conducted in group 3 (n = 16, 56, 8/8). The TACE with oxaliplatin,age, stage, lymphatic nodes status, number of metastasis and metastasis average size, bloodless volume, postoperative complications, extended HR, metastatic index, extrahepatic metastasis or bilobar involvement have been evaluated with Cox regression analysis.

Results: The surveillance median has composed 37.1 months. Median, 5-year and 10-year recurrence-free survival (RFS) have amounted to 12.6 months and 23.1±6.7% in group 1. Median and 5-year RFS have amounted 36.7 months and 40.0±15.5% in group 2; 12.4 months and 6.3±6.1% in group 3, respectively (p = 0.017). RFS was higher in group 2 versus group 1 (p = 0.04) and group 3 (p = 0.003). Median, 5-year and 10-year overall survival (OS) have totalled 31.9 months and 31.7±7.5%, 25.6±7.2% in group 1. Median 5-year OS have made up 54.4 months and 50.0±15.8% in group 2; 29.5 months and 9.4±8.2% in group 3, respectively. Statistically significant differences of OS haven't been obtained (p = 0.08). TACE with oxaliplatin (HR 0.31 [95% CI 0.12–0.82] p = 0.004), lymphatic nodes status (HR 1.74 [95% CI 1.17–2.58] p = 0.006) and postoperative complications (HR 2.34 [95% CI 1.12–4.89] p = 0.02) have been independent prognostic factors on RFS. TACE with oxaliplatin and lymphatic nodes status have been independent prognostic factors on OS (HR 0.29 [95% CI 0.10–0.86] p = 0.03; HR 2.42 [95% CI 1.6−3.7] p = 0.0003 respectively).

Conclusions: Using TACE with oxaliplatin can improve RFS. Only TACE with oxaliplatin and lymphatic nodes status result as independent prognostic factors of RFS and OS in liver colorectal metastases patients.

No conflict of interest.

2240 POSTER

Correlation between KRAS mutational status and radiomorphologic features of colorectal cancer-related liver metastases (CLM)

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Background: In patients with colorectal cancer with liver-only metastases, hepatic metastatectomy offers possibility for cure. KRAS mutation status in metastatic colorectal cancer (mCRC) is a predictive marker of response to anti-EGFR monoclonal antibodies. The addition of anti-EGFR therapy to first line chemotherapy significantly increases overall response rate. However, this gain in response rate did not translate proportionately to gains in rates of resection and conversion to resectable disease. While different EGFR mutations have been correlated with varying clinical phenotypes of metastatic disease in non-small cell lung cancer, no such observations have been made as yet in mCRC. The aim of this study was to examine the correlation between KRAS mutational status and radiomorphological appearance of colorectal cancer-related liver metastasis (CLM).

Methods: Patients with CLM and known KRAS status were identified from institutional database. CT scans at diagnosis of metastatic disease and at best response were evaluated to identify number of CLMs (solitary, 2−5, 6−10, >10), margins (sharp vs fuzzy as surrogate of infiltrative growth pattern) and contrast-enhancement (as surrogate for vascularity). Comparisons were made between patients with KRAS mutant (mt) and KRAS wild type (wt) with either t-test or Fisher's exact as appropriate.

Results: 68 patients were identified, with 29 mt and 39 wt, with 46 and 61 liver lesions in each groups respectively. Comparing wt to mt, number of CLM were comparable (solitary: 6 vs 8; 2−5: 9 vs 15; 6−10: 3 vs 4; >10: 11 vs 12; p = 0.615). Mean size of LM for mt group was 3.51 cm (95% CI 2.78–4.24) with no significant difference from mean size in wt of 3.48 cm (95% CI 2.75–4.22), p = 0.962. At best response, mean size was 2.28 cm (95% CI 1.73–2.83) for mt and 3.00 cm (95% CI 2.19–3.81) for wt (p = 0.141). 13.8% of mt had contrast-enhancement at baseline compared to 15.4% of wt (p = 0.732), while 10.5% of mt and 7.4% of wt had contrast-enhancement at best response (p = 0.645). For mt, 42.1% had infiltrative margins at baseline and 52.4% at best response (p = 0.746) while for wt, 51.9% had infiltrative margins at baseline and 70.4% at best response (p = 0.264).

Conclusion: Our data did not suggest radiomorphological differences amongst CLM due to KRAS mutational status. KRAS-related pathophysiology is unlikely to contribute to low rate of resection despite higher response rates in KRAS wild type.

No conflict of interest.

2241 POSTER

Neoadjuvant short-course versus long-course radiation for distal T3 rectal cancer

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Background: The two broad approaches to preoperative therapy for distal rectal cancer − short-course and long-course radiation. The outcomes of these approaches reported in nonrandomized trials are not comparable because patients selected for treatment with short-course radiotherapy included those with T1−3 disease. The aim of this study was to compare survival, local control, postoperative complications and anal sphincter preservation in the two treatment groups: short-course (sRT) versus long-course radiotherapy (lRT) as a neoadjuvant modality for the management of lower rectal cancer.
Materials and Methods: The study randomized 172 patients with T3N+/−M0 distal rectal cancer. Patients receive either neoadjuvant short-course radiotherapy (5 × 5 Gy) and surgery within 1−2 days (Group 1) or long-course radiotherapy (30 Gy in 15 fractions of 2 Gy) and surgery 4 weeks later (Group 2). The median follow-up of living patients was 38 (range 32−58) months.
Results: Complete response − 8.8%, partial response − 42.3% in Group 2. The actuarial 3-year overall survival was 67.9% in the Group 1 and 88.6% in the Group 2 ($P = 0.01$). Disease-free survival was 67.9% *versus* 84.2% per cent ($P = 0.001$), crude incidence of local recurrence was 8.8% *versus* 6.9% ($P = 0.170$) respectively. Anal sphincter preservation in Group 1 was 91%, compared with 67.5% in the 2nd group. Number of sphincter saving surgery for patients in Group 1 with initially planned abdominoperineal resection of the rectum increased by 2.7 times ($p < 0.005$). Postoperative complications such as anastomotic leak comparable in both groups (8.8 and 7.5%). Partial and complete tumor regression occurred in 41% of patients in Group 1. Local recurrences were observed in 9 (11.3%) patients in group 2, and 2 (2.5%) patients in Group 1 ($p < 0.005$).
Conclusion: Combined treatment of patients with distal rectal cancer (stage II−III) using neoadjuvant long-course radiotherapy radiotherapy of 30 Gy is safe and effective.
No conflict of interest.

2242 POSTER

Safety and adverse events of neoadjuvant short-course hyperfractionated accelerated radiotherapy (SC-HART) combined with chemotherapy for rectal cancer

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Purpose: Neoadjuvant radiotherapy combined with chemotherapy followed by surgery has been adopted as the standard treatment for rectal cancer. However, the tolerability of neoadjuvant short-course hyperfractionated accelerated radiotherapy (SC-HART) is unclear. The purpose of this study was to examine the safety and feasibility of SC-HART combined with chemotherapy for lower rectal cancer.
Material and Methods: A total of 73 patients with lower rectal cancer was treated with SC-HART followed by radical surgery between March 2008 and May 2012, and were analyzed retrospectively in the present study. SC-HART was performed with a dose of 2.5 Gy twice daily, with an interval of at least 6 hours between fractions, up to a total dose of 25 Gy (25 Gy in 10 fractions for 5 days) combined with chemotherapy. Radical surgery was performed within three weeks following the end of the SC-HART. Adverse events were assessed in acute toxicity prior to surgery, perioperative complications, and late toxicity after surgery according to the CTCAE version 3.0. To analyze the predictive factors of treatment related complications, we examined age (<65 or ⩾65 years old), gender (male or female), tumor differentiation (tub2 or not), and the type of surgery (laparotomy or laparoscopic surgery).
Results: The median age was 65.0 (range: 39−85) years. The median follow-up term was 14.7 (range; 0−53) months. S-1 was administered with SC-HART in 65 pts (89.0%). Sixty-six patients (90.4%) had no apparent adverse events before surgery. One patient stopped chemotherapy because of grade 3 gastrointestinal toxicity (CTCAE v.3). The sphincter preservation rate was 94.5%. Downstaging rate was 38.4%, 67.1% and 65.8% in T stage, N stage, and stage grouping, respectively. Perioperative complications were observed in 20 patients (27.4%). Two different toxicities were recorded in each of five patients. However, there was no perioperative mortality. Late toxicity was observed in 23 patients (31.5%). Two different toxicities were recorded in each of four patients. There were no significant differences in acute toxicity, peripoerative complications and postoperative late toxicity according to grouping with age, gender, tumor differentiation, and the type of surgery. The disease-free survival rate and disease-specific survival rate was 80.8% and 98.6%.
Conclusions: SC-HART combined with chemotherapy for rectal cancer was well tolerated and produced good short-term outcomes. Age, gender, tumor differentiation, and the type of surgery seemed to have no apparent effects on toxicity of SC-HART. SC-HART therefore appeared to have a good feasibility for use in further clinical trials.
No conflict of interest.

2243 POSTER

Result of the implementation of multidisciplinary treatment in gastrointestinal tumor

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Background: Today, much of the cancer treatment involves Surgical Oncology, Medical Oncology and Radiation Oncology with support from other related specialties remain very important in the multidisciplinary therapeutic decisions.
Material and Methods: On December 6, 2010, began with this multidisciplinary decision model in patients with esophageal cancer, stomach, small intestine, colon, rectum and anus. We reviewed all records of patients admitted to this model in December 2010 to November 2012 and we make a historical comparison with patients treated at the same hospital and doctors in 2009 (360 cases).
Results: 1090 patients were treated with gastrointestinal cancer (90 esophageal, 37 of the gastroesophageal junction, 362 stomach, 8 of small intestine, 535 colorectal, 21 anous and 37 excluded (19 without confirmation of malignancy and 18 with tumors in other locations). Gender was 622 men (57%) and 468 women (43%). Diabetics in 13.3% and hypertension essencial in 15.8%. History of another malignancy (prostate, breast and cervical cancer the most common) in 3.3%. In 796 (75.6%) cases received at least one cancer treatment and in 109 patients (10.4%) had the best medical support, seven cases (0.7%) died before the therapeutic decision and in 140 patients (13.3%) did not complete the studies requested or not accept the proposed treatment. The 60% of the patients (623 cases) received chemotherapy (QT) with a total of 3932 cycles with median of 6. In 40% (418 cases) received surgical procedures were serious complications in 61 (14.6%) and mortality of 1.7%.- The radiotherapy were received in 283 patients (the most of them in conjunction with QT).
Conclusions: With this model of multidisciplinary care has been reduced morbidity and mortality. Decreased the percentage of patients lost greater number of supports and Palliative Care.

	Year 2009	UFG 2011–2012
Cases	360	1053
Patients with treatment	256 (71.1%)	796 (75.6%)
Best medical support	24 (6.7%)	109 (10.4%)
Death <20 days	4 (1.1%)	7 (0.7%)
Incomplete	76 (21.1%)	140 (13.3%)
Surgical	192	418
Serious complications	25%	14.6%
Surgical mortality	6%	1.7%

No conflict of interest.

2244 POSTER

Response to neoadjuvant chemoradiotherapy, ypT-stage and lymph node involvement in mid and low rectal cancer

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Background: Tumour regression grading (TRG) is a predictive factor for local recurrence in rectal cancer. The correlation of TRG with overall survival is more controversial. Lymph node status after chemoradiation is one of the most important predictors of disease-free and long-term survival. The aim of this study was to determine the correlation between TRG and lymph node status after neoadjuvant chemoradiation in the resected surgical specimens.
Material and Methods: 130 patients with mid (58%) and low (42%) locally advanced rectal cancer treated with neoadjuvant chemoradiation and

radical surgery were included. 87 (67%) were males and 43 (33%) females. Mean age was 67.4 years. Preoperative staging by endorectal ultrasound and/or MRI was available in all patients. Neoadjuvant radiotherapy consisted of 5 weeks regimen of 45 (65%) or 50.4 Gy (35%). 5FU-based chemotherapy was administered in 88% of cases. Reviewed TRG using Mandard's scoring system was used and patients were categorised into 'responders' (TRG 1−2) and 'non responders' (TRG 3−4−5). Chi square and Spearman correlation tests were used to evaluate correlation between TN change, TRG and lymph node status.
Results: Pathologic complete response was observed in 19 patients (14.6%), T-downstaging in 63 (48.5%) and tumour progression only in one case. The mean number of retrieved lymph nodes was 9.4. Node involvement was T0−1: 9.4%, T2: 22.2%, T3−4: 43.7%. Tumor response (TRG) was: TRG1: 19 (14.6%); TRG2: 18 (13.9%); TRG3: 39 (30%); TRG4: 41 (31.5%); TRG5: 13 (10%). Preoperative staging showed N0 40.8%, N1 54.6% and N2 4.6%. Postoperative pathological evaluation of lymph node status showed no involvement in 68.5%, N1 22.3% and N2 9.2%. Responders were N0 89.2% and N positive 10.8%. Non responders were N0 60.2% and N positive 39.8% ($p < 0.001$).
Conclusions: Response to neoadjuvant therapy according to TRG and ypT-stage was associated with lymph node status (ypN). Patients with node involvement had less response to chemoradiation than those N negative.
No conflict of interest.

2245 POSTER

Pathological node stage is a strong prognostic factor for survival outcome in rectal cancer and might be useful as an indicator for adjuvant second-line chemotherapy

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Background: Until now there is no solid evidence on the practice of adjuvant chemotherapy in the treatment of rectal cancer. Especially for the patients receiving preoperative chemoradiation, the utility of adjuvant chemotherapy remains unclear. To identify a subset of patients more likely to benefit from adjuvant chemotherapy we analyzed patients with primary rectal cancer on the first site of recurrence, disease-free survival and overall survival. A subgroup analysis was made for patients with positive lymph nodes.
Patients and Methods: In this study we analyzed 236 patients with primary rectal cancer, operated between January 2005 and December 2010 in the Netherlands cancer institute. Patients were treated with preoperative therapy followed by radical surgery. Patients with distant metastases at time of surgery were excluded for analysis. Determinants of recurrence and survival were examined using Kaplan–Meier survival curves and Cox regression analysis. Nodal stage of the tumor was set off against survival outcomes.
Results: After exclusion of patients with distant metastases, 185 patients remained eligible. At time of diagnosis positive lymph nodes were observed in 65.1% of these patients. After preoperative therapy the percentage of positive lymph nodes declined to 33.5%. Pathological node stage rather than clinical node stage influenced survival. When stratified for nodal stage, 3- and 5-year overall survival were 92% and 84% for pN0, 83% and 75% for pN1 and both 73% for pN2 ($P = 0.280$). 3- and 5-years disease free survival were respectively 83% and 73% for pN0, 77% and 72% for pN1 and 47% and 42% for pN2 ($P = 0.000$). Pathological node stage was prognostic for developing systemic disease ($P = 0.000$). In the multivariate analyses pathological node stage was an prognostic factor for both overall survival and disease free survival ($P = 0.046$ and $P = 0.002$).
Conclusion: Nodal stage, after preoperative therapy, is a strong prognostic factor for developing systemic disease, for disease free survival and overall survival. To further improve survival outcomes for rectal cancer, patients with positive lymph nodes after preoperative therapy might be considered for second-line adjuvant chemotherapy.
No conflict of interest.

2246 POSTER

Surgical management of synchronous colorectal liver metastasis

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Background: Surgical treatment remains the only method that improves overall 5-year survival. Aim of the study: to carry out comparative analysis of immediate and long-term outcomes of synchronous and staged surgical treatment of patients with synchronous colorectal liver metastasis.
Methods: We retrospectively analyzed medical records (2008–2012) of 98 consecutive patients with synchronously recognized primary carcinoma and hepatic metastases who underwent concurrent (40 patients, Groupe 1) or staged (58 patients, Groupe 2) colonic and hepatic resections performed at our institution.
Results: Concurrent and staged groups were similar in demographics, tumor grade, stage, preoperative comorbidity (cardiac and respiratory), characteristics of hepatic metastases and single vs. multiple lesions. No significant differences were observed between groups (concurrent vs. staged) in type of colon resection ($P = 0.5$) or hepatic resection ($P = 0.1$), overall operative duration (mean, 484 vs. 316 minutes), blood loss (mean, 340 vs. 250 ml), disease-free survival from date of hepatectomy (median, 11 vs. 11 months). Overall duration of hospitalization was significantly shorter for concurrent than for staged resection (mean, 23 vs. 10 days; $P < 0.001$). It is noticed, that in Group 1 of patients there is a bigger risk of development of postoperative complications (37 vs. 30%), 30 % from them were specific to a resection of a liver. Overall 3-year survival rate was shorter for concurrent than for staged resection (42 vs. 55%; ? = 0.22).
Conclusions: The analysis of our research highlights the need for a differentiated approach in the surgical treatment synchronous liver metastases from colorectal cancer. Synchronous resection is safe resection of liver segments $\leqslant 3$, provide the best results. Subsequent research should be directed towards study of prognosis factors and criteria for patients' selection for surgical treatment groups, assessment of economic effect, and patients' life quality.
No conflict of interest.

2247 POSTER

Short-course radiotherapy combined with systemic chemotherapy: Short-term results

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The aim of this study was to estimate toxicity and efficacy in term of tumour response range after short-course neoadjuvant chemoradiotherapy of rectal cancer with different fluorpyrimidines.
Materials and Methods: During January 2011 − April 2012 87 patients with T2−3N0−1M0 rectal cancer were included in a prospective randomized trial. All patients received short-course 5×5 Gy radiotherapy with local hyperthermia on days 3−5, local application of metronidazole 10 g/m^2 on days 3, 5. Local intraluminal hyperthermia has been performed on 'Yalik', 'Yachta-3' and 'Yachta-4' devices during 60 minutes with 41−45ºC. When intraluminal hypethermia has been technically impossible due to tumor stenosis, hyperthermia has been performed with 'Synchrotherm' device via percutaneous applicators. Patients were randomized in 3 groups: 28 patients additionally received 5-fluoruracil 425 mg/m^2 24-hours i.v. infusion on days 1−5 of radiotherpy, 29 patients received Capecitabine 2000 mg/m^2 per os on days 1−14 and 28 patients received Tegafur 800 mg/m^2 per os on days 1−21 starting from the first day of radiotherapy. Study endpoints were treatment toxicity according to NCI-CTC v.3.0 and tumor regression according to Dworak-Rodel scale.
Results: Treatment was generally well tolerated. In 5-FU group II−III degree gastrointestinal toxicity were 21.4% and 17.5% correspondingly. In Capectabine group II and III degree GI toxicity were observed in 17.2% and 10.3% respectively. In Tegafur group II−III degree of GI were in 7.7% and 15.4% respectively. Treatment was carried out according to plan in all patients. 1 patient in each investigated group developed grade II leucopenia. Grade III−IV tumor regression was observed in 32 % of the patients in 5-FU group, 56 % in Capecitabine group and 57 % in Tegafur group respectively.
Conclusion: Preliminary results show identical toxicity profile and tumor regression rates for investigated fluorpyrimidines. Oral fluorpyrimidines can be recommended due to simplicity of use and similar treatment outcome. But this results needs future studies.
No conflict of interest.

2248 POSTER

Incidence of complete pathological response after neoadjuvant chemoradiotherapy for locally advanced rectal cancer: A retrospective review in a tertiary care center in the UAE

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Background: Neoadjuvant chemoradiotherapy (nCRT) is the standard of care for treatment of locally advanced rectal cancer(LARC) followed by radical surgery. The benefits of nCRT were demonstrated in tumour downstaging, sphincter preservation, and decreased local recurrence. Complete pathological response (pCR) is now a recognised endpoint. New approaches for pCR patients are being proposed. The aim of this work is to assess the incidence of pCR in patients with LARC after nCRT and to determine if results are sufficient to consider a wait and see approach.
Materials and Methods: Between April 2010 and 2012, a retrospective chart review was conducted. All patients who received 50.4 Gy in 28 fractions with concomitant oral capecitabine over 5 weeks followed by radical surgery were included.
Results: Twenty-nine patients with LARC received nCRT. Mean age was 50 years (20−68). Mean tumour distance from the anal verge was 5 cm (0−12 cm). Mean duration from nCRT to surgery was 10 weeks (5−12 weeks). One patient (3.5%) was unresectable at operation. Twenty-seven (93%) had negative resection margins. One (3.5%) had a positive circumferential margin. Twelve (41.3%) had a Mandard tumour regression grade one, of whom: one (3.4%) had TisN0, two (6.8%) had ypT0N1 disease and nine (31%) had a pCR (ypT0N0). PreCRT staging in the pCR group included 9% Stage IIIA, 81.8% Stage IIIB, and 9% Stage IIIC. 18.1% (n = 2) of the pCR group required re-operation for postoperative complications compared with 24.1% (n = 7) in the incomplete responders. At a mean follow up of 14.5 months, none of the patients with pCR and 8.3% of the non-responders developed resectable metastatic disease. None developed local recurrence.
Conclusion: Our study demonstrates a high incidence of pCR with nCRT for LARC with a low incidence of metastatic disease, and no local recurrence. This is the first cohort reported from the UAE. Our pCR incidence compares favourably to that reported in the literature. Our findings indicate that it may be feasible to avoid surgery in some pCR patients. Further randomised prospective studies are needed to consider a non-operative approach in patients with clinical and imaging complete response.
No conflict of interest.

2249 POSTER

Impact of timing of adjuvant chemotherapy on prognosis of colon cancer patients

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Background: The impact of timing to start adjuvant chemotherapy (TTAC) after surgery was addressed by several studies with somewhat contradictory results. These studies were largely from a period prior to widespread use of oxaliplatin in adjuvant chemotherapy (AC). In addition to deficient reporting of AC completion and performance status (PS), new molecular factors such as K-ras status that may have prognostic relevance were not considered. The present study aims to assess the impact of TTAC on prognosis of colon cancer patients and to find particular subgroups of patients who may get benefit from early initiation of AC, if any.
Patients and Methods: A single center retrospective study where colon cancer patients who received AC were grouped into early and late TTAC groups taking 8 weeks as a cutoff and DFS of both groups were compared. Also, DFS according to different prognostic parameters [age, grade, stage, LN ratio, lymphovascular invasion (LVI), k-ras status] were compared in early and late TTAC groups to determine subgroups that may benefit from early start of AC.
Results: 81 patients with stage II and III colon cancer were screened. 17 patients were excluded (9 due to lack or incomplete course of AC, 8 had no recorded date of surgery). 64 patients with full course of AC were included (75% folfox/xelox, 25 % capecitabine FU/LV). These patients had no significant comorbidity (PS 0 or 1 in 69%, 2 in 31%). K-ras results of 38 patients were available (66% wild, 34% mutant). Different parameters were balanced in the two TTAC groups. DFS was significantly improved in early compared to late TTAC group (HR = 2.6, P = 0.04). In patients with stage II disease, early TTAC group had better DFS (HR = 6.0, P = 0.01) while no difference was found between early and late groups in stage III patients (HR = 1.1, P = 0.88). Similarly, early TTAC group had better DFS in patients with LN ratio <0.2 (HR = 4.6, P = 0.03) with no difference between the two groups in those with high LN ratio $\geqslant$0.2 (HR = 1.6, P = 0.46). No significant difference was found between early and late TTAC groups according to age, k-ras status, LVI or tumour grade.
Conclusion: Colon cancer patients treated with full course of AC (mostly folfox/xelox) with no significant comorbidity have improved DFS with shorter TTAC <8 weeks. Our data suggests that stage II disease and low LN ratio <0.2 are potential predictors of benefit from early start of AC.
No conflict of interest.

2250 POSTER

Role of immunohistochemistry in the treatment of patients with colorectal cancer complicated with abdominal carcinomatosis

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Background: To study the particularities of protein p53 expression and proliferated cells of nucleus antigens (PCNA) in the development of carcinomatosis in patients with colorectal cancer and its effect on the efficiency of conducted methods of treatment.
Materials and Methods: In 36 patients with colorectal cancer complicated with abdominal carcinomatosis has been used complex approach to diagnostics and treatment with immunohistochemical studies. In all cases has been revealed the adenocarcinoma of various stages of differentiation. All patients received palliative colostomy whereupon systemic polychemotherapy has been carried out on FOLFOX scheme against a background of immune therapy and hyperglycaemia. Tumour tissue apoptosis has been studied after each course of chemotherapy.
Results: Study results of protein p53 expression in the colon epithelium, affected by cancer were shown positive result in the nucleus of cancer cells in 23 of 36 patients. The amount of p53-positive cancer cells in patients with adenocarcinoma on average was 48.1$\pm$0.71%. The expressed increase ($p < 0.05$) of the amount of p53 positive cancer cells was reported in patients with moderately differentiated form with elevation of stage of cancer malignancy. This explains the lower stage of sensitivity to conducted chemotherapy, in this group of patients the particular regress of tumour was observed only in 1 patient, stabilisation or process in 6, and the progress developed in 15 patients, whereas in patients with p53 negative reaction was shown the particular regress of tumour in 2 patients and stabilization was revealed in 9 and progress was in 1 patient. Study of PCNA expression in cancer cells showed that positive reaction was recorded in 26 of 36 examined patients. The amount of PCNA positive cells of adenocarcinoma on average was 52.4$\pm$3.3%. It has been noted the direct dependence between amount of PCNA − positive cells in cancer and stage of their malignancy. So, the average amount of such cells being at 1 stage of morphologic malignancy 37.4$\pm$1.6%, at 2–49.8$\pm$1.9% at 3–57.8$\pm$4.1%.
Conclusion: Consequently the colorectal cancer complicated with abdominal carcinomatosis is multifactorial pathology, stage of revealing and particularities of proliferate activity, the level of protein p53 expression and PCNA depends on morphologic stage of malignancy as well.
No conflict of interest.

2251 POSTER

Magnetic Resonance Imaging after neoadjuvant chemoradiaton therapy is a suitable device for evaluation of tumour response

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Background: Magnetic Resonance Imaging (MRI) after neoadjuvant chemoradiation therapy (CRT) in rectal carcinoma shows great, sometimes even complete, remission of the tumour. Based on this remission the planned operation could in some cases be changed. A less invasive, e.g. TEM procedure, or even 'wait and see' policy could be appropriated. Aim of this study is to analyse the accuracy of the MRI after CRT with regards to tumour response.
Material and Method: In 2011 to 2012 30 patients were treated with neoadjuvant CRT and were subsequently evaluated using MRI. From these patients data concerning T-stage, N-stage and CRM was recorded, derived from interpretations of preoperative MRI images and definitive pathology results.
Results: The sensitivity of MRI for classifying a stage T_3/T_4 tumour after CRT was 89.5% in our population, the positive predictive value (PPV) was 70.1%. The sensitivity for identifying a CRM <5 mm was 90.0% with a

negative predictive value (NPV) of 87.5%. In detecting malignant lymph nodes the sensitivity was 75.0% with a NPV of 80%.
In 4 patients we observed a morphological T4 tumour, but on diffusion weighted imaging (DWI) we found no tumour activity. The pathology results for these patients showed a complete remission of the carcinoma.
Conclusions: Our analysis showed that the MRI after chemoradiation therapy is an accurate device to determine local tumour evolvement, distance to the mesorectal fascia and the presence of malignant lymph nodes. With regards to the high sensitivity for detecting T3/4 tumours, small resection margins and presence of malignant lymph nodes the MRI after CRT is an important device in the perioperative diagnostic process. And therefore plays an important role in determining a treatment policy. The MRI after CRT is a suitable device to evaluate the tumour response. Based on its results a less invasive treatment for the rectal carcinoma or even a 'wait and see' policy could be appropriate.
No conflict of interest.

2252 POSTER

Patterns of metachronous metastases after curative treatment of colorectal cancer

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Background: Population-based data on patterns of metachronous metastases of colorectal cancer are scarce. This study aimed to provide information on timing, anatomical location, and risk factors of metachronous metastases based on a large consecutive series of non-selected patients.
Material and Methods: All patients operated with curative intent for colorectal cancer ($T_{any}N_{any}M_0$) between 2003 and 2008 in the Dutch Eindhoven Cancer Registry were included (n = 5671). By means of active follow-up by the Cancer Registry staff within ten hospitals, data on development of metastatic disease were collected for all patients. Median follow-up was 5.0 years.
Results: Of the 5671 colorectal cancer patients, 1042 (18%) were diagnosed with metachronous metastases. Most common affected sites were the liver (60%), lungs (39%), extra-regional lymph nodes (22%), and peritoneum (19%) (numbers include multiple organ involvement, e.g. liver and lungs in 19% of patients). 86% of all metastases was diagnosed within three years after the primary diagnosis and the median time to diagnosis was 17 months (interquartile range 10−29 months). Male gender (HR = 1.2, 95% CI 1.02–1.32), an advanced primary tumour stage (T4 vs. T3 HR = 1.6, 95% CI 1.33–1.92) and lymph node stage (N1 vs. N0 HR = 2.8, 95% CI 2.42–3.30 and N2 vs. N0 HR = 4.5, 95% CI 3.71–5.41), high-grade tumour differentiation (HR = 1.4, 95% CI 1.18–1.63), a positive resection margin (HR = 2.1, 95% CI 1.69–2.71), and primary tumours located in the rectum (HR = 1.4, 95% CI 1.14–1.78) were significantly associated with increased risk for developing metachronous metastases.
Conclusions: Almost one fifth of colorectal cancer patients who were free of metastases at initial diagnosis developed metachronous metastases during follow-up. Different patterns of metastatic spread were observed for colon and rectal cancer patients and differences in time to diagnosis were found for the affected sites. Knowledge on these patterns and risk factors for metachronous metastases may enhance tailor-made follow-up schemes leading to earlier detection of metastasized disease and increased curative treatment options.
No conflict of interest.

2253 POSTER

Aflibercept (afl) in combination with FOLFIRI for the 2nd-line treatment of patients (pts) with metastatic colorectal cancer (mCRC): Interim safety and quality-of-life (QoL) data from the Italian subgroup of the Aflibercept Safety and Quality-of-Life Program (ASQoP)

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Background: In the phase 3 VELOUR trial, afl+FOLFIRI (irinotecan, 5-FU, leucovorin) demonstrated a statistically significant overall survival benefit compared with FOLFIRI alone in mCRC pts previously treated with an oxaliplatin-containing regimen. The VELOUR trial supported the initiation of the multinational Aflibercept Safety and Quality-of-Life Program (ASQoP; NCT01571284) to collect additional safety and QoL data from mCRC pts. Interim data collected by Italian investigators are reported.
Methods: At the cut-off date, 48 pts (safety population) from 17 Italian sites had completed >1 cycle of afl+FOLFIRI. Treatment cycles were repeated q2wks up to disease progression, unacceptable toxicity, death, or investigator/pt decision. FOLFIRI starting dose and dose modifications were at the investigator's discretion. Safety was assessed at each cycle and up to 30 days after last drug administration. The EuroQol EQ-5D™, selected as a utility measure instrument, was self-administered within 3 days prior to first treatment and at the beginning of every odd treatment cycle. The EQ-5D population consists of pts completing the questionnaire at baseline and at least once postbaseline, and who received at least part of 1 treatment dose. The percentage of pts with grade 3/4 AEs in the safety population of the Italian subset of ASQoP was compared with that in VELOUR.
Results: Baseline demographic characteristics of the Italian ASQoP subset were similar to VELOUR. EQ-5D data from 26 pts were analyzed; 54% were male; median age 60 years; 88.5% had ECOG score of 0. Mean±SD utility index at baseline was 0.77±0.20 and remained unchanged at cycle 3 (0.78±0.26) in 24 evaluable pts. 50% of pts of the Italian ASQoP subset experienced >1 G3/4 AE vs 83.5% in VELOUR. G3/4 hypertension and diarrhea were 14.6% and 6.3%, respectively, vs 19.1% and 19.3% in VELOUR. G3 infections (SOC) occurred in 8.3% vs 12.3% in VELOUR. No fatal events were reported.
Conclusion: Enrollment in ASQoP has enabled collection of additional safety and QoL data for afl in mCRC pts. Preliminary health-related QoL data from the Italian subset suggest that treatment with afl does not result in decrements in QoL for patients treated with afl+FOLFIRI. These interim results support the favorable safety profile of afl+FOLFIRI and have identified no new safety signals. The incidence of AEs with the afl+FOLFIRI combination in the Italian subset of ASQoP is lower than in VELOUR and clinically manageable in practice.
Conflict of interest: *Corporate-sponsored research: Steering Committee Peak Study (Amgen)*

2254 POSTER

Prospective investigation of association between UGT1A1 polymorphisms and irinotecan toxicity in Korean patients with advanced colorectal or gastric cancer treated with FOLFIRI regimen

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Background: This was a prospective observational study to assess the association between UGT1A1 variants and irinotecan-related toxicities including neutropenia and diarrhea in patients with gastric and colorectal cancer in clinical practice.
Methods: Wild-type allele (wt) and mutant allele (mut) for UGT1A1 *6 and *28 were genotyped in colorectal and gastric cancer patients who received FOLFIRI as 1st or 2nd line palliative chemotherapy. Safety including Gr $\frac{3}{4}$

neutropenia, febrile neutropenia and diarrhea was evaluated for the first cycle of FOLFIRI treatment.
Results: A total of 1,575 patients (948 colorectal and 627 gastric cancers) were enrolled. Median age was 60 (range: 20−90). Genotype frequencies of wt/wt, wt/mut and mut/mut for UGT1A1*6 were 1011, 486, 65 and for *28 were 1204, 331, 25, respectively. Patients were grouped as 'defective genotype' if the patient had a mut/mut genotype for either UGT1A1*6 or *28 or a wt/mut for both *6 and *28; and the others were grouped as 'control genotype'. The dose of irinotecan was 180 mg/m^2 and 150 mg/m^2 in 63.5% (1,000/1,575) and 32.3% (509/1,545) of the patients. Grade $\geqslant 3$ neutropenia, febrile neutropenia and diarrhea were observed in 70.1% (1,105/1,575), 1.9% (30/1,575) and 1.3% (21/1,575) at the 1st cycle of FOLFIRI. On multivariate analysis, defective genotype, female gender, older age significantly increased the risk of Gr $\geqslant 3$ neutropenia ($P<0.0001$, $P = 0.0125$, $P = 0.0011$). These findings were consistent within subgroups according to cancer origin and line of chemotherapy. However, only defective genotype was significantly associated with febrile neutropenia ($P = 0.028$). No factor was associated with Gr $\geqslant 3$ diarrhea.
Conclusions: Our findings indicated that UGT1A1*6 and *28 genotyping is significantly associated with severe neutropenia and febrile neutropenia, but not severe diarrhea in a Korean population.
No conflict of interest.

2255 POSTER

Hepatic administration of drug-eluting beads loaded with Irinotecan in unresectable liver metastasis from colorectal cancer (LMCRC) refractory to systemic chemotherapy: Retrospective analysis McGill University Health Centre

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Background: Transarterial chemoembolization (TACE) has been investigated in patients with LMCRC. Limited experience and available data suggest that TACE can achieve disease stabilization or improvement even in heavily pretreated patients. Retrospective analysis of loco-regional chemotherapy using irinotecan-loaded drug eluting beads (DC beads) in real life setting was performed at McGill University Hospitals.
Methods: The analysis included patients with LMCRC, ECOG 0−1, who failed at least 2 lines of chemotherapy and received repeat embolizations with 2 ml of microspheres preloaded with 100 mg of Irinotecan (4 ml loaded with 200 mg of Irinotecan as a maximum single dose). Beads were delivered selectively into hepatic arteries and procedure repeated as per treating physician's discretion. All patients were treated according to standard hospital procedure for chemoembolization using prophylactic treatments against nausea and vomiting, infections, and upper quadrant right pain. Follow-up analyses were done using CT scans at 1−2 months after the procedure and then every 3 months or when clinically needed.The primary endpoint of this analysis was overall survival (OS) defined as the time from the last treatment with TACE to death. Survival data was analyzed by the Kaplan–Meier method. Secondary endpoints were safety using CTCAE version 4.0 and progression free survival (PFS).
Results: Twenty six patients were treated using Irinotecan drug eluting beads. No complications due to the procedure occurred. Patient's median age was 57 years (range 45−82 years), with 50% male vs 50% female. The median number of total treatments per patient was 3 (range of 1−5). With an average follow up of 1 year, the median OS was 5.4 months (95% CI; 1.1–22.7 months). The median PFS was 72 days (20–437 days) based on radiological assessments for all patients. The most reported post embolization events were: nausea (8/26); vomiting (6/26); right upper quadrant pain (12/26), fatigue (9/26) and increased transaminases (1/26 grade 3). Five out of 26 patients (19%) required hospitalization post-TACE treatment due to severe persistent pain.
Conclusion: Our data suggests that TACE with irinotecan-loaded drug eluting beads could be a palliative therapy for patients with LMCRC. Nevertheless, a randomized trial is needed in order to optimize the timing of the procedure for improved survival rate.
No conflict of interest.

2256 POSTER

A prognostic score based on tumour characteristics to predict survival of patients with metastatic colorectal cancer: Results from a prospective study

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Background: Prognostic scores are useful to compare patients (pts) between different clinical studies. Several laboratory and clinical factors have been reported to affect survival of pts with metastatic colorectal cancer (mCRC). These results are based on data from clinical trials that generally exclude specific groups of pts, e.g. those with comorbidities. Here we present the development and validation of a prognostic score based on tumour characteristics of unselected pts treated in clinical practice.
Methods: Using the Tumour Registry Colorectal Cancer (TKK), we split data from pts at the start of 1st-line therapy in a learning (796 pts; 2006–2008) and validation sample (908 pts; 2009–2012). The TKK prospectively documents treatment of CRC pts by office-based oncologists in Germany. Pts receive standard treatments according to physician's choice.
Six prognostic factors were identified in the learning sample using univariate and multivariate analyses based on Cox proportional hazards regression. A score was proposed stratifying patients into three prognostic groups. The predictive performance was validated in the independent validation sample.
Results: Median follow-up of all pts was 44 months, median overall survival (OS) was 23 months (64% events). KRAS mutation status (mutated; hazard ratio [HR] 1.5, confidence interval [CI] 1.2−1.8) and number of metastatic sites at start of palliative therapy ($\geqslant 2$; HR 1.5, CI 1.2−1.9); tumour stage ($\geqslant 3$; HR 1.4, CI 1.1−1.9) and grading ($\geqslant$ G3; HR 1.3, CI 1.1−1.6) at primary diagnosis; and resectability ($\geqslant$ R1; HR 1.5, CI 1.2−1.8) and lymph node ratio ($\geqslant 0.4$, HR 1.3, CI 1.0−1.6) of primary tumour were identified as prognostic risk factors. Pts were stratified into three groups according to risk. Median OS was 31 months for pts with low risk (1−2 risk factors, 42 % of pts), 21 months for pts with intermediate risk (3 risk factors, 28 % of pts, HR 1.6) and 15 months for pts with poor risk (4−6 risk factors, 30 % of pts, HR 2.5). The difference in OS is statistically significant ($p < 0.02$, adjusted for multiplicity). Results were confirmed in the validation sample.
Conclusions: At the start of palliative treatment, pts with mCRC can be stratified into three risk groups based on six tumour characteristics, with superior OS for pts with low and intermediate risk. This score could significantly facilitate comparability of pts between clinical studies. The effectiveness of different treatments may be evaluated in the three risk groups.
No conflict of interest.

2257 POSTER

Genomic classifier (ColoPrint) predicts outcome and chemotherapy benefit in stage II and III colon cancer patients

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Background: Although benefit of chemotherapy in stage II and III colon cancer patients is significant, many patients might not need adjuvant chemotherapy because they have a good prognosis even without additional treatment. ColoPrint is a gene expression classifier that distinguish patients with low or high risk of disease relapse. It was developed using whole genome expression data and validated in independent validation studies (JCO 2011, Ann Surg 2013).
Material and Methods: ColoPrint was validated in stage II ($n = 96$) and III patients ($n = 95$) treated at the MD Anderson Cancer Center. Frozen tissue specimen, clinical parameters and follow-up data (median follow-up 64 months) were available. Stage II patients from this study were pooled with patients from previous studies ($n = 416$) and ColoPrint performance was compared to high risk factors described in the ESMO clinical consensus guidelines.

Results: In the MDACC patient cohort, ColoPrint classified 56% of stage II and III patients as being at Low Risk. The 3-yr Relapse-Free-Survival (RFS) was 91% for Low Risk and 78% for High Risk with a HR of 2.42 (p = 0.025). In uni-and multivariate analysis, ColoPrint and stage were the only significant factors to predict outcome. Low Risk ColoPrint patients had a good outcome independent of stage or chemotherapy treatment (91% 3-yr RFS for treated patients, 90% for untreated patients) while ColoPrint High Risk patients treated with adjuvant chemotherapy had 3-yr RFS of 84%, compared to 70% 3-year RFS in untreated patients (p = 0.037). In the pooled stage II dataset, ColoPrint identified 63% of patients as Low Risk with a 3-yr RFS of 93% while High Risk patients had a 3-year RFS of 82% with a HR of 2.7 (p = 0.001). In the univariate analysis, no clinical factor reached statistical significance. Using clinical high risk factors as described in the ESMO clinical consensus guidelines, 56% of patients were classified as low risk with a 3-yr RFS of 90% while high risk patients had a 3-yr RFS of 88% with a HR of 1.31 (p = 0.38).
In the subgroups of stage 2 patients with T3-MSS (n = 286) ColoPrint classified 57% as Low Risk with a 3-yr RFS of 94% for Low Risk and 81% for High Risk patients with a HR of 3.17 (p = 0.003). In the univariate analysis, no clinical factor reached statistical significance.
Conclusions: ColoPrint significantly improves prognostic accuracy, thereby facilitating the identification of patients at higher risk who might be considered for additional treatment.
Conflict of interest: *Other substantive relationships: L.Stork-Sloots and I. Simon are employees of Agendia*

2258 POSTER

Evaluation of erectile dysfunction risk factors in young male survivors of colorectal cancer

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Background: Improved long-term survival of colorectal patients who were treated with surgery and/or chemotherapy ± radiotherapy (RT) has led to increased awareness of long-term side effects, including effecting sexual life, which can ultimately affect quality of life in these patients. Due to the absolute risk factors of erectile dysfunction (ED) have not been defined in colorectal patients, the aim of this research is to identify severity and absolute risk factors of ED in male colorectal cancer survivors.
Patients and Methods: A total of 61 male survivors of colorectal cancer treated with surgery and/or chemotherapy ± RT were recruited from medical oncology outpatient clinics during routine follow-up visits in 2011–2012 were analyzed. Patients older than 55 years-old and erectile dysfunction history before diagnosis were excluded. Medical information of patients was obtained from medical charts.
Results: A total of 61 male colorectal cancer survivors were included in this study. The mean age of the study population was 44.3±7.5 and 47.6±6.7 (range, 18−55 years) at the time of diagnosis and intervention, respectively. According to the International Index of Erectile Function (IIEF) score, 83.6% of patients had some degree of ED. The severity of ED; 42.6% of patients have mild ED, whereas 16.4% and 24.6% have moderate and severe ED according to the IIEF score, respectively. In terms of age, moderate-severe ED was observed in 50.0% of patients ⩾40 years old, whereas 31.0% moderate-severe ED was observed in patients younger than 40 years old (P = 0.01). According to the tumor location; in rectal cancer patients compared to the colon cancer, moderate-severe ED was 67.8% and 18.2%, respectively (P = 0.01). In terms of the type of surgery; in APR patients, the moderate-severe ED was 66.7%, in LAR patients, the moderate-severe ED was 60.0%, whereas 17.2% moderate-severe ED was observed in non-APR, non-LAR patients (P = 0.02). At the time of intervention, stoma was found in 15 (24.6%) of patients. The moderate-severe ED was found in 80.0% of patients with stoma whereas moderate-severe ED was found in only 28.2% of patients without stoma (P = 0.003). The 37.7% of the survivors had treated with pelvic RT; the moderate and severe ED was observed in 69.6% of patients treated with pelvic RT, whereas moderate-severe ED was observed only in 23.7% of patients who treated without RT (P = 0.005). Also there was no significant correlation between smoking status, hypertension, diabetes mellitus, cardiovascular disease, stage of the tumor and ED. Also hormonal disturbances such as serum FSH, LH and testesterone levels did not affect the presence of ED and its severity.
Conclusion: Overall, 83.6% of the male survivors of colorectal cancer had some degree ED according to the IIEF. The risk factors of the ED was older age, tumor location, type of surgery, presence of stoma and RT. Clinicians should be aware of this risk factors to offer adequate treatment options and new treatment strategies are necessary to reduce further ED in colorectal cancer survivors.
No conflict of interest.

2259 POSTER

Phase II trial of combined chemotherapy with irinotecan, S-1, and bevacizumab (IRIS/BV) in patients with metastatic colorectal cancer (mCRC): Hokkaido Gastrointestinal Cancer Study Group (HGCSG) tria l- comparison of the efficacy of KRAS status

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Background: Mutations of the KRAS gene were identified as predictive markers in mCRC for anti-EGFR antibodies. Previously reported data suggest that the longer overall survival (OS) observed with bevacizumab (BV) treatment in mCRC is independent of alterations in the KRAS status. We analyzed the efficacy of BV combined irinotecan and S-1 (IRIS/BV) in mCRC relative to KRAS status.
Patients and Methods: In the retrospective analysis (n = 53) of patients who participated in the Phase II trial of IRIS/BV, additional statistical analyses were done with data from KRAS status. In this trial, eligible patients had to have mCRC with a confirmed diagnosis of adenocarcinoma, an age of >20 years, and no history of prior chemotherapy. S-1 40−60 mg twice daily p.o. was given on days 1−14 and irinotecan 100 mg/m^2 and bevacizumab 5 mg/kg i.v. were given on days 1 and 15 of a 28-day cycle. The Response Evaluation in Solid Tumors (RECIST) criteria version 1.0 was used to assess tumor response. The Kaplan–Meier method was used to determine Progression-free survival (PFS) and OS. Log- rank test was used to compare with mutant or wild-type KRAS in terms of PFS and OS. All statistical tests were performed using SPSS.
Results: The target number of 53 patients was enrolled as of March 2009. KRAS status was assessed in 43 patients (wild=27, mutant=16). Response rate was 63.0% with wild-type and 68.8% with mutant-type KRAS, that was not significant (p = 0.531). And median OS was 49.0 months with wild-type and 38.0 months with mutant-type KRAS, that was not significant (p = 0.906) as well.
Conclusions: IRIS/BV provides clinical benefit in patient with mCRC expressing either mutant or wild-type KRAS. This analysis has shown that the efficacy of IRIS/BV does not affect the KRAS mutational status and urgently requires further large-scale validation studies.
Conflict of interest: *Advisory board: YS has declared adoversory board from Taiho.Daiichi, Yakult,Otsuka, Merck, and Bistol. YK has declared adversory board from Yakult, Tauho, Chugai, Merck, Pfizer, Daiichi,Takeda, and Novartis.YK. Corporate-sponsored research: YKha decleared corporate-sponsored research with Taiho,Lilly, Nocartis, Yakult, Daiichi, Merck, takeda and Kurha. Other substantive relationships: YS has decleared other substantive relationships with Synergy.*

2260 POSTER

Aflibercept/FOLFIRI vs placebo/FOLRIRI in metastatic colorectal cancer: post-hoc analysis of survival by prior bevacizumab use subsequent to exclusion of patients who had recurrence during or within 6 months of completing adjuvant oxaliplatin-based therapy

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Background: The phase 3 VELOUR trial (NCT00561470) showed that aflibercept + FOLFIRI (AF) significantly improved overall survival (OS) when compared with FOLFIRI + placebo (PBO). In VELOUR, 10% (124) of the patients (pts) in the ITT population had recurrence during or within 6 mos of completing adjuvant oxaliplatin-based therapy (ADJ-only). Exclusion of ADJ-only pts from the ITT population demonstrated

improvements in median OS in the AF arm. Analysis of the ITT population by prior bevacizumab (bev) treatment also demonstrated improved OS with AF in both the prior bev use and the no prior bev use groups. We report OS by prior bev treatment after exclusion of ADJ-only pts.
Methods: 186 pts in the AF and 187 in the PBO groups were stratified to prior bev while 426 in the AF and 427 in the PBO groups were stratified to no prior bev. Within the prior bev group, 9 pts in the AF and 8 in the PBO groups comprised the ADJ-only group. Of 853 pts stratified to the no prior bev group, 51 pts in the AF and 56 in the PBO comprised the ADJ-only group. Baseline characteristics and efficacy were determined for the ITT population excluding ADJ-only pts by prior bev treatment. OS and progression-free survival (PFS) are reported as median estimates using the Kaplan–Meier product limit and hazard ratios (HRs) with 95% confidence intervals (CIs) from Cox proportional hazard model.
Results: In this post-hoc analysis of the prior bev group, there were 177 pts in the AF and 179 in the PBO groups following exclusion of ADJ-only pts. We observed an improved median OS with AF vs PBO of 2.14 mos (13.80 vs 11.66); HR = 0.812 (95% CI, 0.634–1.042). Median PFS was 6.7 vs 3.9 mos for the AF group compared with PBO; HR = 0.645 (95% CI, 0.498–0.835). In the no prior bev group, there were 375 pts in the AF and 371 in the PBO groups following exclusion of ADJ-only pts. Median OS was improved with AF vs PBO by 1.31 mos (13.73 vs 12.42); HR = 0.766 (95% CI, 0.645–0.908). Median PFS was 6.9 vs 5.3 mos for the AF group compared with PBO; HR = 0.777 (95% CI, 0.655–0.921).
Conclusions: Excluding the ADJ-only pt population from the analysis of OS by prior bev use shows improvements over PBO in median OS and PFS in both the prior bev as well as the no prior bev treated groups. This post-hoc analysis reinforces the therapeutic benefit of AF in clinically relevant pt populations.
Conflict of interest: *Advisory board: Sanofi, AstraZeneca, Roche, Lilly, Pfizer Ns Bayer. Corporate-sponsored research: Velour study (Sanofi). Other substantive relationships: Full time Sanofi employee*

2261 POSTER

Can the yield of repeat colonoscopy be improved by SNPs at the TGFBR1, mix4 and CHR8 loci as risk markers for CRC?

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Background: Standard recommendations for screening for colorectal cancer (CRC) specify a colonoscopy about age 50 and if normal a repeat after 10 years. The yield of the follow-on colonoscopy in this setting is poor. There is a highly significant association between certain SNP variants at the TGFBR1 locus and CRC, and weaker associations between a mix4 or CHR8 variant and CRC (WCGIC 2012, abstract O-0027). We have suggested that TGFBR1 could potentially be useful to screen for CRC (ASCO 2013, abstract e14591). We now present the sensitivities and specificities of tests using various combinations of SNP variants and discuss the consequences for screening.
Materials and Methods: Tumour samples were obtained from 187 CRC patients and blood from 94 healthy control subjects, all Caucasian. After gDNA extraction, selected amplicons were amplified by PCR, followed by melting curve analysis. The SNP sites for TGFBR1 were rs334348, rs334349 and rs1591; (TGFBR1) mix4, rs7871490; and CHR8, rs7014346. Sensitivity was calculated as the ratio of test-positive cases to total cases, and specificity as the ratio of test-negative controls to total controls.
Results: For TGFBR1, contrasting homozygous variants (VV) versus heterozygotes plus homozygous normals (VN+NN) for CRC cases and controls, the sensitivity as found to be 42.8% and specificity 89.4%. Comparing TGFBR1 (VV+VN) with (NN) showed a sensitivity of 82.4% and specificity of 42.6%. Contrasting TGFBR1 and CHR8 variants (VV+VN) with (NN) showed a sensitivity of 95.2% and a specificity of 19.1%. Finally, comparing TGFBR1, CHR8 and mix4 variants (VV+VN) with (NN) gave a sensitivity of 98.9% and a specificity of 12.8%.
Conclusions: There is a trade-off between sensitivity and specificity depending on how the TGFBR1 heretozygotes are considered. When they are combined with the homozygous normals, sensitivity is low and specificity high; when combined with the homozygous variants the sensitivity is high and the specificity low. Sensitivity relates to the test's ability to identify positive results. Thus we conclude that the heterozygotes should be included with the homozygous variants in any eventual screening test. Including further loci (CHR8 and mix4) raises the sensitivity to a very high level but reduces specificity. Using a test to predict cancer risk would be cost-saving and much easier on patients and could possibly, in patients at risk, call for a colonoscopy sooner and more frequently while increasing yield. A prospective clinical trial to prove the cost-benefit is indispenbable.
No conflict of interest.

2262 POSTER

Updated overall survival (OS) analysis of novel predictive KRAS/NRAS mutations beyond KRAS exon 2 in PEAK: A 1st-line phase 2 study of FOLFOX6 plus panitumumab (pmab) or bevacizumab (bev) in metastatic colorectal cancer (mCRC)

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Background: From a prospective-retrospective analysis of this estimation study, PEAK showed trends towards improved progression-free survival (PFS) and OS in patients (pts) with wild-type (WT) *RAS* (exons 2, 3, 4 of *KRAS*/*NRAS*) mCRC tumors treated with pmab+FOLFOX6 relative to bev+FOLFOX6. Here we report updated results for the intent-to-treat set (ITT) and the novel *RAS* analyses.
Material and Methods: Pts randomized were required to have WT *KRAS* exon 2 mCRC (ITT). This analysis assessed the effect of pmab or bev+FOLFOX6 on PFS and OS in WT *RAS* mCRC. Bidirectional Sanger sequencing and SURVEYOR®/WAVE® analysis were independently conducted to detect mutations in *KRAS* exon 2 (codons 12/13), exon 3 (codons 59/61), exon 4 (codons 117/146); *NRAS* exon 2 (codons 12/13), exon 3 (codons 59/61), exon 4 (codons 117/146).
Results: 285 pts were randomized, 278 received treatment (tx). The *RAS* ascertainment rate was 80%. OS tx HRs (pmab:bev) for the WT *KRAS* exon 2 was 0.62 (95% CI:0.44–0.89), descriptive p-value=0.009. *RAS* analyses results are shown (Table).
Conclusions: From this updated analysis in pts with WT *RAS*, PFS and OS HR strongly favored pmab+FOLFOX6 relative to bev+FOLFOX6. In the WT *KRAS* exon 2, MT *RAS* group, a trend toward inferior PFS in the pmab+FOLFOX6 arm relative to the bev+FOLFOX6 arm was shown. OS tx HRs favored pmab+FOLFOX6 in pts with WT *KRAS* exon 2 (ITT) with 9.9 mos median difference. The safety profile for both arms was similar with previously reported studies with no new toxicities identified. These additional *RAS* mutations beyond *KRAS* exon 2 appear to be predictive for pmab tx effect.

	Pmab + FOLFOX6	Bev + FOLFOX6	HR[d] (95% CI)	Descriptive p-value
WT *KRAS* ITT, n [a]	142	143		
Median PFS-mos (95% CI)	10.9 (9.7–12.8)	10.1 (9.0–12.0)	0.84 (0.64–1.11)	0.224
PFS events (%)	100 (70)	108 (76)		
Median OS-mos (95% CI)	34.2 (26.6-NR[e])	24.3 (21.0–29.2)	0.62 (0.44–0.89)	0.009
OS events (%)	52 (37)	78 (55)		
WT *RAS* [b], n	88	82		
Median PFS-mos (95% CI)	13.0 (10.9–15.1)	10.1 (9.0–12.7)	0.66 (0.46–0.95)	0.025
PFS events (%)	57 (65)	66 (80)		
Median OS-mos (95% CI)	41.3 (28.8–41.3)	28.9 (23.9–31.3)	0.63 (0.39–1.02)	0.058
OS events (%)	30 (34)	40 (49)		
WT *KRAS* exon 2, Mutant *RAS* [c], n	24	27		
Median PFS-mos (95% CI)	8.4 (6.5–10.7)	8.8 (7.3–11.2)	1.13 (0.63–2.05)	0.683
PFS events (%)	22 (92)	23 (85)		
Median OS-mos (95% CI)	27.0 (15.1-NR)	16.6 (13.3–21.6)	0.41 (0.19–0.87)	0.020
OS events (%)	10 (42)	21 (78)		

[a]WT *KRAS* exon 2; [b]*WT KRAS* exons 2, 3, 4 and *NRAS* exons 2, 3, 4; [c]WT *KRAS* exon 2 and Mutant *KRAS* exons 3 or 4 or Mutant *NRAS* exons 2, 3, or 4.
[d]Stratified Cox proportional hazards model.
[e]Not Reached.

Conflict of interest: *Ownership: Hua Yu, Kelly S. Oliner, and William Y. Go: stockholders of Amgen Inc. Advisory board: Lee Schwartzberg, Fernando Rivera, and Jean-Luc Canon: Advisory Boards for Amgen Inc. Fernando Rivera: Advisory Boards for Roche. Board of directors: None. Corporate-sponsored research: Fernando Rivera: Amgen Inc and Roche. Jean-Luc Canon: Amgen Inc. Other substantive relationships: Hua Yu, Kelly S. Oliner, and William Y. Go are all full-time, paid employees and stockholders of Amgen Inc.*

2263 POSTER

Quality of life as prognostic factor of relative survival in elderly patients with colorectal cancer: A population-based study

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Background: The aim of this study was to evaluate the prognostic value of baseline HR-QoL assessment on survival in a population-based cohort of elderly patients with newly diagnosed colorectal cancer (CRC).
Methods: All patients aged 65 and over, diagnosed with a new CRC and registered in the Digestive Cancer Registry of Burgundy between 2003 and 2005 were eligible. Four hundred and one patients were asked to complete EORTC Quality of life Questionnaire QLQ-C30 at inclusion, 3, 6 and 12 months after diagnosis. Spitzer Index (SI) was also completed by each patient's personal physician at the same time points. Relevant QLQ-C30 dimensions and SI were considered using dichotomized variables with the median cut-point. The analysis was firstly performed incident cases still alive one year after diagnosis and secondly among patients with baseline QoL assessments.
Uni- and multivariate regression analyses were performed using the Esteve model with the Dickman approach to evaluate prognosis factors for relative survival (RS). Conditional relative survival (CRS5=RS 5 yrs/RS 1 yr) was computed in order to assess survival according to study participation.
Results: One hundred fifty-six patients replied to baseline QoL questionnaire, 90 to other time-point and 155 did not participate to the study. Respondents to baseline QoL questionnaire were younger and more often treated with curative surgery than non-respondents.
Overall 5 year RS was 63% [57, 69]. In the analysis performed among the 328 patients still alive one year after diagnosis, a Charlson Index superior to 3 (CSR5 = 38% [25, 51]), an advanced tumor stage (CSR5 = 18% [10, 28]), non-response to the QLQ-C30 (CRS5 = 68% [61, 74] and a lower QoL (CRS5 = 49% [35, 64]) were significantly associated with lower survival.
Among the 156 patients with baseline QoL, role functioning was the only QoL dimension significantly predictive of relative survival in the multivariate analysis (HR = 4.3, $p < 0.001$). Advanced tumor stage (HR = 16.3, $p < 0.001$) was associated with lower survival.
Conclusions: Those results suggest that baseline QoL assessments are strong independent predictors of elderly colorectal cancer patients' survival. Moreover, even when focusing the analysis on patients still alive one year after diagnosis and thus avoiding selection bias, non-response to the cohort study is significantly associated to lower survival.
No conflict of interest.

2264 POSTER

Increased lymph node yield in colon cancer: No increase in overall node positivity rate except for pT1 stage

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Background: Few data are available on the effect of increasing lymph node yield after resection for colon cancer on metastasis-positive node rates.
Patients and Methods: 9115 patients resected for stage I−III ($T_{any}N_{any}M0$) colon cancer diagnosed in the southern Netherlands between 2000 and 2010 were included. Trends in nodal evaluation and node positivity were analyzed. Multivariate logistic regressions were used to assess determinants of adequate nodal evaluation and node positivity. Adequate nodal evaluation was defined as $\geqslant$12 lymph nodes examined in accordance with the recommendation of the International Union Against Cancer. Cox regression was used to discriminate independent risk factors for death.
Results: Overall, the proportion adequate nodal evaluation increased from 13.2% in 2000–2002 to 55.5% in 2009–2010 ($p < 0.0001$), whereas the proportion node positivity remained unchanged (37.8%). In pT1 patients, proportion of node positivity increased from 5.1% to 12.1% ($p = 0.004$). Node-positive patients more often received adequate nodal evaluation (adjusted OR N+ versus N0 1.22; 95% CI 1.10–1.35). A more extensive nodal evaluation was associated with node positivity (adjusted OR $\geqslant$12LNs versus 1−8LNs 1.26; 95% CI 1.12–1.42). Elderly were less likely to have node-positive disease (adjusted OR 70−79 years versus <50 years 0.72; 95% CI 0.58–0.90). Risk of death was correlated with number of nodes evaluated for both node-negative patients (HR $\geqslant$12LNs versus 1−8LNs 0.64; 95% CI 0.56–0.72) and for node-positive patients (HR $\geqslant$12LNs versus 1−8LNs 0.61; 95% CI 0.54–0.69).
Conclusion: In patients with stage I−III colon cancer, the number of lymph nodes evaluated has significantly increased between 2000 and 2010, without an increase in the overall proportion of node positivity. However, we detected a higher proportion of patients with pT1 stage who had lymph node metastasis. This finding stresses the importance to keep striving for adequate nodal evaluation to avoid unjust withholdment of adjuvant treatment and prognostic information to individual patients.
No conflict of interest.

2265 POSTER

The individual and combined effects of colorectal cancer and diabetes on health-related quality of life and sexual functioning: 1+1=3?

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Background: This study compares persons without colorectal cancer and diabetes (CRC-DM-), persons with only diabetes (CRC-DM+), persons with only colorectal cancer (CRC+DM-), and persons with both colorectal cancer and diabetes (CRC+DM+) on Health-Related Quality of Life (HRQoL) and sexual functioning. In addition, the additive interaction effect of diabetes and colorectal cancer was tested.
Material and Methods: Persons older than 60 years who participated in a survey in 2010 among patients with colorectal cancer or among a normative Dutch population, were included. Having diabetes was self-reported. Both samples completed the EORTC-QLQ-C30 and four scales of the EORTC-QLQ-C38 to assess HRQoL and sexual functioning, respectively.
Results: Response rates among those aged 60 years or older were 85% and 73% for the normative population and colorectal cancer patients, respectively. In total 624 CRC-DM-, 78 CRC-DM+, 1726 CRC+DM-, and 328 CRC+DM+ persons were included in the analysis. No additive interaction effect of both diabetes and cancer was observed on any of the subscales of HRQoL, except for pain. Having colorectal cancer was associated with less optimal scores on all the HRQoL subscales, except global health and pain, while diabetes was mainly associated with less favorable scores on global health, physical functioning, fatigue and dyspnoea. However, all associations were not clinically relevant. Sexual dysfunction was mainly apparent among male CRC+DM+ persons. Erection problems were reported among 15% of CRC-DM-, 27% of CRC-DM+, 48% of CRC+DM- and 59% of CRC+DM+ persons (P-value <0.0001). After adjustments, CRC+DM- and CRC+DM+ persons were more likely to report erectile dysfunction compared to CRC-DM- persons with odds ratios of 4.7 and 6.5, respectively. Moreover, more CRC+DM+ persons reported ejaculation problems compared to CRC+DM- persons with 48% versus 39% respectively (P-value=0.04). After adjustments this effect remained significant with male CRC+DM+ persons being 1.6 times more likely to report ejaculation problems compared with CRC+DM- persons.
Conclusion: Colorectal cancer or its treatment but not diabetes seems to contribute to a decreased HRQoL and sexual functioning compared with the normative population. No additive interaction between diabetes and cancer was found, except for pain, thus having diabetes and cancer does not result in a worse HRQoL and sexual functioning than the sum of both individual effects.
No conflict of interest.

2266 POSTER

Reduced benefit of bevacizumab in patients with advanced colorectal cancer who continue to smoke

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Background: It is well known that cigarette smoking is the most important cause of lung cancer and other types of tumor. We set out to analyze the role of cigarette smoking in patients undergoing chemotherapy combined with bevacizumab at the Veneto Oncology Institute IRCCS /Istituto Oncologico Veneto/ in Padua (Italy) in order to see if the smoking continuation during chemotherapy treatments affects positive results.
Material and Methods: It is an observational retrospective monoistitutional analysis that covers 187 patients (59% male) undergoing chemotherapy in combination with bevacizumab for the treatment of colorectal cancer and included in the Onco-AIFA national register for monitoring of innovative anticancer drugs. The observation period begins in June 2006 and finishes in February 2012. From the Onco-AIFA register we obtained the personal data as well as the pathology and treatment details, while from hospital

discharge records and medical records we were able to acquire socio-demographic information and the number of health benefits.
The Kaplen-Meier method was used to analyze the OS (overall survival) and PFS (progression free survival).
Results: Among the information collected we concentrated on the data related to smoking and we found out that 55% of patients were non-smokers, 26% smokers and the remaining 19% ex-smokers.
We observed responses to treatment for 183 patients (98%): 5 complete response (3%), 51 partial response (27%), 93 stable disease (50%), 34 progressive disease (18%). The study revealed that being a smoker is a determinant of the OS of patients: in particular non-smokers showed a median survival of 25 months, ex-smokers of 20 and smokers of 17 ($p = 0.021$). The median PFS was calculated for 166 patients and it was 12 months for non-smokers, 10 ex-smokers and 7 smokers ($p = 0.036$).
Conclusions: Overall, smoking was significantly associated with shorter OS and PFS in patients with colorectal cancer. This is the first observation about chemotherapy combined with bevacizumab that in colorectal cancer the results can be influenced by smoking status.
Therefore, in addition to an increased risk, there is a reduced benefit in terms of clinical conditions and response since tabacco reduces the effects of anticancer chemotherapy.
No conflict of interest.

2267 POSTER

Factors determining hospital delay in an unrestricted population of colorectal cancer patients in the western part of The Netherlands

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Background: The aim of this study was to investigate factors determining pre- and in-hospital delay in an unrestricted population of colorectal cancer patients in the Western part of The Netherlands, in order to identify possibilities for shortening time intervals.
Methods: All patients with newly diagnosed colon (n = 2,146) and rectal carcinoma (n = 1,036) in the period 2006–2008 were included in analyses of in-hospital delay (interval between first hospital visit and first treatment >35 days). Patients in four hospitals (one third of all patients) were also available for analyses of pre-hospital delay (interval between enrolment and first hospital visit >7 days). Patient, tumour, treatment and process factors predicting pre- and in-hospital delay were examined in logistic regression models.
Results: Median pre-hospital time interval was 2 days (IQR: 0−16) for colon cancer patients (excluding emergency surgery: 4 days (0−18)), and 7 days (1−21) for rectal cancer patients. Median in-hospital time interval was 32 days (17−49) for colon (excluding emergency surgery: 36 days (23−52)) and 43 days (33−60) for rectal cancer patients. In multivariate analyses, lower tumour stage was independently associated with increased pre-hospital delay in colon cancer patients, and first hospital visit prior to histological confirmation of cancer was associated with decreased pre-hospital delay in colon and rectal cancer patients. Furthermore, higher age, more comorbidities and lower tumour stage were independently associated with increased in-hospital delay in colon cancer patients. Colon and rectal cancer patients with first hospital visit prior to histological confirmation of cancer, complete diagnostic assessment, or discussed in a multidisciplinary meeting had a higher probability of increased in-hospital delay. Finally, rectal cancer patients starting with chemotherapy had a lower probability of in-hospital delay compared to patients who underwent elective surgery or radiotherapy.
Conclusions: After adjustment for patient and tumour characteristics, guidelines-based diagnostic assessment (considered high quality of care) was associated with hospital delay. Residual variation between hospitals and less delay in patients starting with chemotherapy suggest that improvements in patient logistics are possible.
No conflict of interest.

2268 POSTER

The impact of toxicity and efficacy on quality of life in KRAS wild-type metastatic colorectal cancer patients treated with first-line chemotherapy plus cetuximab

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Background: Skin reactions are common side-effects of cetuximab treatment and may be a limiting factor for its use in many countries including Japan. In the CRYSTAL study adding cetuximab to first-line chemotherapy (CT) improved clinical outcome in patients (pts) with *KRAS* wild-type metastatic colorectal cancer without markedly impacting on quality of life (QoL). In the absence of clinical data in Japan the impact of treatment toxicities and efficacy (early tumor shrinkage [ETS] and response) on QoL was further investigated including additional criteria in the CRYSTAL study.
Material and Methods: QoL was assessed by the European Organization for Research and Treatment of Cancer QoL questionnaire core-30 (EORTC QLQ C-30) focusing on global health status (GHS)/QoL and social functioning (SF) scales at wks 8 and 32. Analyses assessed change from baseline QoL scores by toxicity (diarrhea, anorexia, nausea, vomiting, fatigue, mucositis, and skin reactions), baseline covariates and ETS (<20% vs $\geqslant$20% at wk 8 only) and tumor response at wks 8 and 32. Multivariate analyses were performed to explain changes in QoL scores.
Results: QoL was evaluable in 476 pts with at least one complete baseline EORTC QLQ C-30. In the multivariate analysis, in the CT + cetuximab arm 155 pts at wk 8 and 55 at wk 32 were used for GHS/QoL, and 154 pts at wk 8 and 55 at wk 32 were used for SF. In the CT arm, 157 pts at wk 8 and 59 at wk 32 were used for GHS/QoL, and 164 pts at wk 8 and 58 at wk 32 were used for SF. Skin reactions did not markedly ($p > 0.2$) impact on GHS/QoL or SF in either treatment arm at the selected timepoints. No clear pattern was observed for the other toxicities. For example, diarrhea significantly affected GHS/QoL at wk 8 in the CT arm ($p = 0.041$) and at wk 32 in the CT + cetuximab arm ($p = 0.022$), and SF at wk 8 in the CT arm ($p = 0.037$), but not at wk 32 in either treatment arm. ETS significantly impacted on GHS/QoL ($p = 0.041$) and on SF ($p = 0.078$) in the CT + cetuximab arm but not in the CT arm (GHS/QoL, $p = 0.14$ and SF, $p = 0.44$). GHS/QoL and SF at baseline had the most pronounced impact ($p < 0.01$) on corresponding QoL scores at wks 8 and 32. No clear pattern was observed for other baseline covariates.
Conclusions: This multivariate analysis confirmed that toxicity, particularly skin reactions, did not markedly impact on QoL in mCRC patients treated with first-line CT + cetuximab. QoL score at baseline and ETS affected GHS and SF scores in this treatment setting.
Conflict of interest: *Ownership: Merck KGaA (RE, employment and stock ownership FB, employment PvH, employment). Corporate-sponsored research: Merck Serono (EVC)*

2269 POSTER

Efficacy of glutamine added to calcium/magnesium on oxaliplatin-induced peripheral sensory neuropathy in patients with colorectal cancer, a phase III study

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Background: Oxaliplatin (Ox)-based chemotherapy (OxCT) has significantly improved overall survival in patients with various settings of colorectal cancer (CRC). Peripheral sensory neuropathy (PSN) is the dose limiting toxicity leading to dose reduction or treatment discontinuation which may compromise efficacy and patients' quality of life. Calcium/magnesium (CaMg) significantly reduces PSN occurrence, dose reduction and treatment interruption without affecting OxCT efficacy in randomized trials. In a phase II randomized study, glutamine (Glu) reduced the incidence and severity of OxCT induced PSN.
Methods: A Canadian, multicenter, randomized, open-label, phase III clinical trial was initiated to assess the benefit of Glu when added to

CaMg on the occurrence of OxCT PSN in patients with CRC (NCI-CTCAE grade (G) 2−4). Secondary outcomes include cumulative dose of Ox at the occurrence of G 2−4 PSN and incidence of subsequent dose-reduction and dose-delay. A total of 200 Ox-naive patients with ECOG ⩽2 were treated in adjuvant or metastatic 1st-line setting (mCRC) with an OxCT (FOLFOX4, mFOLFOX6, XELOX). Both arms received OxCT with CaMg (1g Ca, 1g Mg IV before and after Ox) for 6 months with (arm A n = 103) or without (arm B n = 97) Glu with a 6-month follow-up. Glu was given as 30 g/d for 7 days starting 2 days before Ox.
Results: Baseline characteristics were balanced between the 2 groups. Most of the patients received OxCT in the adjuvant setting (71%), with either mFOLFOX6 (89%) or FOLFOX4 (11%). Patients with mCRC (29%) received either mFOLFOX6 (88%), FOLFOX4 (9%) or XELOX (3%). Occurrence of G 2−4 PSN and median time to 1st occurrence were not significantly different between the 2 arms (arm A: 36.9%, 177 days; arm B: 36.1%, 174 days, p > 0.5). No difference was observed in the median cumulative dose of Ox at 1st occurrence of G 2−4 PSN (arm A: 655 mg; arm B: 680 mg, p > 0.5) or in the median number of cycles (10 in both arms). No difference was seen in dose reduction rates (32% and 34%, p > 0.9) and in CT delay occurrences (11.7% and 9.3%, p > 0.5) due to G 2−4 PSN, in arm A and B respectively.
Conclusions: The addition of glutamine does not further enhance the benefit of CaMg in PSN prevention in CRC patients treated with oxaliplatin-based regimen. The benefit of CaMg is comparable to historical controls.
Conflict of interest: *Ownership: None. Advisory board: Bayer (P.D.), BMS (N.A.), Novartis (P.D.), Roche (J.M., N.A.), Sanofi (B.S., J.M., P.K., N.A., P.D.), Tyco (P.D.). Board of directors: None. Corporate-sponsored research: Amgen (P.K., P.D.), Novartis (P.D.), Roche (P.K., N.A., P.D.), Sanofi (J.M., P.K., R.L., N.A., P.D.). Other substantive relationships: Educational grants (P.K.), Sanofi (N.A.)*

2270 POSTER

Effect of peri-operative high protein nutritional support on post-operative complications and costs of treatment in patients with colorectal cancer

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Background: Purpose of the study was to investigate the impact of high protein oral nutrition supplement (ONS) on clinical and economical outcomes in patients with colorectal cancer (CRC).
Primary Objective of the study was to assess the effect of pre- a post-operative nutritional support on frequency of complications, rehospitalization rate and length of stay (LoS) independently of initial nutritional status of patients.
Secondary Objective was to assess the impact of nutrition support on costs of treatment.
Patients and Methods: Study group (SG; n 37) represented patients with CRC without distant metastases for whom radical surgery was indicated. Patients aged 18−80 years were included (mean age 64). Nutritional support represented daily application of 2 pieces of high protein ONS (Nutridrink Protein®, 600kcal, 40g of protein), performed 10 days before surgery and 2 weeks postoperatively, consumed between meals.
Control group (CG; n 106) created patients with the same inclusion criteria as SG with conventional nutritional support.
Parameters monitored: wound/anastomosis dehiscence, infection in wound, re-hospitalization related to basic diagnosis, nutritional risk before and after surgery (protocol of The Working Group on Nutritional Care in Oncology, The Czech Oncology Society), nutritional status (weight, BMI) before and 1 month after surgery, (LoS, ONS consumption, patients palatability, ONS benefits for the patients, costs of treatment (procedures, materials, drugs incl. antibiotics, total costs) during hospitalization and 6 months after surgery excluding chemo/radiotherapy.
Results: 37 patients in SG were compared with 106 patients in CG. There was significant decrease of BMI before and after surgery (mean BMI 24.6 versus 25.3, respectively, p = 0.014) and slow-down of loss of weight after surgery (mean 5.4% before, mean after surgery 2.5%, p = 0.055).
31 patients (86.1%) liked ONS product and 33 patients (91.7%) appraised its benefits.
SG showed 2.3× lower relative occurrence of wound dehiscence, 2.9× lower relative occurrence of anastomosis dehiscence, 2.1× lower relative occurrence of infection in wound and 1.8× lower relative risk of rehospitalization. Mean LoS in SG was 9.6±5.8 days, in CG 12±6.4 days. It was approved that longer LoS determine higher total costs of hospitalization in both groups of patients (p = 0.01).
All treatment expenses were significantly decreased in SG vs CG, including costs of antibiotics during hospitalization and 6 months after surgery as well (p = 0.01). Patients without complications had significantly lower costs of drugs (p = 0.02), including antibiotics (p = 0.01) vs patients with complications. Mean total costs per 1 day in hospital was reduced by 10% in SG compare to CG. Mean total costs per 1 day in hospital in patients without complications declined to 508.4 EUR, median 443.8 EUR, compared to the group of patients with complications (mean total costs 527.2 EUR, median 548.7 EUR).
Conclusion: Pre- and post-operative nutritional intervention with high protein ONS reduces occurrence of post-operative complications, LoS and significantly reduces costs of treatment during hospitalization and 6 months after surgery as well in patients with CRC regardless of initial nutritional status. Nutridrink Protein® was well tolerated with positive evaluation of its benefits by patients.
No conflict of interest.

2271 POSTER

Positron emission tomography (PET) interest in the follow-up of colorectal cancer stage II and III: PETCOLON study

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Background: Survival after relapse of the colorectal cancer depends on the possibility of curative action. To detect relapses earlier, we designed a phase III open-labelled, multicenter, randomised study to compare Positron Emission Tomography (PET) with 18 fluorodesoxyglucose (^{18}FDG) to conventional follow-up.
Material and Methods: Patients were aged 18 or more. All patients underwent curative surgery for colorectal cancer, and could have received an adjuvant treatment with chemo or radio-chemotherapy, regarding to initial staging. Patients with uncontrolled diabetes were excluded from the screening. Confirmed Stage II or III was mandatory, and initial assessment to find metastases was performed, using complete colonoscopy, liver ultrasound and Chest X-Ray (or chest and abdominal CT-scan). Patients were randomized no more than 3 months after surgery to either control arm (standard follow-up: carcinoembryonic (ACE) levels, US liver and chest X-Ray or CT Scan) or PET performed every 6 months, during 3 years. All PET were blindly reviewed by an independent committee including nuclear and oncologist practitioners.
Results: Fifteen centres in France participated. A total of 376 patients were randomized from March 2004 to January 2010: 203 males and 173 females. One hundred and eighty-four patients were included in control arm and 192 in PET arm. The mean age was 65 years old. There were 22% of rectal cancers. One hundred and ninety-four patients were stage III (52%). Two hundred and seventy-two received chemotherapy after surgery (72%).
Conclusion: The primary objective is the delay between surgery and detection of colorectal cancer relapse during the 3 years of follow-up. Some results will be available for the congress, especially about systematic review of PET.
No conflict of interest.

2272 POSTER

Patients' experience of pain and anxiety during high-dose-rate brachytherapy for rectal cancer

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Background: Pain and anxiety has been reported as the primary concerns of patients with head and neck, gynecological and prostate cancer who undergo high-dose rate (HDR) brachytherapy. However, the medical literature provides virtually no data about the degree of these symptoms experienced by rectal cancer patients who undergo brachytherapy. We conducted a pilot study to examine rectal cancer patients' experience during brachytherapy, including the intensity and trajectory of anxiety and pain.
Methods: Rectal cancer patients (*N* = 25) who received brachytherapy treatment at a hospital in Montreal, Canada completed verbal analog scales

(VAS) for pain and anxiety at four specific time-points, on four procedure days.
Results: On all four days, prior to insertion of the applicator, patients reported moderate to severe anxiety. Pain significantly increased from when patients were lying on the table to immediately after insertion of the applicator, on all four days, $p < 0.001$. The insertion of the applicator was the most painful point of the procedure. Anxiety decreased below the baseline level after the applicator was removed. Pain, however, remained elevated even after removal. A subset of patients (12−32%) required additional conscious sedation. Despite additional pain medication, patients who received pain medication reported more frequently moderate/severe pain compared to those who did not, $p < 0.05$).
Conclusion: HDR rectal brachytherapy is well tolerated by majority of patients with rectal cancer. However, it is a stressful and painful procedure for at least some participants. The insertion of the applicator was found to be a point of maximal pain. For some, the pain medication was not completely successful at alleviating their pain, suggesting that perhaps additional psychosocial interventions may be needed, with particular emphasis on the time of insertion of the applicator as a target for these interventions.
No conflict of interest.

2273 POSTER

Clinical significance of serum epiregulin level in prediction of clinical outcome and skin toxicity in KRAS wild-type metastatic colorectal cancer patients treated with anti-epidermal growth factor receptor antibodies

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Background: Binding of ligands such as EGF, TGF-alfa, and epiregulin to the epidermal growth factor receptor (EGFR) leads to activation of intracellular signal pathways, but the clinical effect of serum EGFR ligands on the treatment with anti-EGFR antibodies is uncertain. We conducted this study to evaluate the predictive roles of serum ligands in terms of prognosis and skin toxicity in the anti-EGFR antibody treatment of *KRAS* wild-type patients with metastatic colorectal cancer (mCRC).
Material and Methods: Between August 2008 and August 2011, serum samples stocked in the department of clinical laboratories in the National Cancer Center Hospital were obtained from *KRAS* wild-type patients who received anti-EGFR antibody treatment as third-line or subsequent chemotherapy. Main inclusion criteria were as follows: ECOG PS 0 to 2, refractory or intolerant to fluoropyrimidine, oxaliplatin, irinotecan as prior chemotherapy, adequate renal and liver functions. Serum concentrations of ligands were measured by enzyme-linked immunosorbent assay. Clinical outcome and skin toxicities (acneiform eruption and paronychia) were monitored during anti-EGFR antibody treatment from a database in our hospital.
Results: A total of 103 patients were enrolled to the present study. At the pre-treatment serum levels, patients with high levels of epiregulin had shorter progression-free survival (PFS) and overall survival (OS) compared to those with low levels of epiregulin (PFS, 6.6 months vs 4.9 months, HR = 0.618, $P = 0.016$; OS, 13.8 months vs 7.4 months, HR = 0.621, $P = 0.035$; log-rank test). Although there was no significant difference, a better response rate was observed in patients with low epiregulin compared to those in the high epiregulin group (40.4% vs 23.5%, $P = 0.091$). Eleven patients (11%) had no skin toxicity, and 92 (89%) patients had some skin toxicity during the treatment. The occurrence of skin toxicity was associated with lower pre-treatment concentration of serum epiregulin ($P = 0.031$). On the other hand, the concentration of serum EGF, TGF-alfa, etc. had no correlation with efficacy and skin toxicity of anti-EGFR antibody treatment.
Conclusions: Our study indicated that high levels of epiregulin at pre-treatment were associated with resistance to treatment with anti-EGFR antibodies and lesser skin toxicities in *KRAS* wild-type patients with mCRC.
No conflict of interest.

2274 POSTER

Peripheral immunosuppressive cell levels as predictive marker for the clinical outcome in stage IV colorectal carcinoma

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Background: Immune suppressive cells, Myeloid-Derived Suppressor Cells (MDSCs) and T Regulatory Cells (Tregs) have been identified as negative prognostic biomarkers in distinct solid tumors. In colorectal cancer (CRC), increased peripheral levels of MDSCs have been correlated to worse survival (Solito S *et al.*; Blood 2011). Although Tregs infiltrated in tumors have been associated with favourable clinical outcome (Salama P *et al.*; JCO 2009), their significance in peripheral blood remains unclear. The aim of the present study was to evaluate the role of these cells in the peripheral blood as a prognostic marker in CRC patients.
Methods: Blood sample was collected from 49 CRC naive patients (Stage IV) prior to 1st line treatment and 33 healthy donors. Flow cytometric analysis of MDSCs ($HLA\text{-}DR^{-}Lin^{-/low}CD33^{+}CD11b^{+}$) and Tregs ($CD3^{+}CD4^{+}CD25^{high}CD127^{low/-}FoxP3^{+}CD39^{+}$) was performed in fresh samples. MDSC and Treg levels of patients and normal controls were analyzed by using unpaired t-test. ROC analysis (area = 0.8539) was used to define high versus low MDSC levels, whereas the median value of Tregs in normal controls was used as a cut-off. Among patients that relapsed, Kaplan–Meier analysis was used to compare time to tumor progression (TTP) with high and low levels of MDSCs and Tregs.
Results: The median percentages of MDSCs and Tregs in patients were significantly increased compared to controls (Mann Whitney test: $p < 0.0001$; $p = 0.0111$, respectively). MDSCs were positively correlated to Treg levels (Spearman's $r^2 = +0.408$; $p = 0.048$). Patients with high levels of MDSCs at baseline, but not Tregs ($p = 0.7165$), relapsed earlier to those with low levels ($p = 0.0348$; 9.83 vs. 4.93 months, respectively).
Conclusions: CRC patients have elevated peripheral levels of immuno-suppressive cells. MDSCs seem to be an independent prognostic factor for TTP. The significance of the observed correlation of MDSCs with Tregs and the suppressive mechanisms of these cells will be further investigated. Updated survival data will be presented in an increased cohort of patients.
No conflict of interest.

2275 POSTER

Tumor genetic analysis of PRIME: KRAS, NRAS, and BRAF mutations as predictive biomarkers in patients with metastatic colorectal cancer (mCRC) receiving first-line treatment with panitumumab (pmab) + FOLFOX4

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Background: The results from a phase 3 pmab monotherapy study suggested that patients with mutant (MT) *KRAS* or *NRAS* mCRC tumors beyond *KRAS* exon 2 may not respond to pmab treatment.
Methods: The primary objective of this prospectively defined retrospective analysis of PRIME was to evaluate the treatment effect of pmab + FOLFOX4 vs FOLFOX4 alone in patients with mCRC based on *RAS* (*KRAS* or *NRAS*) or *BRAF* mutation status. Eligibility was defined by baseline wild-type (WT) *KRAS* exon 2 tumor status from the primary analysis. To identify mutations in *KRAS exon 3, exon 4*; *NRAS exon 2*, *exon 3, exon 4*; and *BRAF exon 15,* 'gold standard' bidirectional Sanger sequencing and WAVE-based SURVEYOR® from Transgenomic were independently performed. An updated exploratory analysis of OS (when OS data was available for >80% of patients in both the WT and MT *KRAS* exon 2 subgroups), the most mature estimate in PRIME, was used in this analysis.
Results: The *RAS* ascertainment rate was 90% of enrolled patients. In patients with WT *RAS* mCRC, median OS improved by 5.6 months for patients receiving pmab + FOLFOX4 vs FOLFOX4 alone. The OS treatment hazard ratio (HR) was 0.77 (95% confidence interval [CI], 0.64–0.94; $p = 0.009$). 17% of patients (108/641) were WT *KRAS* exon 2/MT other

RAS. The OS treatment HR for this subgroup was 1.39 (95% CI, 0.91–2.13; p = 0.118). Treatment HRs for patients with WT or MT *BRAF* were inconsistent with a predictive biomarker (table). No new safety signals were identified.

Conclusions: This analysis of an exploratory, updated OS dataset suggests that the benefit:risk of pmab + FOLFOX4 treatment is increased by excluding additional patients with mutations in *RAS* beyond *KRAS* exon 2. In patients with WT *RAS* mCRC, an improved OS benefit (p = 0.009) was observed in the pmab + FOLFOX4 vs FOLFOX4 alone arm. Consistent with *KRAS* exon 2 mutations, inferior outcomes were observed in the WT *KRAS* exon 2/MT *RAS* subgroup in the pmab + FOLFOX4 arm. There was no evidence in this study that *BRAF* mutations had predictive value.

	Pmab + FOLFOX4 (N = 320)	FOLFOX4 (N = 321)	HR (95% CI)	Descriptive p-value
WT *RAS* [a], n	259	253		
Median OS − mos	25.8	20.2	0.77	0.009
(95% CI)	(21.7–29.7)	(17.6–23.6)	(0.64–0.94)	
WT *KRAS* exon 2/MT other *RAS*, n	51	57		
Median OS − mos	17.1	17.8	1.39	0.118
(95% CI)	(10.8–19.4)	(13.0–23.2)	(0.91–2.13)	
MT *RAS* [b], n	272	276		
Median OS − mos	15.5	18.7	1.21	0.040
(95% CI)	(13.4–17.9)	(16.5–21.5)	(1.01–1.45)	
WT *RAS & BRAF*, n	228	218		
Median OS − mos	27.7	20.9	0.74	0.004
(95% CI)	(23.8–31.1)	(18.2–24.6)	(0.60–0.91)	
MT *BRAF*, n	24	29		
Median OS − mos	10.5	9.2	0.92	0.769
(95% CI)	(6.4–18.9)	(8.0–15.7)	(0.50–1.67)	

[a]WT in *KRAS* and *NRAS* (exons 2, 3, and 4); [b]MT in any *KRAS* or *NRAS* (exons 2, 3, or 4).

Conflict of interest: *Ownership: K Oliner, A Rong, R Sidhu, and S Patterson own stock in Amgen Inc. Advisory board: JY Douillard: Amgen Inc. S Siena: Amgen Inc., Bayer, Roche, Sanofi Aventis, Cellgene, Genomic Health. J Tabernero: Amgen Inc., Boehringer Ingelheim, Bristol-Myers Squibb, Genentech, Imclone, Lilly, Merck KGaA, Millenium, Novartis, Onyx, Pfizer, Roche, Sanofi Aventis. R Burkes: Amgen Inc., Boehringer Ingelheim, Sanofi Aventis, Lilly, Bayer. Y Humblet: Amgen Inc. M Barugel: Amgen Inc. Other substantive relationships: K Oliner, A Rong, R Sidhu, and S Patterson are employees of Amgen Inc.*

2276 POSTER

Aflibercept in combination with FOLFIRI for the second-line treatment of patients with metastatic colorectal cancer: Interim safety data from the global Aflibercept Safety and Quality-of-Life Program (ASQoP and AFEQT studies)

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Background: In the phase 3 VELOUR trial, aflibercept + FOLFIRI (irinotecan, 5-FU, and leucovorin) demonstrated a statistically significant overall survival benefit compared with FOLFIRI alone in metastatic colorectal cancer (mCRC) patients (pts) previously treated with an oxaliplatin-containing regimen. Evidence from the VELOUR trial supported the initiation of the global Aflibercept Safety and Quality-of-Life (QoL) Program composed of 2 clinical studies (ASQoP [NCT01571284]; AFEQT [NCT01670721]) to capture utility values from QoL instruments and collect safety data from a target population similar to that in VELOUR in a real-life setting. We report early safety data from these ongoing studies.
Methods: ASQoP and AFEQT are single-arm, open-label trials evaluating safety and health-related QoL of aflibercept in mCRC pts previously treated with an oxaliplatin-containing regimen. Estimated total enrollment is ~1100 mCRC pts from ~180 global sites. Eligible pts receive aflibercept (4 mg/kg) q2wks on day 1 of each cycle followed by FOLFIRI up to disease progression, unacceptable toxicity, death, or investigator/patient decision. FOLFIRI starting dose and subsequent additional dose modifications are at the discretion of the treating physician. Safety assessments follow each cycle and continue until 30 days after last drug administration. The percentage of pts with grade 3/4 adverse events (G3/4 AEs) in the combined safety population of ASQoP and AFEQT are compared with that of VELOUR.
Results: At data cut-off, the safety population comprised 116 pts with at least 1 completed cycle of treatment. Baseline demographic characteristics were similar to those in VELOUR. At least 1 G3/4 AE was experienced by 54.3% of pts vs 83.5% in VELOUR. Most reported G3/4 AEs were G3. There were no reports of G4 hypertension or diarrhea. More data will be reported at the congress.

Grade 3/4 Adverse Event	Percentage of patients	
	ASQoP and AFEQT	VELOUR
Proteinuria	0.9	2.9
Stomatitis	3.4	12.8
Diarrhea	8.6	19.3
Infections	12.1	12.3
Hypertension	16.4	19.1

Conclusions: In VELOUR, AEs occurred early in treatment, were often a single occurrence, generally reversible, and consistent with AEs commonly seen by medical oncologists. Interim safety analysis from ASQoP and AFEQT has identified no new safety signals. The early interim analysis provides additional safety data and suggests a lower toxicity in this real-life setting.
Conflict of interest: *Advisory board: Sanofi, AstraZeneca, Roche, Lilly, Pfizer Ns Bayer, Amgen. Corporate-sponsored research: Sanofi. Other substantive relationships: Sanofi full time employee*

2277 POSTER

Survival after resection of colorectal liver metastases: Is the primary nodal status still a prognostic factor?

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Background: Several prognostic variables determine survival after resection of colorectal liver metastasis (CRLM). These prognostic factors are included in clinical risk scores (CRS), which are used to predict outcome. Fong's CRS (1999) is most widely used and validated. It includes lymph node status of the primary tumor as a prognostic factor. Since its introduction however, the use of adjuvant chemotherapy in node positive colon cancer patients has improved survival significantly. Furthermore, the TME (total mesorectal excision) technique and the use of neoadjuvant radiotherapy for rectal cancer has improved outcome in these patients. This study focuses on the impact of nodal positivity of the primary tumor after liver resection for CRLM.
Methods: Between January 2000 and December 2009, all consecutive patients who underwent curative liver resection for CRLM were prospectively included. Patients were excluded if no resection of the primary was performed, if therapy was with no curative intent or if nodal status of the primary tumor was unknown. Minimal follow up was 2 years. Survival of patients was analyzed by location of primary tumor (colon or rectum) and by lymph node status (Npos vs. Nneg) of the primary tumor.
Results: Of 446 consecutive liver resections, 429 patients met the inclusion criteria. In 246 patients a primary colon carcinoma (148 Npos, 98 Nneg) and in 183 a primary rectal carcinoma (99 Npos, 84 Nneg) was found. All patient- and tumor characteristics were comparable; only adjuvant chemotherapy was administered more in colon primaries (p < 0.0001). Median follow up was 37 months (0–145), in colon primaries 38 (0–131) and 36 months (0–145) in rectal primaries. The estimated 5-year survival after liver resection was 54% (colon) vs. 48% (rectum) respectively (p = 0.213). The estimated 5-year survival of primary colon carcinoma patients was comparable between Npos and Nneg patients (50% vs. 57%, p = 0.33). In rectal carcinoma patients it was 37% (Npos) vs. 59% (Nneg) (p = 0.003). Comparison between the colon and rectal node positive tumors also showed a significant difference (50% vs. 37% respectively, p = 0.04).
Conclusions: The present data show that nodal positivity of the rectal primary tumor is a prognostic factor for survival, but not in case of primary colon cancer. The more frequent use of adjuvant chemotherapy after resection of the primary in the group with colon cancer could be an explanation for this phenomenon.
No conflict of interest.

2278 POSTER

Metachronous peritoneal carcinomatosis after curative treatment of colorectal cancer

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Introduction: Population-based data on metachronous peritoneal carcinomatosis (PC) after curative resection of colorectal origin are scarce. The aim of this study was to investigate the incidence of and risk factors for developing metachronous PC from colorectal cancer as well as survival since diagnosis of PC.
Material and Methods: Data on metachronous metastases were collected between 2010 and 2011 for all patients diagnosed with M0 colorectal cancer between 2003 and 2008 in the Dutch Eindhoven Cancer Registry. Median follow-up was 5.0 years. Survival was defined as time from metastases diagnosis to death.
Results: During follow-up, 1042 (18%) patients were diagnosed with metastatic disease of whom 197 (19%) developed metachronous PC. The peritoneal surface was the only site of metastasis in 81 (41%) patients while 116 (59%) patients were diagnosed with both PC and metastases elsewhere. Median survival after diagnosis of PC was 6 months compared to 15 months for patients with distant metastases in other organs. Patients with an advanced primary tumour stage, positive lymph nodes at initial diagnosis, primary mucinous adenocarcinoma, positive resection margin and a primary tumour located in the colon were at increased risk of developing metachronous PC.
Conclusions: Approximately one fifth of initially M0 colorectal cancer patients who developed metastases during follow-up is diagnosed with PC. Prognosis of these patients is poor with a median survival of 6 months after PC diagnosis. Identifying patients at high risk for developing metachronous PC is important as it may contribute to more accurate patient information, tailor-made follow-up schemes, and more adequate treatment.
No conflict of interest.

2279 POSTER

Risk of treatment-related mortality with bevacizumab treatment in advanced cancers

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Background: Treatment with combination bevacizumab and chemotherapy has been associated with improvement in progression-free survival (PFS) for many advanced cancers. A prior meta-analysis of a limited number of randomised controlled trials (RCTs) reported increased risk of bevacizumab treatment-related mortality (TRM). As bevacizumab is frequently administered as prolonged maintenance therapy following completion of standard course of chemotherapy, previous studies have not accounted for the differences in duration of drug exposure. We performed an updated meta-analysis to estimate the overall risk of bevacizumab treatment-related mortality accounting for differences in drug exposure.
Methods: RCTs comparing combination bevacizumab chemotherapy or targeted biological therapy vs chemotherapy or targeted biological therapy alone were included. We extracted data on TRM events, and computed pooled relative risks (RR) adjusted for treatment arm median PFS, expressed as the ratio of the mortality rates in the bevacizumab arm versus the control group. In trials with more than 2 bevacizumab containing arms, RR was estimated separately for each arm.
Results: A total of 16 282 patients with various advanced solid tumours from 24 RCTs were included. Combination bevacizumab chemotherapy or targeted biological therapy was not associated with a statistical significant increase of TRM after accounting for differences in duration of drug exposure (unadjusted RR 1.39, 95% CI 1.14−1.7; adjusted RR 1.09, 95% CI 0.89–1.33). TRM was significantly higher when bevacizumab was combined with platinum or taxane chemotherapy (unadjusted RR 1.53, 95% CI 1.19–1.97; adjusted RR 1.31, 95% CI 1.01–1.69). Higher (5.0 mg/kg per week; adjusted RR 1.30, 95% CI 0.97–1.74) or lower (2.5 mg/kg per week; adjusted RR 0.94, 95% CI 0.70–1.26) dose of bevacizumab were not significantly different (P = 0.13) and did not impact on TRM. TRM varied significantly according to different advanced cancers (P = 0.001), with higher risks observed for non-small cell lung (adjusted RR 1.46, 95% CI 0.96–2.24), pancreatic (adjusted RR 1.76, 95% CI 0.98–3.18), and ovarian (adjusted RR 1.75, 95% CI 0.91–3.38) cancers but lower risks observed for breast (adjusted RR 0.51, 95% CI 0.30–0.88), renal (adjusted RR 0.51, 95% CI 0.22–1.17), and colorectal (adjusted RR 0.97, 95% CI 0.61–1.53) cancers.
Conclusion: Combination bevacizumab chemotherapy or targeted biological therapy was not associated with an overall increase in TRM after accounting for prolonged bevacizumab exposure. The use of platinum or taxane chemotherapy with bevacizumab increased the risk of TRM. The increased risks of TRM also varied with different advanced cancers but not with different doses of bevacizumab.
No conflict of interest.

2280 POSTER

Utility assessment of health-related quality of life in 2nd-line metastatic colorectal cancer patients: interim analyses of the global Aflibercept Safety and HR-QoL Program

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Background: In the phase 3 VELOUR trial, aflibercept + FOLFIRI provided a significant overall survival benefit compared with FOLFIRI alone in metastatic colorectal cancer (mCRC) patients previously treated with an oxaliplatin-containing regimen. Evidence from the VELOUR trial supported the initiation of the global Aflibercept Safety and Quality-of-Life (QoL) Program composed of 2 clinical studies (ASQoP [NCT01571284] and AFEQT [NCT01670721]) that capture utility values derived from QoL instruments and collect every-day safety data from a target population similar to that in VELOUR in a real-life setting. This analysis reports early interim data on QoL-based utility values from both the ASQoP and AFEQT studies.
Methods: Target recruitment in ASQoP is 900 patients across 150 multiple country investigational sites and 200 patients in AFEQT across sites in France. The EuroQol EQ-5D™ instrument was selected as the utility measure. The QoL population of the EQ-5D consists of all patients who completed the EQ-5D questionnaire at baseline and at least 1 assessment postbaseline, and who received at least part of 1 dose of study treatment. The EQ-5D instrument was self-administered at baseline within 3 days prior to first treatment administration and subsequently at the beginning of every odd cycle of treatment.
Results: At the data cut-off date, for the current analysis, EQ-5D data from 67 patients were analyzed; 56.7% were male; median age was 64 years (range 33 to 78 years); and 73.1% had Eastern Cooperative Oncology Group scores of 0. Mean (± SD) utility index at baseline was 0.77 (± 0.22). Utility index remained stable in 63 evaluable patients at cycle 3 and in the 30 evaluable patients at cycle 5, with a mean (± SD) change from baseline of +0.01 (± 0.24) and −0.02 (± 0.25), respectively.
Conclusion: Initial trends suggest that treatment with aflibercept does not result in decrements in QoL for 2nd-line mCRC patients. These results have important implications in advanced cancer settings, as patient-reported outcomes provide an informed perspective on the patient's health status and well-being.
Conflict of interest: *Ownership: Sanofi. Advisory board: Sanofi, AstraZeneca, Roche, Lilly, Pfizer Ns Bayer, Amgen. Corporate-sponsored research: Sanofi. Other substantive relationships: Sanofi full time employee*

2281 POSTER

HER-2 overexpression in colorectal cancer is associated with KRAS wildtype status − analysis of a large consecutive series

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Background: Despite current developments including monoclonal antibodies, fusion proteins and tyrosine kinase inhibitors survival of metastatic colorectal cancer (CRC) remains poor. Therefore, evaluation of new targets is a critical issue. Human Epidermal growth factor Receptor

2 (HER2) is a cell membrane surface-bound receptor tyrosine kinase, involved in signal transduction pathways leading to cell proliferation and differentiation (e.g. MAPK and PI3K/AKT pathways). HER2 overexpression and/or amplification occur in about 20% of patients with breast and gastric cancer. For this molecular subset of patients distinct molecular targeting drugs are available (e.g. trastuzumab, pertuzumab). Data on the prevalence of HER2 overexpression and/or amplification in CRC are conflicting, with positivity rates ranges from 0 to 83%. Moreover, higher rates have been reported in rectal cancer (up to 30%).
Material and Methods: The current analysis included 763 consecutive patients with colorectal cancer, which underwent surgery for primary tumor or metastatic disease. All malignant lesions were collected in the Department of Pathology and staged according to TNM system. Besides determination of KRAS mutational status, HER2 amplification was measured by fluorescent in situ hybridization (FISH) according to the guidelines for breast and gastric cancer (ratio HER2/CEP17 $\geqslant$2).
Results: The median age of the collective was 69.7 years (range 26.5–98.7 years). 335 were female and 428 male patients. Primary tumor (PT) site was colon in 548 patients (caecum to sigmoid colon) and rectum in 211 patients (including recto-sigmoid junction). 503 PTs were left-sided (66.27%). KRAS, analyzed in 753 tumors, was mutated in 38.6% (n = 291, male 151, female 140) of which 67.4% were left-sided. Out of 763 evaluable specimens14 (1.83%) showed HER2 gene amplification by FISH. Distribution of HER2 amplified CRC were 5 (35.7%) right sided and 9 (64.3%) left sided. HER2 amplified patients had a median age of 64.1 years; 3 were female and 11 were male. Concomitant KRAS mutation was noted only in one tumor (p = 0.006).
Conclusion: In colorectal cancer HER2 amplification occurs rarely, if screened by FISH analysis (about 2%). Activation of the MAPK pathway by KRAS mutation is rare in HER2 amplified CRC.
No conflict of interest.

2282 POSTER

Early tumour shrinkage has a favorable impact on clinical outcome in KRAS wild-type colorectal liver-limited metastases treated with cetuximab plus chemotherapy

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Background: Recently, early tumour shrinkage (ETS) was reported to predict outcome in metastatic colorectal cancer treated with cetuximab (cet). This study was to evaluate the impact of ETS on long-term outcome in patients (pts) with wild-type-KRAS unresectable colorectal liver-limited metastases (CLLM) receiving cet plus chemotherapy (CT, FOLFIRI or mFOLFOX6).
Material and Methods: 138 pts treated in a randomized controlled trial (70 in arm A received CT plus cet and 68 in arm B received CT alone) previously reported (Jianmin et al, ESMO 2012, abstract-557, ClinicalTrials.gov, number NCT01564810) were included into this analysis. ETS was defined as a reduction of $\geqslant$20% in the sum of the longest diameters of target lesions compared to baseline at the first evaluation (8 weeks). Outcome measures were progression-free survival (PFS) and overall survival (OS).
Results: 132 pts were available for evaluation, and ETS occurred more frequently in arm A than that in arm B (45/68 vs. 26/64, p = 0.003). Irrespective of treatment arm, pts achieved ETS were associated with longer OS (arm A: 38.0 vs. 18.7 months, p < 0.001; arm B 30.6 vs.17.7 months, p = 0.003) and PFS (arm A: 11.8 vs. 4.8 months, p < 0.001; arm B 8.0 vs. 4.6 months, p = 0.001) when compared to pts with no-ETS. Among pts with ETS, there were statistic difference between arm A and arm B in terms of PFS (11.8 vs. 8.0 months, p = 0.041) but not of OS (38.0 vs. 30.6 months, p = 0.30); the converted resection rates for liver metastases were 40.0% (18/45) in arm A and 19.2% (5/26) in arm B, which were not significantly different (p = 0.072). For pts without liver surgery, pts observed ETS also gained an increased survival benefit over those no-ETS in arm A with regards to OS (p = 0.01) and PFS (p < 0.001) though it was not full certified in arm B (OS: p = 0.054; PFS: p = 0.041). For pts in arm A, cet-induced skin toxicity correlated with the occurrence of ETS (p = 0.048). In addition, cox regression for OS using indicated a hazard ratio of 0.39 (95% CI 0.21–0.72, p = 0.003).
Conclusions: ETS $\geqslant$20% at 8 weeks may serve as a predictor of favourable outcome in pts with wild-type-KRAS CLLM receiving cet plus CT.
No conflict of interest.

2283 POSTER

Which treatment outcomes should be addressed in the pre-radiation consultation with rectal cancer patients? A Delphi consensus study among patients and radiation oncologists

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Background: Preoperative radiation (PRT) in rectal cancer is associated with several adverse effects, which should be balanced against the possible benefits for each individual patient. The Dutch national guidelines for the treatment of colorectal cancer states that clinicians need to 'thoroughly discuss the possible benefits and harms of radiation with the patient'. However, which treatment outcomes (benefits and side effects) should be addressed, is not specified and large variation exists in what radiation oncologists tell patients in clinical practice. Our aim was to reach consensus among experts on treatment outcomes to be addressed with new rectal cancer patients.
Material and Methods: An online three round Delphi study was conducted with two expert panels: one of 35 radiation oncologists and one of 31 rectal cancer patients. 37 possible treatment outcomes of radiation were shown, which were based on 45 taped pre-radiation consultations, complemented with outcomes from the literature. Prevalence and severity of outcomes were described. The panel members were asked to indicate whether the outcomes should be addressed in the consultation. Response categories were 1) Essential; 2) Desired; 3) Not necessary; and 4) Avoid. When $\geqslant$80% of the experts agreed on the answer category, it was considered that consensus was reached. Responses from the panels were analyzed separately and fed back in the next round. Radiation oncologists received feedback on patients' responses.
Results: In the first Delphi round, radiation oncologists reached consensus on three outcomes (Essential: infertility in women; menopause; Not necessary: altered appetite). Patients reached consensus on three other outcomes (Essential: infertility in men; prevention of pregnancy; erectile dysfunction). In the second round all outcomes except the three they agreed on were included in each panel. Final results will be presented.
Conclusions: For informed shared decision making, relevant information on benefits and side effects should be given along with a treatment recommendation. This study shows that there is lack of clarity on which treatment outcomes should at the minimum be addressed in the pre-radiation consultation with rectal cancer patients. Reaching consensus is a first step towards more standardized information provision, in which all patients receive information on the major benefits and side effects of PRT, supplemented with outcomes that might be of interest to the individual patient.
No conflict of interest.

2284 POSTER

Relation of response based on morphologic and RECIST criteria with pathologic response in patients with colorectal liver metastases undergoing neoadjuvant or conversion treatment with bevacizumab

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Background: We aimed to assess efficacy of bevacizumab (BEV) as neoadjuvant or conversion treatment in patients with colorectal liver metastases (CLM) and the relation of the response based on morphologic and RECIST criteria with their outcome after surgery.
Material and Methods: Observational retrospective chart review in patients with CLM treated with neoadjuvant or conversion chemotherapy with BEV as first or second line treatment. Response determined using RECIST and computed tomography morphologic criteria was correlated with pathologic response and disease-free survival (DFS).
Results: 52 patients were evaluated: 78% had synchronic metastases; 10% had initially resectable metastases, 16% irresectable and 74% potentially resectable. 86% and 14% received first and second line BEV prior to surgery, respectively. Initially unresectable metastases become resectable in 86%. R0 was achieved by 88%. A complete pathologic response was seen in 9% and 57% achieved a major response. Median overall survival after surgery was 46 months. DFS after treatment initiation and after surgery was 17 and 9 months respectively. A trend to an extended DFS was seen in patients with complete/major pathologic response compared with those with minor response (18 vs. 15 months; p = 0.19). The relation of morphologic and RECIST response with pathologic response and DFS was analyzed in 25 patients. Partial response (PR) was achieved in 65%, and 31% and 4% had stable and progressive disease respectively.

An optimal morphologic response was reported in 32% and incomplete and no response by morphology was seen in 32% and 36% respectively. There was no difference in median DFS between patients with optimal morphologic response and those with incomplete or no morphologic response (6 vs. 11 months respectively; p = 0.09). Similarly, RECIST response (PR vs. no response) had not a significant association with DFS (18 vs. 17 months; p = 0.39). However, while a similar proportion of patients with morphologic optimal response (50%) and RECIST PR (69%) achieved a complete or major pathologic response (p = 0.28), a significant superior proportion of patients with morphologic incomplete or no response had minor pathologic response compared with RECIST non-responders (100% vs. 25%; p = 0.002).
Conclusions: Our preliminary findings suggest that suboptimal morphologic response to neoadjuvant or conversion treatment with BEV is significantly associated with poor pathologic response after resection of CLM. Nevertheless, a larger cohort will be needed to adequately evaluate morphologic response in this scenario.
No conflict of interest.

2285 POSTER

Changes in body weight during and after colorectal cancer treatment

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Background: In an earlier study [van Waalwijk MA et al. Journal of Comorbidity 2011;1:19−27] among stage III colon cancer patients, preliminary results showed significant weight gain over an unknown period in the group receiving adjuvant chemotherapy. The aim of this study was to investigate weight change in various phases of the treatment of stage II/III colorectal cancer patients receiving adjuvant chemotherapy.
Patients and Methods: All stage II/III colorectal cancer patients, diagnosed in the period 2007 to July 2011 and treated with surgery and adjuvant chemotherapy in the Maxima Medical Center Eindhoven/Veldhoven and the Catharina Hospital Eindhoven, were included. Information about body weight and chemotherapy was retrospectively collected from medical records. Patient, tumor and other treatment characteristics were retrieved from the Eindhoven Cancer Registry. Data were analysed using paired sample t-tests and multivariate linear regression analyses.
Results: 256 patients with a mean age of 64±11 years were included (56% male). 43% of the patients were overweight at diagnosis (BMI 25−30) and 13% were obese (BMI>30). In the period from diagnosis to minimal 6 months of follow-up, body weight decreased during surgery (−2.2±4.1 kg; p = 0.000; weight available in 112 patients); increased during adjuvant chemotherapy (+3.7±5.0 kg; p = 0.000; weight available in 43 patients) and further increased during the follow-up period (+2.2±7.5 kg; p = 0.008; weight available in 87 patients). For weight change per week the same trend was seen. In the total period from diagnosis to minimal 6 months of follow-up, 28% of the patients lost weight; 19% remained stable and 53% gained weight of which 27% gained more than 5 kg. Multivariate regression analysis showed that in the period from diagnosis to the end of chemotherapy as well as in the period from diagnosis to minimal 6 months of follow-up only the number of chemotherapy courses was independently associated with weight gain.
Conclusion: In patients with stage II/III colorectal cancer receiving adjuvant chemotherapy, weight gain occurs during and after chemotherapy after a decline in weight during surgery. Weight gain is related to the number of chemotherapy courses. To clarify the underlying mechanism and consequences of weight gain in stage II/III colorectal cancer patients receiving chemotherapy, more research is needed. Oncology care providers should inform these patients about the possibility of weight gain and promote a healthy life style.
No conflict of interest.

2286 POSTER

The efficacy of palonosetron/dexamethasone plus NK1 receptor antagonist (aprepitant) therapy for prevention of chemotherapy induced nausea and vomiting in colorectal cancer patients

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Background: All antiemetic guidelines for patients receiving anthracycline/cyclophosphamide (AC)-based moderately emetogenic chemotherapy (MEC) recommend the addition of aprepitant to a regimen of 5-HT3 receptor antagonist and dexamethasone to prevent chemotherapy induced nausea and vomiting (CINV). While recent study showed the efficacy of aprepitant in patients with a wide range of tumor types who received AC and non-AC-based MEC regimen, colorectal cancer (CRC) patients' specific efficacy has been unknown. To investigate the efficacy of addition of aprepitant in the standard MEC regimen in CRC patients, we conducted a multicenter randomized phase II study.
Material and Methods: From August 2011 to March 2013, 60 patients were enrolled and were randomly allocated to the standard regimen [palonosetron plus dexamethasone] or the aprepitant regimen [standard regimen + aprepitant]. Patients used diaries to report the time and data of nausea, vomiting, additional antiemetic use, and dietary intake situation from day1−7. The primary endpoint was the proportion of complete response: CR (no vomiting and no rescue medication). The secondary endpoints were the proportions of complete protection (CR and no nausea at least moderate), no vomiting, no rescue medication, no nausea, no nausea at least moderate, time to treatment failure (first vomiting or rescue treatment), and dietary intake situation.
Results: Fifteen patients were excluded because of insufficient diary and protocol violation. Finally, we analyzed 45 patients (26 male, 19 female) for this study. Twenty-one patients (47%) received the aprepitant treatment and 39 patients (87%) received oxaliplatin-based regimen. During the overall phase (day1−7), the proportion of CR was 68.4% in the aprepitant regimen, and 57.7% in the standard regimen (P = 0.543). During the delayed phase (day2−7), the proportion of CR was 73.7% in the aprepitant regimen, and 57.7% in the standard regimen (P = 0.351). The secondary endpoints did not differ significantly, and there were no notable differences in adverse events between the groups.
Conclusions: In the CRC patients receiving MEC, the addition of aprepitant to standard antiemetic regimen could not provide superior efficacy in preventing CINV in both the overall phase and the delayed phase in this small study. However, 16% increase of CR during the delayed phase in the aprepitant regimen compared to the standard regimen in the CRC patients should be verified by large scale randomized controlled study.
No conflict of interest.

2287 POSTER

Pre-operative staging of rectal cancer: The diagnostic accuracy of magnetic resonance imaging in predicting nodal status

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Background: Rectal cancer is a common malignancy with high rates of local pelvic recurrence. Careful pre-operative staging is essential for planning optimal therapy in these patients(pts). Two important prognostic factors include the circumferential resection margin (CRM) and lymph node (LN) status. Magnetic resonance imaging (MRI) is increasingly being used as part of pre-operative staging due to its proven accuracy in determining the CRM. This enables the appropriate selection of pts for neoadjuvant therapy prior to curative surgical resection. The evaluation of nodal status remains problematic. We assessed our institution's experience of neoadjuvant therapy versus upfront surgery in stage I−III rectal cancer to ascertain the accuracy rates and clinical usefulness of MRI as a tool in the pre-operative evaluation of LN status.
Methods: We retrospectively reviewed a prospectively maintained database for all pts with a diagnosis of stage I−III rectal cancer from January 2006 to September 2012 in a specialist colorectal cancer centre. We extracted & analysed data with respect to preoperative MRI staging & definitive histopathological confirmation of LN status.

Results: A total of 210 pts were identified that had surgery for rectal cancer with curative intent. Of these, 112 pts received neoadjuvant therapy while 98 had upfront surgery.
Of those who proceeded directly to surgery, there were 41 females & 57 males. Average age in this sub-group was 73.4 years (range 33 −90). LN staging by MRI was accurate in 45.9% cases (n = 45). LN status could not be evaluated (Nx) in 15.3% (n = 15) on pathology & 2% (n = 2) radiologically. In 19.4% (n = 19) more advanced LN staging was apparent on histology while in 17.3% (n = 17) LN stage was deemed more aggressive by MRI.
Of those who had neoadjuvant therapy, there were 75 males & 37 females. Average age was 62.3 years (range 26−82). In this cohort, 81.3% pts (n = 91) had both a preoperative MRI & pathology report available for comparison. MRI in this group matched histology in 61.5% cases (n = 56). Nx was recorded in 1.1% (n = 1) on pathology & 2.2% (n = 2) on MRI. In 17.6% (n = 16) more aggressive LN involvement was evident at histology while 17.6% (n = 16) had less advanced disease at tissue sampling.
Overall in this study, MRI accurately predicted LN status in 53.4% cases (n = 101). The sensitivity of lymph node invasion was 55% while the specificity was 37%.
Conclusions: While MRI is a valuable tool in determining those pts with rectal cancer that would benefit from neoadjuvant therapy, its predictive value for nodal status has limitations. With further analysis of the dataset at our institution, we aim to identify other factors involved & create a predictive nomogram for the rectal cancer pt with locally advanced disease. We plan to validate this work by including data from other Irish cancer centres.
No conflict of interest.

2288 POSTER

Image guided surgery: Differentiation of benign and malignant tissue in colon cancer patients using optical spectroscopy

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A key prognostic value for both quality of life and survival after colorectal surgery is the presence of local recurrence. Incomplete local excision is the cause of the majority of these recurrences. According to the Dutch national colorectal registry (Dutch Colorectal Cancer Audit), resection was microscopically incomplete in 4% of patients after colon resection. For rectal cancer these figures vary from 9% to 30% according to the level of rectal cancer. Diffuse reflectance spectroscopy (DRS) is a non-invasive technique, discriminating between tissue types based on their optical properties. Within seconds, it defines an 'optical fingerprint' which can be used for tissue discrimination. This proof-of-principle study explores the potential of this new technique in the discrimination between malignant colon tissue and the benign surrounding tissue.
Resection specimens from 19 colon cancer patients were investigated. DRS measurements of the tumor and its benign surrounding tissue (e.g. colon wall, tenia epiploica and mesocolon) were performed directly after resection. An optical needle shaped probe (diameter 2.5 mm) sensitive for a broad light spectrum (400–1600 nm) was used in combination with white light luminescence. The same probe was used to perform fluorescence spectroscopy (FS) after laser excitation with 377nm (blue) light. Trajectory measurements were performed, measuring from the benign tissue into the tumor, to examine tissue transitions. For correlation with histology, a biopsy was taken from the trajectory path. An analytical model extracts a number of validated physiological and metabolic parameters. The robustness of the technique was accessed using a classification and regression tree (CART) algorithm.
A total of 860 measurements were taken in the 19 examined specimens. Distinctive parameters were fat fraction, the amount of collagen, beta-carotene and scattering. Both DRS and FS proofed capable of differentiating tumor from benign tissue with a sensitivity and specificity of 92% respectively 91%. The trajectory measurements enabled real-time recognition of the tissue transitions in all 19 patients.
The changes in optical characteristic during these trajectory measurements could be correlated to histological findings.
The results show high sensitivity of DRS for differentiation of benign and tumorous tissue in colon cancer patients. During surgery, DRS can give real-time guidance in tissue recognition in situations were tactile and visual feedback are limited, for example during laparoscopy. The use of real-time DRS in probing dubious resection margins and its use during the surgical resection of colorectal cancer is currently under investigation.
Conflict of interest: *Corporate-sponsored research: Philips Research is the employer of B.H.W. Hendriks.*

2289 POSTER

Patients' experience of rectal high-dose rate brachytherapy

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Background: High-Dose Rate (HDR) brachytherapy is a form of radiation therapy that targets directly various cancerous tumors directly with a devise used to penetrate the body via its natural orifices. While we know that patients often experience varying degrees of pain, discomfort and potentially distress related to cancer treatments, they tend not to report these experiences during the procedure. Because no knowledge exists regarding patient's experience of HDR brachytherapy, the capacity to adapt this innovative treatment to the patient's needs is limited. The aim of the study is to better understand the complexity of the embodied experience of HDR brachytherapy of rectal cancer patients.
Methodology: Twenty-five rectal cancer patients were interviewed using a semi-structured qualitative interview schedule following the completion of their HDR brachytherapy treatment delivered at the Jewish General hospital, in Montreal, Quebec.
Results: The experience of pain and discomfort varies greatly between patients and are linked to the meaning patients attributed to the: treatment, sense of time, body's position, applicator used to penetrate the body as well as patient's sense of agency and empowerment during the procedure. The actual orifice (rectum) used to penetrate the body with the applicator also conveys a gendered meaning to the social experience of patients with the treating team present during the procedure.
Conclusion: These results suggest the importance of informing clinicians about the variation in the experience of pain of patients undergoing this treatment and that the intensity of pain needs to be assessed during the procedure along with itsemotional and semantic dimensions.
No conflict of interest.

2290 POSTER

Metastatic colorectal carcinoma patients: The Glasgow Prognostic Score (GPS) at the era of anti-EGFR therapies

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Background: The Glasgow Prognostic Score (GPS), combination of C-reactive protein and albumin, has proven its prognostic value in metastatic colorectal cancer' (CRCm) patients receiving conventional cytotoxic therapy. Recently, anti-EGFR therapies have been validated in CRCm and roll forward the patients' overall survival. Therefore, we aimed to evaluate the effectiveness of the GPS in patients receiving anti-EGFR therapy in addition to conventional chemotherapy.
Materials and Methods: From January 2007 to February 2012, CRCm' patients who received 5-fluorouracil based chemotherapy with the addition of an anti-EGFR, Cetuximab, were included in the present study. Patients were eligible for the study if they met the following criteria: advanced pathologically proven CRCm, age >18 years, C − reactive protein and albumin evaluation, adequate renal function (creatinine clearance >40 ml/min), and Eastern Cooperative Oncology Group performance status (ECOG) evaluation before treatment initiation. Patients received chemotherapy in addition to cetuximab in accordance with digestive oncology multidisciplinary staff' proposal and in line with the French recommendations for treatment of CRCm cancer.
Results: 49 patients received cetuximab plus 5-fluorouracil based chemotherapy (colon, n = 34; rectum, n = 15) and were treated with a median follow-up of 35 months (3–198). Median age was 48 years old. Patients received in addition to cetuximab mainly oxaliplatin (n = 34; 60%) or irinotecan 15 (30%) based chemotherapy. At time of diagnosis, 55%, 29% and 16% of patients were GPS 0 (n = 27), GPS 1 (n = 14) and GPS 2 (n = 8), respectively. 55%, 29% and 14% of patients add one, two or $\geqslant$3 metastatic sites, respectively. Median progression free survivals were 20, 10 and 9 months in the GPS 0, 1 and 2 groups, respectively. Median overall survivals were 48, 28 and 25 months in the GPS 0, 1 and 2 groups, respectively.
Conclusion: The results of the present study confirm that the GPS is still a simple and effective prognostic factor at the era of cetuximab therapy in CRCm patients.
Conflict of interest: *Advisory board: Professor Goldwasser has acted as paid consultant for Bayer Healthcare and Pfizer. Dr Mir has acted as paid consultant for Roche, Servier, and Pfizer. Dr Coriat has acted as paid consultants for Roche and Novartis. For the remaining authors there are no conflicts of interest.*

2291 POSTER

Metastatic colorectal carcinoma patients: The Glasgow prognostic score (GPS) at the era of anti-VEGF therapies

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Background: The Glasgow prognostic score (GPS), an inflammation based scored combination of C-reactive protein and albumin, has been identified as a prognostic score in metastatic colo-rectal cancer (CRCm) patients receiving conventional cytotoxic therapy.
Since 2001, Bevacizumab, a humanized monoclonal antibody targeting VEGF, has been validated in CRCm and improved overall survival associated with chemotherapy. The aim of the present study was therefore to assess the effectiveness of the GPS in patients receiving anti-VEGF therapy in addition to conventional chemotherapy.
Materials and Methods: From August 2005 to August 2012, patients with CRCm who received chemotherapy in addition to an anti-VEGF, bevacizumab, were included in the present study. Clinical stage, C-reactive protein, albumin and Eastern Cooperative Oncology Group performance status (ECOG) were recorded at the time of initiation of treatment by bevacizumab. Patients received chemotherapy in addition to bevacizumab in accordance with digestive oncology multidisciplinary staff proposal and in line with the French recommendations for treatment of CRCm cancer.
Results: 81 patients received bevacizumab plus 5-fluorouracil based chemotherapy (colon, n = 60; rectum, n = 21) and were treated with a 14 months median follow-up (1−58). Median age was 65 years old. Patients received in addition to bevacizumab mainly oxaliplatin (n = 42; 52 %) or irinotecan (n = 27; 34%) based chemotherapy. At the time of diagnosis, 55%, 31% and 14% of patients were GPS 0 (n = 45), GPS 1 (n = 25) and GPS 2 (n = 11), respectively. 53%, 32% and 14% of patients add one, two or $\geqslant$3 metastatic sites, respectively. Median progression free survivals were 10, 6.3 and 5.1 months in the GPS 0, 1 and 2 groups, respectively. Median overall survivals were 18, 9.7 and 6.2 months in the GPS 0, 1 and 2 groups, respectively.
Conclusion: Our study confirmed, at the era of anti-VEGF therapy, the efficacy of the GPS score to identify patients with a worsen survival. The GPS deserves confirmation in a larger cohort.
No conflict of interest.

2292 POSTER

Clinico-pathological characteristics of younger, middle aged, and older patients with colon cancer

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Background: There are limited data about tumor features and treatment outcomes in both young and elderly patients with colorectal cancer.
Methods: Total of 393 patients treated for colorectal cancer from 2000 to 2011: group A (younger; 67 patients; age, 17 to 41 y); group B (middle aged; 238 patients; 50 to 70 y); and group C (older; 88 patients; 75 to 93 y) were studied. Patient and tumor features, treatment, and survival were compared. T-tests and Chi-squared tests were used to determine statistical differences between age groups. The Kaplan–Meier method was used to estimate the survival distributions and calculate median survival; while Cox regression was used to estimate the hazard ratios.
Results: The 3 groups had similar sex distribution. Older patients were more likely to be African American (odds ratio [OR], 2.1; $P \leqslant .005$), and to have a right colon primary tumor (OR, 2.6; $P \leqslant .01$). Younger patients were more likely to have a sigmoid primary tumor (OR, 2.1; $P \leqslant .01$). Frequency of mucinous tumors was similar between the 3 groups. Younger patients were more likely to have worse tumor grade (OR, 2.2; $P \leqslant .02$). The most common site of distant metastasis was the liver in all 3 groups. However, older patients were less likely to have lung metastasis (OR, 0.4; $P \leqslant .001$), while younger patients were more likely to have bone metastasis (OR, 3.3; $P \leqslant .001$). Older aged women were less likely to have ovarian metastasis (OR, 0.1; $P \leqslant .001$) in comparison to the other two groups. Older patients had peritoneal metastasis less frequently (OR, 0.5; $P \leqslant .01$). Most tumors (77%) were KRAS wild type. Notably, younger patients had higher frequency of inflammatory bowel disease (6%) than middle aged (1%) or older (0%) patients ($P \leqslant .007$). Chemotherapy was first line treatment more frequently in younger and middle aged patients combined (91%) than older patients (57%; $P \leqslant .001$). The most common chemotherapy was FOLFOX plus bevacizumab in younger and middle age patients; however, capecitabine was the most common chemotherapy used in the older patients. Median survival was: younger, 23 mo [range, 18 to 31 mo]; middle aged, 26 mo [23 to 29 mo]; older, 18 mo [12 to 28 mo]. The 2-year survival was similar between the 3 groups (younger, 49%; middle aged, 54%; older, 40%). Multivariate analysis showed that tumor differentiation, surgery status, and radiation status were independent predictors of survival.
Conclusions: In our patients populations, younger patients with colon cancer are more likely to have poorly differentiated tumors. Younger and middle aged patients are more likely to receive more aggressive treatment. Yet, all groups had equivalent two-year survivals. Pattern of metastases may be different. These results support the need for further prospective investigation in a larger population.
No conflict of interest.

2293 POSTER

Family history and colorectal cancer: A study to investigate the incidence of hereditary and familial colorectal cancer

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Background*:* The complete medical approach to colorectal cancer often includes not only the treatment of the individual who is sick, but also requires the study of his family, as cancer is eventually linked to some kind of inherited genetic mutation. It is, therefore, very important to completely understand the epidemiology and the genetic aspects of this type of cancer, in order to successfully assist the patient and his family. This study aims to investigate the incidence of colorectal cancer associated to inherited mutations, classifying them, based on the guidelines of the Brazilian Clinical Genetics Society (BCGS), into three categories: hereditary (inherited mutations that can lead directly to cancer), familial (inherited mutations that can predispose to secondary oncogenic mutations) and sporadic (related to non-inherited mutations).
Material and Methods: This research was made based on data collected from 291 patients attended between the years of 2006 and 2011 at the State University of Campinas' oncology service. Data gathered include several of the patient's characteristics, such as age at the diagnosis and familial history related to cancer, as well as tumour related information, such as stage of the tumour and pathological findings. This data was analysed accordingly to the BCGS guidelines and Amsterdam I and II criteria, aiming to determine the role of genetics in each of the 291 cases.
Results: 14% of the patients could not be assigned to one of the three categories, because they alone met the Amsterdam criteria for hereditary cancer, but their family did not present, at the time, positive cancer history. 6.5% of the patients were qualified to hereditary colorectal cancer, while 2.5% of them met the criteria for familial colorectal cancer. The rest of the patients (77%) were assigned to the sporadic colorectal cancer group.
Conclusions: The amount of individuals with colorectal cancer related to inherited mutations indicates that inheritance does not play a major part in this type of cancer, but cannot be ignored. Further research is needed to ensure what's precisely the inherited mutations role in colorectal cancer. This research also shows that it's important to provide proper genetic testing for individuals who are suspected to have a hereditary/familial colorectal cancer, but do not meet all the criteria for the diagnosis, after all, they represent an important share of the total analysed (14%).
No conflict of interest.

2294 POSTER

Physicians and patients adherence rates to recommended screening with colonoscopy for first-degree relatives of patients diagnosed with colorectal cancer before the age 50

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Background: Screening is an important intervention to reduce the colorectal-cancer incidence and mortality. We evaluated physicians' adherence to screening recommendations for first degree relatives of patients diagnosed with colorectal cancer under the age of 50.
Methods: Patients attended to ICESP between July 2007 and January 2010 and diagnosed with colorectal cancer before age 50 answered a questionnaire that evaluated the rate of indication of colonoscopy or other screening exam to their first degree relatives by their treating physicians. The answers provided us the physicians' adherence rate to the recommendation of screening and, allowed us to estimate the rate of adherence of patients' relatives to these recommendations.
Results: Two hundred and three patients were considered eligible for the study, and from those 62 (30.54%) answered the questionnaire. A simple t test showed that the sample had the same medium age of the total population (respectively 43.4 and 43 years). These two groups were compared with Mann-Whitney non-parametric test for tumor

location and cancer stage. There was no statistic significant differences between them (p 0.9671 to tumor location and p 0.7799 to cancer stage). Of the 62 patients in the research 39 (62.9%) declared they had received the recommendation for their relatives to undergo a screening colonoscopy. Two other patients (3.2%) received a fecal occult blood test recommendation for their relatives. The other 21 patients (33.9%) declared they had not received any specific recommendation from their doctors. The study also evaluated the adherence of patients and their relatives to the recommendations made by the physicians. Among the 39 patients that received the recommendation for colonoscopy, only 8 (20.5%) stated that all their siblings had the exam, 10 patients (25.6%) said that some of their siblings had the colonoscopy, and 20 patients (51.3%) stated that none of their siblings had the exam. One patient did not know said if the relatives had the exam.
Conclusion: The adherence of two thirds of physicians to the guidelines regarding colorectal-cancer screening in a reference center was underwhelming. However, the low adherence of patients' relatives to the screening recommendations is more worrisome. We identified the need for more education for both, patients and physicians, regarding potentially life-saving screening, as well as developing tools to encourage physicians to discuss the issue with their patients.
No conflict of interest.

2295 POSTER

Evaluation of vitamin D status and risk factors of osteopenia/osteoporosis in colorectal cancer survivors

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Background: The incidence of colorectal cancer increases with vitamin D deficiency as shown in recently published studies. In addition, prospective studies showed that low vitamin D levels associated with increased mortality of colorectal cancer, especially in stage III and IV. But the exact incidence of vitamin D deficiency and the relation between vitamin D deficiency and osteopenia/osteoporosis is still not known. The aim of this study is to identify severity of vitamin D deficiency and absolute risk factors of osteopenia/osteoporosis in colorectal cancer survivors.
Methods: A total of 113 survivors of colorectal cancer treated with surgery and/or chemotherapy ± RT were recruited from medical oncology outpatient clinics during routine follow-up visits in 2011–2012. Patients younger than 40 years and patients with osteopenia/osteoporosis history before diagnosis were excluded. Medical information of patients was obtained from their medical records. Patients completed a survey questionnaire that was designed to obtain information about consisted of demographic characteristics. Bone mineral densitometry (BMD) was performed, and serum 25-OH vitamin D levels were also checked on the same day of the questionnaire. According to the BMD; between −1.0 and −2.5 was accepted as osteopenia, lower than −2.5 was accepted as osteoporosis. The patients was divided into 2 groups. Group A is patients with normal BMD, whereas group B is patients with osteopenia/osteoporosis patients.
Results: The median age of the study population was 58 (40−76). Thirty-four (30.1%) patients of the study population were female, whereas 79 (69.9%) patients were male. The median follow-up of the study population was 48 months (14–120 months). Vitamin D deficiency was found in 109 (96.5%) of patients; mild deficiency (20−30 ng/ml) in 19 (16.8%) patients, moderate deficiency (10−20 ng/ml) in 54 (47.8%) patients and severe deficiency (<10 ng/ml) in 36 (31.9%) patients. Osteopenia was found in 58 (51.4%) patients whereas osteoporosis was found in 17 (15.0) patients. Normal BMD was observed in 38 (33.6%) of patients. No apparent effect of type of surgery, presence of stoma, chemotherapy, radiotherapy and TNM stage was found in the risk of osteopenia and osteoporosis. Also, the severity of the vitamin D deficiency was no effect in the risk of osteopenia and osteporosis (P =0.93). In female patients, osteopenia/osteoporosis were observed in 79.5% patients whereas 60.7% of male patients (P = 0.03).
Discussion: In our study, vitamin D deficiency and osteopenia/osteoporosis was observed in 96.5% and 66.4% of colorectal cancer survivors, respectively. There is no absolute risk factor of osteopenia and osteoporosis in colorectal cancer survivors. To our knowledge, in the literature, our study is the first study that evaluates all the risk factors of osteopenia ans osteoporosis in colorectal cancer survivors.
No conflict of interest.

2296 POSTER

A phase II study of third-line combination chemotherapy with bevacizumab plus S-1 for metastatic colorectal cancer with KRAS mutations: Additional analysis of overall survival in the SAVIOR study

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Background: We performed a phase II clinical trial to confirm the efficacy and safety of third-line combination chemotherapy with S-1 plus bevacizumab in metastatic colorectal cancer (mCRC) patients with mutated KRAS. We reported that the disease control rate, the primary endpoint, was 69.0% (95% confidence interval [CI], 49.2–84.7), and the median progression-free survival, a secondary endpoint, was 3.7 months (95% CI, 2.1−6.6) (ASCO-GI 2013).
Material and Methods: Subjects were mCRC patients with mutated KRAS, who showed aggravation even after 2 regimens with oxaliplatin and irinotecan. S-1 (80–120 mg/body) was administered for 4 weeks and withdrawn for 2 weeks. The dose of S-1 was decided according to the subjects' body surface area. Bevacizumab (5 mg/kg) was administered on Days 1, 15, and 29. This treatment was provided until progression. In the present study, we additionally analyzed survival from the starting dates of first-line therapy and second-line therapy and survival according to whether or not patients received fourth-line therapy (subsequent therapy).
Results: A total of 31 patients were enrolled from August 2009 through July 2011, and 29 with assessable lesions according to the Response Evaluation Criteria In Solid Tumors were included in efficacy analyses. Median overall survival (OS) from the date of enrollment, a secondary endpoint, was 9.0 months (95% CI, 7.0–12.0). Median OS from the date of starting first-line therapy was 23.3 months (95% CI, 18.3–31.2), and median OS from the date of starting second-line therapy was 17.0 months (95% CI, 11.3–19.5). Median OS from the date of enrollment was 12.0 months (95% CI, 5.9–20.0) in the patients who received fourth-line therapy (n = 11), as compared with 8.3 months (95% CI, 4.6–11.2) in those who did not receive fourth-line therapy (n = 18).
Conclusions: Survival from the dates of starting first-line therapy and second-line therapy in patients enrolled in this study did not differ appreciably from survival in other studies. This fact and the demographic characteristics of the patients indicate that our subjects were appropriately selected. Our results suggest that combination chemotherapy with S-1 plus bevacizumab is a potentially effective third-line treatment for mCRC with mutated KRAS. Further clinical trials are needed to confirm our results.
No conflict of interest.

2297 POSTER

Clinicopathologic characteristics and outcome of colorectal cancer in young patients: Experience in a cancer clinic in Indonesia

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Background: Colorectal cancer (CRC) generally affects persons older than 40 years. Controversies still exist regarding the feature and prognosis of young CRC patients.
Objective: The present study determined the clinicopathologic characteristics in younger patients and evaluated short-term outcome in comparison with older patients with CRC.
Material and Methods: The records of 336 CRC patients who visited 'Tulip' integrated cancer clinic Dr Sardjito General Hospital Yogyakarta Indonesia

in 2007–2011 were retrospectively analyzed. Clinical and histopathologic parameters and overall 1-year survival rates of 57 patients aged 40 years or less were compared with 279 patients aged more than 40 years.
Results: Young patients represented 17% of data observed. Median age in young cases was 34 year and in old cases was 58 year. Performance status in young cases was marginally better than old cases ($p = 0.052$). Compared with old patients, young patients had more frequent symptom of bloody stool ($p = 0.083$) as early sign. For sex ($p = 0.303$), tumor site ($p = 0.879$), staging ($p = 0.728$), histologic grading ($p = 0.930$) and presentation of synchronous metastasis ($p = 0.870$), no significant differences between both groups were observed. Young and old patients had the same overall 1-year survival rates ($p = 0.690$). In addition, majority of young cases were covered by government insurance for the poor people ($p = 0.001$) indicating that they came from lower economic background.
Conclusions: Clinicopathologic features and short-term outcome in young CRC patients in the local cancer clinic were similar to old cases. However, young cases showed more frequent bloody stool as early complaint although a significant difference was not reached. These results urged a mandatory for all patients with suspicious symptoms, especially young individuals, to undergo early adequate diagnosis.
No conflict of interest.

2298 POSTER

Cellular interactions during gastrointestinal cancer development

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Background: Cellular interactions of tumor and stromal components largely determine the formation of the phenotype of the tumor. Herewith, the tumor cells themselves are the active participants in intercellular interactions by secreting of metabolites into the stroma. Some contribution to carcinogenesis can make blood cells and their functional state. Thus, the platelets can secrete the number of growth factors − VEGF, PDGF, PD-ECGF/TP that activate angiogenesis and proliferation. Local immunity disorders also promote the tumor progression. For example, increased levels of adenosine under the low activity of adenosine deaminase (ADA) lead to the development of lymphocyte dysfunction. It is interesting the role of platelet derived endothelial cells growth factor (PD-ECGF/??) which can realize some effects due to enzyme activity because it is structurally identical to thymidine phosphorylase (TP).
Objective: To investigate the TP and ADA activities in platelets and lymphocytes of the peripheral venous blood and venous blood flowing directly from the affected organ.
Methods: Activity of cellular enzymes was determined spectrophotometrically in samples from 25 men with advanced cancer of the stomach or intestine. The patients had a median age of 58 years. The group consisted of 25 cases with adenocarcinoma histologically. The material for the study: platelets and lymphocytes of venous blood that was taken from the cubital vein and blood flowing from the affected organ; the tumor tissue and mucosal resection margin distant from the tumor (control).
Results: The platelets thymidine phosphorylase activity changes in the blood flowing from the tumor were unidirectional with the tumoral TP activity. It was in platelets 22.90 ± 5.49 nmol/mg·ml (in platelets of the peripheral venous blood − 11.15 ± 5.76 nmol/mg·ml). The cancer tissue TP activity was 52.48 ± 15.32 nmol/mg·ml. It was higher then in control tissue (33.17 ± 8.98 nmol/mg·ml). ADA activity of lymphocytes flowing from the tumor was lowest. It decreased from 35.85 ± 10.04 nmol/mg·ml in lymphocytes of the peripheral venous blood to the 15.28 ± 6.22 nmol/mg·ml.
Conclusions: Thereby platelets and tumor cells are capable of responding by increased PD-ECGF/TP expression, under the influence of local signals, such as hypoxia, and also immunosuppressive effect may occur.
No conflict of interest.

2299 POSTER

Intraoperative radiotherapy reduces local recurrence rates in patients with locally advanced rectal cancer with microscopically involved circumferential resection margins

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Background: Local control is one of the main goals of the surgical treatment of rectal cancer. The most important predictive factor for local control is the circumferential resection margin (CRM). Unfortunately, CRM involvement still occurs in 19−24% of the patients with locally advanced rectal cancer (LARC), despite the use of (chemo-)radiotherapy and total mesorectal excision (TME). In patients with a CRM at risk, local recurrence rates may be reduced by administering intra-operative radiotherapy (IORT). One single dose of IORT is considered the biological equivalent of two to three times the dose given by conventional fractionation and this dose, preceded by an external radiation dose, may be sufficient to eradicate microscopic remnants. In addition, IORT may also be beneficial in patients with a clear but narrow CRM (<2 mm), because these patients have a higher risk of local recurrence. This study evaluated the effect of IORT in patients with LARC after TME with a microscopic involved CRM or a clear but narrow CRM.
Methods: Between 1996 and 2012, all surgically treated patients with LARC and a CRM less than 2 mm after (chemo-)radiotherapy followed by TME were analyzed. These patients were divided into a group with radical resections with a clear but narrow CRM (<2 mm) and a group with a microscopic involved CRM. In these groups, the outcome of the patients who were treated with IORT was compared to the outcome of patients who were treated without IORT.
Results: Ninety-five of the 409 surgically treated patients with LARC had a CRM less than 2 mm after neoadjuvant (chemo-)radiotherapy. Forty-three patients had a radical resection with a clear but narrow CRM and 48 patients had a microscopic involved CRM. Four patients were excluded from further analysis due to a macroscopic irradical resection. Of the patients with radical resection with a clear but narrow CRM, 21 patients were treated with IORT and 22 patients were treated without IORT. The baseline characteristics of the patients treated with and without IORT were similar. There was no difference in the cumulative 5-years local recurrence-free survival (70 vs. 79%, $p = 0.63$). Of the patients with a microscopic involved CRM, 31 patients were treated with IORT and 17 patients were treated without IORT. Baseline characteristic of the patients treated with and without IORT were similar, except that patients treated without IORT had more stage IV disease (52 vs. 13%, $p = 0.01$). In this group, there was a significant difference in the cumulative 5-years local recurrence-free survival in favor of the 31 patients treated with IORT compared with the 17 patients who were not treated with IORT (84 vs. 41% $p = 0.01$). Multivariable analysis confirmed that IORT was independently associated with a decreased local recurrence rate in these patients.
Conclusion: IORT reduces local recurrence rates in patients with LARC with a microscopic involved CRM.
No conflict of interest.

2300 POSTER

Long-term outcome of sphincter preserving operation after preoperative short-term radiotherapy and delayed surgery for T3 rectal cancer

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Background: It is said that short-term radiotherapy (sRT) and immediate surgery does not lead to increase the sphincter preserving rate for rectal cancer. We hypothesised that a long interval before surgery is necessary to allow for a tumour response and to improve chances of sphincter preservation. The purpose of this study is to review the long-term outcome of sphincter preserving operation after sRT and delayed surgery for T3 rectal cancer.
Material and Methods: Between January 2001 and December 2011, patients with cT3N0−2 mid or low rectal cancer after sRT were enrolled in this study. 140 patients were treated with a total dose of 25 Gy (25 Gy in 10 fractions for 5 days) with sensitiser (S-1; 80 mg/m^2 day1−10). Radical surgery with TME was performed 3−4 weeks (median: 24 day) following the end of the sRT. No eligible patients received lateral lymph node resection except for 15 patients with lateral lymph node swelling.
Results: The median follow-up term was 45.6 (range: 15–146) months. Patient characteristics were as follows; Male-to-female ratio; 98 : 42. The median age was 65.0 (range: 39−85) years. Median distance from anal verge was 6.5 (0−9) cm. Preoperative radiologic diagnosis was N-/N+; 49/91. Histology was well or moderately differentiated/poorly or mucinous = 127/13. Type of resection was APR/non-APR= 8/132 (anal preserving rate; 94.3%). The reason for APR was that 4 were elderly patient or their private affairs. 2 were selected by patients and 2 were invaded to anal verge. Postoperative T stage was ypT1 or 2/ypT3 or 4 = 54/86, Postoperative N stage was ypN- /yp N+ = 87/53. Tumour regression grade by Dworak classification was TRG0 /1 /2 /3 /4 =0 /52 /38 /45 /5. Median length of distal margin (DM) and circumferential resection margin (CRM) was 11 (0−40) mm and 4 (0−7) mm. Long-term outcome were as follows; the local recurrence rate was 8/140 (5.7%). 1 (12.5%) had anastomosis site recurrence, 1 (12.5%) had anterior pelvic organ recurrence, and 6 (75.0%) had lateral pelvic recurrence. The overall survival rate at 5 years was 80.1% and the recurrence-free survival rate was 68.5%.

Conclusions: We presented a long-term outcome of sphincter preserving operation after preoperative short-term radiotherapy and delayed surgery for T3 mid to low rectal cancer. sRT with delayed surgery could expect for high rate of sphincter preservation and produced feasible long-term outcomes.
No conflict of interest.

2301 POSTER

Phase II trial of short-course radiotherapy alone followed by delayed surgery for locally advanced rectal cancer

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Background: The short-course radiotherapy (SCRT) regimen has been used in part of Europe as preoperative treatment in rectal cancer. It is a convenient regimen because it consists of only 5 fractions of 5 Gy without chemotherapy followed by immediate surgery. However, one criticism of the SCRT regimen is the lower complete pathological response rate (pT0) when compared to the long-course regimen which consists of 25−28 fractions of 1.8 Gy with chemotherapy followed by delayed surgery. We performed a prospective phase II study to investigate the feasibility and the rate of pT0 after the SCRT but followed by delayed surgery.
Materials and Methods: Operable patients with pathologically proven localized rectal cancer staged as T3−4N0/+ or T2N+ were eligible. They received 25 Gy in 5 consecutive fractions to the posterior pelvis. Patients were oriented to have TME surgery 8 weeks after the SCRT. Pathological response to the treatment and radiotherapy and surgical toxicities were assessed in all patients.
Results: Between October 2008 and December 2011 the target sample of 52 patients finished the treatment according to protocol. Median age was 68 years; median tumoral distance from the anal verge was 6.5 cm. Median interval to surgery was 52 days. 38/52 (73%) patients underwent low anterior resection. The median number of days in hospital for the surgical procedure was 8 days. All patients were able to undergo a complete surgical resection with 100% having pathological negative margins. 5/52 (10%) patients had complete pathological response. Toxicity was acceptable and comparable with the rates reported for SCRT followed by immediate surgery and the long course followed by delayed surgery.
Conclusions: From the results of our study and the recent publications it appears that: 1) an appropriate surgical resection with acceptable toxicity can be achieved with SCRT alone followed by delayed (4−8 weeks) surgery; 2) there is a better rate of complete pathological response (10%) with the SCRT followed by delayed compared to immediate surgery (0.7%). Our study is underpowered to evaluate whether a SCRT followed by delayed surgery achieves pT0 rates similar to the long-course. This question remains open and warrants further investigation.
No conflict of interest.

2302 POSTER

Post-chemoradiation laparoscopic resection and intraoperative electron-beam radiation therapy in locally advanced rectal cancer: Long-term outcomes

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Background: It has been previously reported that in selected patients with rectal cancer, laparoscopic surgery resulted in similar safety, resection margins, and completeness of resection to that of open surgery, and recovery was improved after laparoscopic surgery. We analysed long-term outcomes in a group of patients with locally advanced rectal cancer (LARC) treated with preoperative combined therapy followed by laparoscopic surgery and intraoperative electron-beam radiotherapy (IOERT).
Material and Methods: From 06/05 to 12/10, 125 LARC patients were treated with 2 courses of induction FOLFOX-4 (oxaliplatin 85 mg/m^2/d1, intravenous leucovorin at 200 mg/m^2/d1−2, and an intravenous bolus of 5-fluorouracil 400 mg/m^2/d1−2) and preoperative chemoradiation (4500–5040 cGy) followed by a total mesorectal excision (laparoscopic 35%, open surgery 65%) and a IOERT presacral boost.
Results: Patients in the laparoscopic surgery group lost less blood (median 200 mL vs 350 mL, $p < 0.01$) and hospital stay was shorter (7 days vs 11 days; $p = 0.02$) than did those in the open surgery group. Laparoscopic procedures did not take longer (270 min vs 302 min; $p = 0.67$) than open surgery procedures. In the laparoscopic and open surgery groups, postoperative morbidity (32% vs 44%; $p = 0.65$), RTOG grade $\geqslant 3$ acute (25% vs 25%; $p = 0.97$), and RTOG grade $\geqslant 3$ chronic toxicity (7% vs 9%; $p = 0.48$) were similar. With a median follow-up time for the entire cohort of patients was 59.5 months (range, 7.8−90); locoregional control (HR 0.91, $p = 0.89$), disease-free survival (HR 0.80, $p = 0.65$) and overall survival (HR 0.67, $p = 0.52$) did not differ significantly between the groups.
Conclusions: Post-chemoradiation laparoscopically assisted surgical-IOERT approach is feasible with an acceptable risk of postoperative complications, shorter hospital stay and similar long-term outcomes when compared to the open surgery approach.
No conflict of interest.

2303 POSTER

Prognostic factors analysis of postoperative radiotherapy for upper rectal cancer: Ten years experience from Cancer Hospital, Chinese Academy of Medical Sciences 2000–2010

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Background: Whether postoperative radiotherapy (RT) will benefit for stage II/III upper rectal cancer after a complete resection is not clear. The aim of this study was to compare the outcomes of treatment with or without adjuvant chemoradiotherapy (CRT) or RT in pathological T3−4N0−2 upper rectal cancer.
Material and Methods: This retrospective analysis included 547 primary upper rectal cancer patients who were extracted from 3995 rectal cancer patients admitted in Cancer Hospital, Chinese Academy of Medical Sciences from January 2000 to December 2010. Lower margin of the tumor located 10−16 cm from the anal verge determined by colonofiberscope, underwent radical proctectomy (R0) and pathologically staged as II/III were included. Nearly two-thirds patients received adjuvant CRT/RT (S+RT, 375) and the rest did not (S, 172).
Results: The median age was 59 years old (range 23−84) and the male to female ratio was 1.75:1. The patients were pathologically staged as stage IIa (25.4%), IIb (16.6%), IIc (3.5%), IIIa (2.7%), and IIIb (36.7%) and IIIc (15.0%) according to 7th TNM staging system. Of 375 patients in S+RT, 287 (76.5%) received RT concurrently with chemotherapy. With a median follow-up of 51 months (range 5–159), the 5-year overall survival (OS), disease free survival (DFS), cancer specific survival (CSS), locoregional recurrence free survival (LRFS) and distant metastasis free survival (DMFS) were 79.0%, 76.8%, 83.0%, 94.0% and 80.1%, respectively. The addition of postoperative CRT/RT did not improve estimated 5-year OS (S+RT 79.0% vs S 78.5%, P=.465), DFS (S+RT 75.5% vs S 79.5%, P=.739), CSS (S+RT 81.6% vs S 86.1%, P=.411), LRFS (S+RT 94.2% vs S 93.2%, P=.408) and DMFS (S+RT 78.6% vs S 83.4%, P=.565). But the fact was that more patients in S+RT had positive lymph nodes as compared with those in S (54.7% vs 39.8%, $P = 0.001$). In the subgroup of patients staged as T4bN0 or anyT, N1b-2b, multivariate analysis indicated postoperative CRT/RT was independently associated with higher OS (HR 0.462, 95% CI 0.240–0.887, $P = 0.2$), DFS (HR 0.576, 95% CI 0.321–1.031, $P = 0.63$), CSS (HR 0.522, 95% CI 0.256–1.063, $P = 0.73$) and LRFS (HR 0.362, 95% CI 0.142–0.920, $P = 0.33$).
Conclusions: The outcomes of upper rectal cancer treated with radical surgery with or without postoperative RT was definitely good. More patients with adverse N stage would like to receive postoperative RT, however, patients in advanced stage (T4bN0 or anyT, N1b-2b) maybe benefit from the postoperative RT.
No conflict of interest.

2304 POSTER

Outcome of stereotactic ablative body radiotherapy in patients with lung oligo-metastases from colo-rectal cancer primary

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Background: The reported early clinical experience in Stereotactic Ablative Body Radiotherapy (SABR) in patients (pts) with lung oligo-metastases (L-OMD) is promising. Our objective was to assess our multi-

institutional experience with SABR in heavily pre-treated colo-rectal cancer (CRC) patients with isolated L-OMD.
Material and Methods: From April/09 to Jan/13, 44 pts received SABR for isolated L-OMD from CRC primaries. 10 pts (22%) had multiple L-OMD treated concurrently. All had primary disease controlled at the time of SABR. The median age was 70 years (39−84). All patients had KPS>80%. 34 pts(77%) had prior chemotherapy (at least 2 lines), and 15pts (33.5%) had prior treatment for L-OMD (sugery, 13 pts, RFA, 2 pts). The median disease free interval from initial diagnosis to diagnosis of L-OMD requiring SABR was 33 months (0–144). Median tumour size was 1.35 cm (0.8−4). Centralised protocols for IMRT- SABR developed by University of Pittsburgh Cancer Institute were used. SABR was performed with using Body Fix^{TM} immobilisation, image-guided dynamic IMRT and respiratory motion management. Target volumes were adapted to account for respiratory motion. Varian Trilogy TX with high definition MLC and on-board image guidance (KV, CBCT, fluoroscopy) were used. Tumor location risk adapted fractionation schedules were used: 60 Gy/3 (20 pts), 60 Gy/5 (6 pts), 48 Gy/4 (10 pts), 60 Gy/8 (7 pts), and 50 Gy/10 (1 pt), delivered in 2−3 weekly treatments.
The primary end-points were local control and survival. Secondary endpoints were pattern of failure and toxicity.
Results: Post-SABR, the median follow-up time was 12 months (2−33). At 1- and 2- years, the actuarial in-field control rates were 82.5% and 51.8%, progression free survival (PFS) 47% and 14.1%, overall survival (OS) 87% and 53% respectively. Median survival time was 24 months from completion of SABR. There was no significant correlation between survival and age, tumor size, number of treated metastases, dose schedule or disease free interval.
After a median of 6 months post-SABR (1−26), 27 pts (61%) experienced a first progression, mainly extra-target new pulmonary nodules (11 pts isolated, 4 pts associated with extra-thoracic metastases). Isolated in-field failure was recorded in 4 pts. Salvage SABR was used in 7 pts with new single pulmonary nodule, while further chemotherapy was recommended in 20 pts. After first progression, the 1- and 2- years OS were 71% and 41% respectively.
No high grade (>G3) acute or long term toxicities were reported.
Conclusions: Our early multi-institutional experience shows that SABR achieves good local control and promising PFS and OS rates, with low toxicity in pretreated, selected patients with isolated L-OMD from CRC primaries. The reported pattern of failure shows high rates of extra-target volume disease progression, illustrating the challenges in patient selection. The best patient group to benefit from SABR remains to be determined.
No conflict of interest.

2305 POSTER

Determination of the delivered dose to scrotum and testis in radiotherapy of rectal cancer by thermoluminescence dosimetry (TLD), with a comparison to the dose calculated by the planning software

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Background: Rectal cancer is a common malignancy, in treatment of which pelvic radiotherapy plays an important role. But this may lead to azospermia and infertility. We designed a study to determine the delivered dose to the scrotum and testes with thermoluminescence dosimetry (TLD) and compare it to the dose calculated by the 3-dimensional planning software.
Materials and Methods: We measured the scrotum and testicular doses by TLD; the TLDs were fixed to the scrotum in six points anteriorly and posteriorly in two random fractions of the radiation course. All patients received a 50 −50.4 Gy radiation dose to the pelvis in a prone position with standard fractionation and 3-dimensional planning, through three or four fields. The average dose of the TLD measurements was compared to the average of 6 relevant point doses calculated by the planning software.
Results: In 33 patients with a mean age of 56 (range 24−72) years, the mean testis dose of radiation measured by TLD was 3.77 Gy (range 4.08–15.81 Gy), equal to %7.5 of the total prescribed dose. The mean of point doses calculated by the 3-dimensional planning software was 4.11 Gy (range 0.17–23.4 Gy), equal to %8.1 of the total prescribed dose. A significant relationship was seen between the position of the inferior edge of the fields and the mean testis dose (P = 0.04). Also body mass index (BMI) was inversely related with the testicular dose (P = 0.049).
Conclusion: In this study, the mean testis dose of radiation was 3.77 Gy, similar to the dose calculated by the planning software (4.11 Gy). This dose could be significantly harmful for spermatogenesis, though low doses of scattered radiation to the testes in fractionated radiotherapy might be followed with better recovery. Based on above findings, careful attention to testicular dose in radiotherapy of rectal cancer for the males desiring continued fertility seems to be required.
No conflict of interest.

2306 POSTER

Does radiotherapy of the primary rectal cancer affect prognosis after pelvic exenteration for recurrent rectal cancer?

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Background: The role of radiotherapy in reducing local recurrence for rectal cancer is well-documented, albeit at the expense of potential short and long term toxicity. Radiotherapy may also render the treatment of local recurrence more challenging should it develop despite previous radiotherapy. This study examined the impact of radiotherapy for primary rectal cancer on outcomes after pelvic exenteration for locally recurrent rectal cancer.
Materials and Methods: Patients who underwent pelvic exenteration for locally recurrent rectal cancer at the Royal Prince Alfred Hospital in Sydney were identified from an electronic exenteration database. Medical records were reviewed for supplementary data on adjuvant therapy and follow-up. Outcomes between patients who did and did not receive radiotherapy were compared. The main outcomes of interest were resection margins, overall survival, disease free survival and surgical morbidities.
Results: Between 1994 and 2012, 108 patients underwent pelvic exenteration for LRRC. Of these, 87 were eligible for analysis (radiotherapy= 41, non-radiotherapy= 46). There was no peri-operative mortality. Patients who received radiotherapy for their primary rectal cancer required more radical exenterations (68% vs 44%, p= 0.020), had significantly lower rates of clear resection margins (63% vs 87% p= 0.010), an increased rate of surgical complications per patient (p= 0.014) and a lower disease free survival (p= 0.022). 5 year overall survivals were 26.8% and 66.9% in the radiotherapy and non-radiotherapy groups respectively. Although this was not statistically significant (p = 0.115), it was considered clinically significant. Further, overall survival and disease free survival in patients with clear margins was also lower in patients who received radiotherapy for their primary rectal cancer (p= 0.049, and p< 0.0001 respectively). This difference in survival persisted on multivariate analysis after correcting for T and N stages of the primary tumour.
Conclusions: This study shows that patients who received radiotherapy as part of their treatment of primary rectal cancer have worse oncological outcomes than those who did not after pelvic exenteration for locally recurrent rectal cancer. Further research is necessary to clarify potential long term adverse effects of radiotherapy in rectal cancer patients.
No conflict of interest.

2307 POSTER

The relation of ypT, ypN and tumor regression grade in rectal cancer treated with preoperative short-term chemoradiotherapy

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Purpose: Preoperative chemoradiotherapy applied to the locally advanced rectal cancer reduces local recurrence and improves survival. We assessed tumor regression grade (TRG) and shrinkage pattern in rectal cancer patients treated with short-term chemoradiotherapy followed by surgical resection.
Methods: Between 2001 and 2011, 140 patients with locally advanced rectal cancer treated with short-term preoperative chemoradiotherapy followed by surgical resection were retrospectively analysed. Patients received preoperative short-term chemoradiotherapy (25 Gy/10 fractions/ 5 days) with S-1 as a sensitizer for 10 days. Operation was performed at 3−4 weeks after the end of chemoradiotherapy. We examined resected samples in pathological status of ypT, ypN and TRG. We evaluated by using the TRG proposed by Dworak et al. We analyzed the relation of ypT, ypN and TRG in pathology, retrospectively.
Results: The ypT distribution was shrinkage pattern (ypT0, ypT1 or ypT2)/ fragmentation pattern (ypT3 or ypT4) = 54/86. The ypN distribution was N(−)/N(+) = 53/87. The TRG distribution was TRG0/TRG1/TRG2/ TRG3/TRG4 =6/45/38/52/0. The shrinkage patterns in T feature were significantly greater in the radioresponders group (TRG2, 3, 4) (48.3% vs 22.6%, P<0.05). Lymph node metastasises were significantly less in the shrinkage patterns group. (81.5% vs 50.0% p < 0.05) Lymph node metastasises tended to be less in the radioresponders group (66.7% vs 54.7% p = 0.15).

Conclusion: Higher TRG closely correlates with better ypT and ypN after short-term preoperative chemoradiotherapy followed by surgical resection.
No conflict of interest.

2308 POSTER

Neoadjuvant radiotherapy in rectal carcinoma: Therapeutic response and toxicity

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Background: Locally advanced rectal carcinoma (LARC) is usually treated with radiotherapy (RT) followed by surgery. There are two schemes for neoadjuvant irradiation: long-course (LC), associated with chemotherapy (CT), and short-course (SC). The aim of this study is to compare response and toxicity to RT using LC and SC irradiation in patients with LARC.
Material and Methods: We included patients with LARC treated between 2002 and 2012 in our Institution using pre-operative RT, either using LC or SC. Response was assessed by pTNM classification and Dworak Regression Grade (DRG). Toxicity was assessed using CTCAE4.0 scale.
Results: 215 patients treated with LC and 55 treated with SC were included. SC patients were older and had lower performance status than LC patients ($p < 0.001$). 20% of SC patients were stage IV and 92.6% of LC patients were stage III ($p < 0.001$). Surgery with curative-intent was performed in 208 LC patients and 47 SC patients; sphincter-preserving surgery was performed in most cases. DRG 4 was obtained in 16.8% vs. 6.4%, nodal downstaging in 66.3% vs 23.4% and loco-regional response in 79.8% vs. 57.4% (LC vs. SC; $p < 0.001$). No acute toxicity was described in SC patients; in other hand, we observed acute toxicity in 77.7% of LC patients ($p < 0.001$), with 7.9% of grade 3 or 4 ($p = 0.028$). No differences in post-operative complications were observed ($p = 0.299$). More LC patients were submitted to adjuvant CT ($p < 0.001$). Worse pathologic response pTN and DRG 0 or 1 in LC treatment are related to more R+ resections ($p < 0.01$).
Conclusions: LC irradiation is associated with better response than SC irradiation, allowing more curative resections, at the expense of an acceptable toxicity.
No conflict of interest.

2309 POSTER

Neoadjuvant chemoradiotherapy in rectal carcinoma: Therapeutic response as prognostic factor

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Background: Chemoradiotherapy (CRT) followed by surgery is a consensual approach for locally advanced rectal cancer (LARC). In this CRT regimen, known as long-course (LC), radiation dose is 45–50.4 Gy/25−28fr/5−5.5wk. Pathologic response (PR) might have prognostic impact in these patients. This study aims to compare disease-free (DFS) and overall survival (OS) in patients with LARC, stratified for PR.
Material and Methods: We included LARC patients treated in our Institution between 2002 and 2011, using LC irradiation. Response was assessed using pTNM classification and Dworak Regression Grade (DRG). Survival was estimated by Kaplan–Meier method and multivariate analysis was performed using Cox Proportional Hazards Regression. A type I error of 0.05 was considered.
Results: 199 patients were included. Complete response (GROUP1) was obtained in 13.6% of patients, ypT1−2 N0 (GROUP2) in 30.2% and ypT3−4 or N+ (GROUP3) in 56.3%. In univariate analysis, DFS and OS were lower in GROUP3 ($p = 0.001$, Hazard Ratio (HR)=3.283 and $p = 0.004$, HR = 8.188, respectively); other significant prognostic factors were R+ resection ($p < 0.001$) and distance to anal verge lower than 6 cm ($p < 0.05$). In multivariate analysis complete PR had significant impact in DFS and R+ resection in DFS and OS ($p < 0.05$). Higher DRG was associated with better DFS ($p = 0.017$).
Conclusions: PR assessed by pTNM staging or by DRG had significant prognostic impact in DFS and OS, in patients with LARC treated with CRT.
No conflict of interest.

2310 POSTER

Effect of neoadjuvant chemoradiotherapy on lymph node harvest in rectal cancer surgery

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Background: Current guidelines suggest for proper TNM staging, 12 lymph nodes per specimen are critical. This study assessed the role of preoperative radiochemotherapy on the number of lymph nodes detected in the tumor-bearing specimen.
Material and Methods: Data on 93 patients who had resection of rectal adenocarcinoma stage II and III at a single cancer center in the United Kingdom were retrospectively reviewed during the period April 2009 to May 2012.
Results: Of a total of 93 patients, 51 received neoadjuvant therapy and 42 did not. Positive lymph nodes (minimum 12) were detected in 85% patients in the neoadjuvant group as compared with 98% patients in the surgery group ($P<0.05$). Significantly fewer total lymph nodes were retrieved in the neoadjuvant therapy patients compared to those who did not receive preoperatively therapy (16 vs. 21, $p < 0.05$). There was a significantly higher extramural venous spread in the surgery alone group. (27 vs.18, $P<0.05$). Tumor regression was seen in 40% patients who received neoadjuvant therapy.
Conclusions: Preoperative radiochemotherapy could induce a significant downsizing and downstaging of advanced rectal cancer. Great care in operative and pathologic examination techniques must be taken to ensure appropriate staging.
No conflict of interest.

2311 POSTER

Sampling rectal mucus DNA − a new method for early diagnosis of colorectal cancer?

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Introduction: Increased colonocyte exfoliation in colorectal cancer (CRC) is well described. Higher DNA counts have been observed in rectal mucus from CRC patients, but the amount of DNA at varying distances from the primary tumour has not been determined.
Methods: 25 specimens from patients with CRC were used to measure the amount of human DNA in muscosal samples at the tumour site and at set distances from it. Results were expressed as ratio of the value at a particular site to value at tumour site. Rectal mucus DNA count was measured in 58 patients with suspected CRC. These were later divided into cancer or benign groups and the amount of rectal mucus DNA in the two groups was compared.
Results: The ratio of DNA counts was significantly higher for measurements taken at up to 15 cm distal to the tumour, compared with those from the most proximal margin of the specimen. However there was no significant difference in the ratio of DNA counts taken from the 20 cm immediately proximal to the primary tumour, and those taken distal to the tumour. The 39 patients who were eventually diagnosed with CRC had higher DNA in their rectal mucus, compared to those ($n = 19$) that had no disease or small benign polyps.
Conclusion: These results suggest distal accumulation of tumour DNA within colonic mucus which can be easily obtained via proctoscopy. This may allow future work on identifying biomarkers within rectal mucus which would indicate preclinical development of CRC and earlier diagnosis.
No conflict of interest.

2312 POSTER

Colorectal liver metastases and peritoneal metastases: Prognostic equivalences and differences after complete surgery

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Background: No where in the literature is there mention of equivalent survival results after curative surgery treating colorectal metastases emerging at different sites.
Objective: To present prognostic similarities and differences between patients treated for liver metastases (LM) and patients treated for peritoneal metastases (PM).

Patients and Methods: A retrospective analysis of prospective databases concerning 287 patients with LM and 119 patients with PM treated by surgery plus chemotherapy between 1993 and 2009. Patients presenting with LM + PM (n = 37) were excluded for methodological reasons. The overall tumour load was the main prognostic factor, LM-patients were divided in 2 subgroups (1−10 LM and 11−50 LM) and PM-patients were divided into 3 subgroups according to the peritoneal cancer index (PCI): 1−5, 6−15, and >15. All of them had also received peri-operative systemic chemotherapy.
Results: 5-year survival rates, mortality and morbidity were not statistically different between the two treatment groups (respectively 38.5%, 2.7% and 11% in the LM-group, and 36.5%, 4.2% and 17% in the PM-group). The 5-year overall survival rate was the highest in the subgroup with minimal peritoneal disease (PCI 1−5): 72.4%. It was similar for the 1−10 LM and 6−15 PCI score subgroups (respectively 39.4% and 38.7%), lower for the 11−50 LM (18.1%) subgroup, and dramatically low for the >16 PCI score (11.8%) subgroup.
Conclusion: Equivalent survival results exist when resected LM and resected PM are compared. Minimal PM carries a far better prognosis than LM. Classification into subgroups according to the overall tumour load (2 subgroups for LM and 3 for PM) enabled us to obtain a simple and clear prognostic assessment.
No conflict of interest.

2313 POSTER

Irreversible electroporation, a novel, non-thermal ablation technique to treat colorectal liver metastases: Results of an 'ablate and resect' study

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Background: Irreversible electroporation (IRE) is a new, non-thermal, image guided technique for tumor ablation. The application of an electric field across cells creates nanopores in the cell membrane, inducing cell death. Surrounding -acellular- connective tissue is relatively preserved, so the framework of vulnerable structures such as blood vessels and bile ducts should remain intact. We present results of the COLDFIRE study: a prospective single centre pilot study of patients with colorectal liver metastases treated with IRE before surgical resection. The aim was to evaluate safety, feasibility and (histological) changes of the ablated tissue after IRE.
Material and Methods: After informed consent, 11 patients with resectable colorectal liver metastases <3.5 cm were included. Exclusion criteria were chemotherapy <6 weeks prior to surgery or a history of cardiac arrhythmias or epilepsy. During laparotomy, one of the resectable metastases was ablated with IRE. Sixty minutes after ablation, the ablation zone was visualized using ultrasound and that same lesion was resected. Safety and feasibility were determined based on blood samples, (S)AE's and procedure time. The vitality of the ablation zone was visualized macroscopically using triphenyl tetrazolium chloride (TTC) and microscopically using different immuno-histological stainings. Inclusion has been completed.
Results: Eleven lesions were treated with IRE in respect to this study with a mean diameter of 2.2 cm. No SAE's occurred during the procedure and technical failure was reported once. Two or 4 electrodes were used for ablation and correct placement took on average 2.5 min per electrode. Median total ablation time was 2.6 minutes (1−7). One ablation took 55 minutes, due to over-current. Median time until resection was 85 minutes (51–153). The ablation zone was hypo-echogenic on ultrasound. The specimen showed red discoloration of the ablated area which turned grey after TTC staining, indicating avitality. Bile ducts and blood vessels were macroscopically intact in all cases.
Conclusion: This study suggests that IRE is a quick, safe and feasible technique for local treatment of colorectal liver metastases. Macroscopic results are promising, but histology needs to be awaited to determine the exact effect on the tissue and to define the transition-zone between reversible and irreversible electroporation.
Trial registration at clinicaltrials.gov, NCT01799044. The trial is sponsored by CCA/V-ICI
No conflict of interest.

2314 POSTER

Factors affecting the number of retrieved lymph nodes in patients with stage II colon cancer − lymph-node size and area ratios of B cells and T cells in lymph nodes

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Background: In patients with stage II colon cancer, large numbers of retrieved lymph nodes have been associated with good survival. We tested the hypothesis that lymph node size was large in patients with many retrieved lymph nodes and then investigated the cause of increased lymph-node size.
Methods: The study group comprised 320 patients with stage II colon cancer who underwent radical (R0) resection from 1991 through 2003. All patients underwent elective surgery performed by the same team of colorectal-cancer specialists. Lymph-node dissection extended to the origin of the feeding artery. The long- and short-axis diameters of retrieved nodes were measured on H-E stained specimens. Lymph nodes are divided into 3 compartments: the cortex, paracortex, and medulla. B cells reside mainly in the cortex, and T cells mainly in the paracortex. B-cells and T-cells were immunohistochemically stained with CD20 and CD3, respectively, and CD20-positive area ratio and CD3-positive area ratio were measured with image analyzer.
Results: A total of 4745 lymph nodes were examined. The mean number of retrieved nodes was 15±10. The long-axis diameters of the lymph nodes were as follows: mean, 4.8±2.6 mm; median, 4.3 mm; and maximum, 20.4 mm. The short-axis diameters were 3.4±1.7 mm, 3.0 mm, and 15.1 mm, respectively. Correlation coefficients (Pearson) for the number of retrieved nodes and their long-axis diameters were as follows: mean, 0.23; median, 0.16; and maximum, 0.59. The respective correlation coefficients for the short-axis diameters were 0.18, 0.13, and 0.54. There were moderate positive correlations between the number of retrieved nodes and the maximum long- and short-axis diameters of the nodes. Based on these results one lymph node with the greatest long-axis diameter was selected per patient and was immunohistochemically stained with CD20 and CD3. The mean area ratio was 0.42±0.10 for CD20 and 0.39±0.08 for CD3. When the cutoff value of the CD20-positive area ratio was set at 0.4, the mean long-axis diameter was significantly greater for nodes with a CD20-positive area ratio of ⩾0.4 than for those with a ratio of <0.4 (9.4±3.7 mm vs. 8.3±3.4 mm; $p < 0.01$). There was no significant relation between CD3-positive area ratio and the mean long-axis diameter. Survival analysis showed that age, depth of invasion, and CD20-positive area ratio were independent prognostic factors. The hazard ratio was 2.31 (95% confidence interval [CI], 1.52–3.62; $p < 0.01$) for age (younger than 63 years vs. 63 years or older), 2.82 (95% CI, 1.86–4.20; $p < 0.01$) for depth of invasion (T3 vs. T4), and 0.58 (95% CI, 0.39–0.85; $p = 0.01$) for CD20-positive area ratio (<0.425 vs. ⩾0.425).
Conclusions: The number of retrieved lymph nodes correlated with the longest diameter of retrieved nodes. The B-cell area ratio of lymph nodes increased in parallel to maximum lymph-node diameter and positively correlated with better survival.
No conflict of interest.

2315 POSTER

Prospective randomized study comparing robotic-assisted surgery with laparotomy for rectal cancer in India

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Background: Rectal cancer is one of the common cancers in India. Surgical management is the mainstay of initial treatment for majority of patients. Open rectal surgery is considered the gold standard treatment for rectal cancer. Minimally invasive surgery has gained acceptance for the surgical treatment of rectal cancer because, compared with laparotomy and is associated with fewer complications, shorter hospitalization, and faster recovery. The aim of this study is to evaluate the safety, feasibility, technique and outcomes (oncological and functional) of robotic rectal surgery in comparison with open surgery in the Indian population.
Materials and Methods: A prospective randomized study was undertaken from April 2011 to March 2013. 90 patients who presented with rectal carcinoma were randomized to either robotic arm (RA) or open arm (OA). Both groups were matched for clinical stage and operation type.
Results: The mean operative time was significantly longer in the RA than in the OA (310 vs 246 min, P<0.001. The operative time but was significantly reduced in the latter part of the RA patients compared with the initial few patients. The mean estimated blood loss was significantly less with RA compared to OA (165.14 ml vs 406.04 ml, P<0.001). None of the patients had margin positivity. The mean distal resection margin

was significantly longer in the RA than OA (3.6 vs 2.4 cm, P < 0.001). One of the most important factors relating to adequacy of rectal excision is the mesorectal grade, which is related to oncological outcome.100% of patients in RA had complete mesorectal excision while five patients in the OA had incomplete mesorectal excision. Incomplete mesorectal excision with distal 'Coning' was more common in OA due to lack of sufficient space in the pelvis. The average number of retrieved lymph nodes was adequate for accurate staging. Number of lymph nodes removed by robotic method is slightly higher than the open method (16.88 vs 15.20) but with no statistical significance. Conversion rate was nil. The mean hospital stay was significantly shorter in RA (7.52 versus 13.24 days, P<0.001). Post-operative and functional outcomes (urinary function, erectile dysfunction & retrograde ejaculation) were comparable between the two groups.
Conclusion: Robotic assisted surgery is an emerging technique in our country. In comparison to open method, it has advantages of decreased blood loss, less postoperative complication and shorter length of hospital stay. The patients who underwent robotic surgery had a superior mesorectal grade and longer distal resection margins. Morbidly obese patients are more suitable for robotic assisted approach, as chances of arm clash decrease due to adequate spacing.We conclude that robotic assisted rectal cancer surgery is safe with low conversion rates, acceptable morbidity and is oncologically feasible.
No conflict of interest.

2316 POSTER

Treatment of ovarian metastases of colorectal carcinoma in the era of hyperthermic intraperitoneal chemotherapy

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Background: Patients with ovarian metastases of colorectal carcinoma have a high risk of developing peritoneal metastases in the course of the disease. The current gold standard in treatment of peritoneal metastases consists of cytoreductive surgery (CRS) in combination with hyperthermic intraperitoneal chemotherapy (HIPEC). This study evaluated outcome of patients with ovarian metastases of colorectal carcinoma who were treated with CRS and HIPEC.
Methods: From the local institute's cancer registry, all female patients with a history of colorectal carcinoma were identified. Patients with ovarian metastases suspected on radiological review or proven by pathological findings were included. Patient, tumour and treatment characteristics were retrospectively obtained. Survival analysis was performed for the patient group that underwent CRS and HIPEC and compared to a control group of women who underwent CRS and HIPEC with only extra-ovarian peritoneal metastases.
Results: In the period 2000–2012, 125 women were treated for ovarian metastases of colorectal carcinoma in our institute. Seventy-eight patients underwent curative oophorectomy with CRS and HIPEC, 43 patients underwent (mostly palliative) oophorectomy only and 2 patients received palliative chemotherapy only. Of the 78 patients undergoing CRS and HIPEC, 57 patients had synchronous peritoneal metastases (73%), 18 had isolated ovarian metastases (23%) and 3 had systemic metastases with complete radiological response following neo-adjuvant chemotherapy (4%). Median overall survival was 40 months (95% confidence interval (CI)25.7–54.3) in the ovarian metastases group and 64 months (95% CI 33.4–94.6) in the control group (p = 0.151). Median progression free survival was 19 months (95% CI 11.7–26.3) in the ovarian metastases group and 17 months (95% CI 10.8–23.2) in the control group (n = 52) (p = 0.688). Primary failure sites were distributed equally between patients with and without ovarian metastases, with intraperitoneal recurrences occurring in 52% and 58% respectively (p = 0.182).
Conclusion: Outcome of CRS and HIPEC for colorectal carcinoma does not differ among women with ovarian metastases when compared to women with only extra-ovarian peritoneal metastases. Moreover, patterns of recurrence were not influenced by the presence of ovarian metastases. These data confirm the role of CRS and HIPEC in patients with ovarian metastases of colorectal origin treated with curative intent.
No conflict of interest.

2317 POSTER

Preoperative neutrophil to lymphocyte ratio over 3.0 independently predicts disease-free survival after curative resection of colorectal cancer

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Background: Neutrophil to lymphocyte ratio (NLR) reflects the host systematic inflammatory response, with some evidence suggesting that a preoperative NLR >5.0 is associated with poorer survival in colorectal cancer patients. This study aims to determine the role of the NLR as a prognostic marker for colorectal cancer patients with non-metastatic disease undergoing curative resection.
Materials and Methods: 506 consecutive patients diagnosed with non-metastatic colorectal adenocarcinoma undergoing curative surgical resection between 2006 and 2011 were included. Receiver Operating Characteristics (ROC) curve analysis was used to identify the optimal sensitivity and specificity for NLR in relation to disease-free and overall survival. Univariate and multivariate Cox regression models were used to determine the role of NLR after stratification by several clinicopathological factors. Patients were followed by a standardised surveillance protocol until February 2013.
Results: Median follow-up was 44.57 months [IQR, 20.97–65.16]. Multivariate Cox regression analysis identified NLR>3 as an independent prognostic factor for disease free survival (OR 2.41, (95% CI 1.12–5.15) P = 0.024,) but not for overall survival (OR 1.23, (95% CI 0.80–1.90) P = 0.347). A high NLR was significantly associated with patient and tumour-related factors: age, low pre-operative albumin levels and ASA status of the patient; higher T and N stage, and presence of microvascular invasion.
Conclusion: For patients diagnosed with CRC, a pre-operative NLR>3 is an independent prognostic factor for disease-free survival. A longer follow-up period may identify associations with overall survival. Considering NLR>3.0, in addition to well-established prognostic variables, may improve the processes of identifying patients at higher risk of recurrence who would benefit from adjuvant therapies, thereby offering more personalised cancer care.
No conflict of interest.

2318 POSTER

Sustainability of an enhanced recovery programme in colonic surgery in the Netherlands

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Background: Implementing an effective innovation into daily routines is a dynamic and difficult process. Even in successfully implemented innovations there is a tendency for return to old routines once the implementation activities have ended. Surgical care, as other specialties, is a domain in healthcare that has a high turn-around and fast changing character. In the Netherlands, the Enhanced Recovery After Surgery (ERAS) programme was implemented in colonic surgery in 33 hospitals by means of a generic implementation strategy. This resulted in enhanced recovery and a decrease of hospital length of stay after colonic surgery from a median of 9 at baseline to 5 days at one-year follow-up. To study whether these results were sustained we assessed the performance of the ERAS programme 3 to 5 years after the implementation activities had been ended.
Material and Methods: A retrospective audit of 30 consecutive patients undergoing colonic surgery in 2012 was performed in 10 hospitals selected out of the original 33 hospitals for having been successful in the implementation of the ERAS programme in the primary study. Whether the ERAS programme was sustained was assessed using hospital length of stay (LOS), functional recovery (FR) and protocol compliance. These retrospective audit data were compared with the pre-implementation and implementation phase data.
Results: Overall median LOS increased from 5 days (IQR 4−8) in the implementation phase to 6 days (IQR 5−10) in the post-implementation phase. Two hospitals achieved a further reduction, one showed an equal LOS, six hospitals showed an increase but did not return to the pre-implementation level, and one hospital relapsed to the same level as before the pre-implementation level.
Overall FR was reached in a median of 3 days in the post-implementation phase (IQR 2−4), which was equal to the median FR in the implementation phase (IQR 3−5).

Table 1 (abstract 2320). Results of the DSCA 2009–2011

Process	Colon							Rectum						
	2009		2010		2011		P-value	2009		2010		2011		P-value
	N	%	N	%	N	%		N	%	N	%	N	%	
Cases discussed in preoperative MDT	2286	46%	3504	56%	4255	68%	<0.01	1625	80%	2249	91%	2400	96%	<0.01
Total colonoscopy	2931	61%	3816	62%	4149	67%	<0.01	1467	76%	1858	77%	2016	83%	<0.01
Preoperative MRI								1625	80%	2016	81%	2129	85%	<0.01
CRM reported in pathology rapport								980	48%	1472	59%	2066	80%	<0.01
>10 lymph nodes in sample	3623	73%	4902	78%	5423	84%	<0.01	1182	58%	1520	61%	1700	68%	<0.01
Outcomes														
All complications	1595	33%	2062	33%	1918	31%	<0.01	793	40%	1007	41%	945	38%	<0.01
Reintervention	706	15%	917	15%	699	13%	<0.01	351	17%	435	18%	352	14%	<0.01
Anastomotic leakage	328	7.5%	429	7.8%	364	6.4%	<0.01	98	11.5%	144	12.4%	112	9.1%	<0.01
Hospital stay (mean in days)	13		12		11		<0.01	16		14		14		<0.01
CRM positive margin								138	14%	175	12%	168	8.5%	<0.01
30-day mortality	223	4.5%	255	4.1%	210	3.4%	<0.01	48	2.4%	48	1.9%	54	2.2%	<0.01
In-hospital mortality	232	4.7%	276	4.4%	230	3.6%	0.02	55	2.7%	55	2.2%	64	2.5%	0.663
In-hospital mortality/30 day mortality	289	5.8%	300	4.8%	256	4.0%	<0.01	77	3.8%	58	2.3%	69	2.7%	0.035
Total	4960		6293		6263			2035		2484		2494		

MDT: Multidisciplinary Team; MRI: Magnetic Resonance Imaging; CRM: Circumferential Resection Margin.

Protocol compliance decreased from 74% in the implementation phase to 70% in the post-implementation phase.
Conclusions: This shows that for the ERAS programme sustainability was reasonably achieved in the 10 most successful hospitals, although it also makes clear that sustainability is indeed not guaranteed. It is by which criteria one measures that sustainability of health care innovations may be judged successful or not. More research is needed to determine which factors contribute and which factors inhibit the sustainability of proven health care innovations.
No conflict of interest.

2319 POSTER

Large variation in the utilization of liver resections in colorectal cancer patients with synchronous liver metastases

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Background: Most patients with synchronous metastases from colorectal cancer have incurable disease. Patients with synchronous colorectal liver metastases (SCRLM) can, however, potentially be cured with resection of primary tumor and resection of the liver metastases. Studies have suggested that up to 40% of the patients with SCRLM should potentially be candidates for resection of the liver metastases. We investigated the utilization and survival of resection of SCRLM in the south of the Netherlands.
Methods: Data on patients with SCRLM without metastases in any other organ, diagnosed in the period 2004–2011, were extracted from the population-based Eindhoven cancer registry (n=1441). We investigated institutional variation in the utilization of SCRLM resections. Kaplan–Meier curves of patients with SCRLM were made according to type of treatment and Cox-regression on overall survival was used to asses which factors influenced the survival of patients with SCRLM.
Results: The percentage of patients that underwent a liver resection increased from 8% in 2004 to 16% in 2011 for patients in which the primary tumor was located in the colon and increased from 15% to 28% in the same period for patients in which the primary tumor was located in the rectum. In the period 2008–2011 the proportion of patients with SCRLM that underwent a liver resection varied between 6% and 33% according to the hospital in which the patients were diagnosed. Overall median survival was 8 months for patients who underwent no resection, 17 months for patients who only underwent a resection of the primary tumor and 55 months for patients who underwent a resection for both the primary tumor and the liver metastases. Cox-regression showed a hazard-ratio of 0.30 (95% confidence interval: 0.23–0.40) for patients who underwent a liver resection after adjustment for gender, age, location of primary tumor, period of diagnosis, number of comorbidities and chemotherapy.
Conclusion: Although it is well known that patients with SCRLM who have undergone resection of the liver metastases have a large survival benefit, there still seems to be an underutilization of this potentially curative therapy in some hospitals in the region.
No conflict of interest.

2320 POSTER

The Dutch surgical colorectal audit

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Background: In 2009, the nationwide Dutch Surgical Colorectal Audit (DSCA) was initiated by the Association of Surgeons of the Netherlands (ASN) to monitor, evaluate and improve colorectal cancer care. The DSCA is currently widely used as a blueprint for the initiation of other audits, coordinated by the Dutch Institute for Clinical Auditing (DICA). This article illustrates key elements of the DSCA and results of three years of auditing.
Material and Methods: Key elements include: a leading role of the professional association with integration of the audit in the national quality assurance policy; web-based registration by medical specialists; weekly updated online feedback to participants; annual external data verification with other data sources; improvement projects.
Results: In two years, all Dutch hospitals participated in the audit. Case-ascertainment was 92% in 2010 and 95% in 2011. External data verification by comparison with the Netherlands Cancer Registry showed high concordance of data items. Within three years, guideline compliance for diagnostics, preoperative multidisciplinary meetings and standardised reporting increased; complication-, re-intervention and postoperative mortality rates decreased significantly (table 1).
Conclusion: The success of the DSCA is the result of effective surgical collaboration. The leading role of the ASN in conducting the audit resulted in full participation of all colorectal surgeons in the Netherlands. By integrating the audit into the ASNs' quality assurance policy, it could be used to set national quality standards. Future challenges include reduction of administrative burden; expansion to a multidisciplinary registration; and addition of financial information and patient reported outcomes to the audit data.
No conflict of interest.

2321 POSTER

Increased disease-free survival following colorectal cancer surgery when performed by a 'high-volume' surgeon

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Background: Patients undergoing surgical resection for colorectal cancer have an improved short-term outcome with regards to adverse events, hospital-stay and postoperative mortality when performed by a 'high-volume' surgeon. To date, however, not much is known about its long-term effects. Therefore, we conducted the current study to evaluate the impact of a 'high-volume' surgeon on disease-free and overall survival.
Materials and Methods: We conducted a retrospective analysis of our prospectively collected colorectal cancer database including all patients who underwent a resection in our hospital between 2004 and 2011. Patients were divided into two groups based on the surgeon who performed the procedure: 'high-volume' (>25 cases/year) or 'low-volume' (<25 cases/year) surgeon. Peri-operative characteristics were collected as well as recurrence rates, follow-up and survival data.

Results: A total of 774 patients underwent a colon or rectal resection for a malignancy. Fourteen 'low-volume' surgeons operated 453 patients, and 3 'high-volume' surgeons operated 321 patients. After a median follow-up of four years a resection performed by a 'high-volume' surgeon proved to be an independent prognostic factor for disease-free survival in the multivariate analysis (hazard ratio [HR] 0.739; 95% CI 0.56-.099; p = 0.039). Although overall survival showed a significant difference in favour of the 'high-volume' surgeon in the univariate analysis (HR 0.495; 95% CI 0.35–0.69; P<0.001) it failed to do so in the multivariate analysis (HR 0.731; 95% CI 0.71–1.68; P = 0.088).
Conclusions: In our analysis an increased volume of colorectal cases performed per surgeon was associated with a longer disease-free survival. Although overall survival showed a statistical significant difference in favour of the 'high-volume' surgeon in the univariate analysis it failed to do so in the multivariate analysis, possibly due to the relatively short follow-up period.
No conflict of interest.

2322 POSTER

Survival after resection plus intra-operative radiofrequency ablation (IRFA) to treat colorectal liver metastases (CLM): Results of an international collaborative study

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Background: Adding IRFA to parenchymal resection to treat CLM is gaining increasing acceptance in specialized HPB teams treating complex, bilobar disease. Objectives were to confirm the promising results of the prospective *CLOCC* and *ARF2003* trials on a larger international scale.
Material and Methods: Four centers combined their clinical databases regarding IRFA for CLM. Demographics, treatments, CLM characteristics, complications (Clavien-Dindo), local recurrence, and survivals (liver progression-free, LPFS, relapse-free, RFS and overall, OS) were analysed.
Results: 280 patients (38% female, median age 61 y) received resection plus IRFA over 2001–2011. 205 had synchronous CLM (73%) and 247 bilateral (88%). 227 patients received pre-operative chemotherapy (173 one line, 37 two lines, 10 three lines, 7 missing); 189 received post-operative chemotherapy (103 one line, 46 two lines, 40 three lines). Median number of tumours resected was 2 (range 1−19) and ablated 2 (1−12). Median size (mm) of largest CLM ablated per patient was 8.5(0.1−50). 96 patients experienced complications: 29 G1, 19 G2, 35 G3, 10 G4, and 3 deaths. 48 patients had local recurrence of ablated CLM. 155 patients developed new CLM, 165 extra-hepatic metastases, and 119 patients died during follow-up. One-year, 3-year and median (months) RFS, LPFS and OS were respectively: RFS 41%(95CI35−47), 14%(95CI9−19), 9m (95CI8−11); LPFS 53%(95CI47−59), 31%(95CI25−37), 15m (95CI11−19); OS 90%(95CI85−93), 58%(95CI51−65), 40m (95CI37−50). Median follow-up was 38m (95CI34−49).
Conclusions: In this difficult-to-treat group, survival results were good and comparable with rates reported after resection only. IRFA complements resection, enabling to treat more patients, and offers the advantage of sparing healthy parenchyma.
No conflict of interest.

2323 POSTER

Aggressive surgical treatment with bony pelvic resection for locally recurrent rectal cancer

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Background: Although introduction of TME has improved local control revolutionarily, approximately 9% of patients with rectal cancer still develop local relapse after curative resection in Japan. The aim of this study was to evaluate the safety and outcome of aggressive surgical treatment with bony pelvic resection for locally recurrent rectal cancer (LRRC) in TME era.
Patients and Methods: A total of 32 patients (8 females; median age, 63 years) with LRRC who underwent extended surgical resection combined with bony pelvis between August 2006 and October 2012 at Nagoya University Hospital were recruited for this study. The mean duration of follow-up was 23 months.
Results: Most of the patients (94%) underwent initial surgery for primary cancer at the referring hospital. Neoadjuvant chemotherapy was applied in 63% of the patients. Sacrectomy was performed in 30 patients and the level of amputation was high (S1) in 6 patients and middle (S2−3) in 18 patients using combined abdominal-sacral approach, and it was low (S4−5) in 6 patients using only abdominal approach. Two patients underwent combined ischiopubic rami resection. Urinary tract reconstruction was usually performed using the ileal conduit. Two patients had concomitant liver metastases at the time of surgery, which was resected completely. Median operative time was 16 hr 47min, and median blood loss was 2701 ml. R0 resection was achieved in 25 patients (78%). Median postoperative hospital stay was 46 days. There was no in-hospital mortality. According to the complication, the most frequent complication was pelvic sepsis in 44%, followed by urinary tract infection in 31%. Re-recurrence occurred in 19 patients (59%). The most frequent recurrent site was the lung in 10 patients (31%) followed by the local in 6 patients (19%). Re-recurrent tumor could be resected in 5 patients. In patients who achieved R0 resection, overall 3-year DFS was disappointing (27 %). However, when the period after resection of re-recurrent tumor with curative intent was regarded as tumor-free time, the overall 3-year tumor-free survival (TFS) was 45% and 3-year local recurrence-free survival (LRFS) was 84%. R0 resection was independent factor for favorable TFS (OR=0.32, p = 0.048) and LRFS (OR=0.07, p = 0.002).
Conclusions: Aggressive surgical resection combined with bony pelvis for highly selected patients with LRRC was safe and could offer high rate of R0 resection. R0 resection was independent factor for favorable TFS and LRFS.
No conflict of interest.

2324 POSTER

Peritoneal carcinomatosis is less frequently diagnosed during laparoscopic surgery compared to open surgery in patients with colorectal cancer

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Background: During resection of a colorectal tumour a careful inspection of the abdomen should be performed to detect metastases. To date, no data were given on intra-operative findings with regard to synchronous peritoneal carcinomatosis. The aim of this study was to compare the proportions of patients diagnosed with PC during laparoscopic resection (LR) and open resection (OR).
Methods: All patients who underwent resection for colorectal cancer in the Eindhoven Cancer Registry area between 2008 and 2012 were included. Proportions of patients with PC were compared between surgical techniques. Multivariate logistic regression analysis was performed.
Results: 6,687 Patients underwent resection for colorectal cancer, of which 1,631 patients (24%) underwent LR, 4,665 patients (70%) underwent OR and in 391 patients (6%) conversion took place. PC was diagnosed in 1.4% of patients undergoing LR, in 5.0% of patients undergoing OR, and in 3.3% of patients in which LR was converted to OR (p < 0.001). After adjustment for patient and tumour characteristics (e.g., T- and N-stage), patients who were treated by LR had a lower chance to be diagnosed with PC during surgery than patients undergoing OR (odds ratio=0.42, p < 0.001).
Conclusions: Patients undergoing surgery for colorectal cancer are less frequently diagnosed with PC during LR in comparison to OR. Since effective treatment is currently available for selected patients with PC, a thorough inspection of the peritoneum during surgery is of paramount importance to offer these patients a chance for long-term survival and even cure.
Conflict of interest: *Other substantive relationships: AGJ Aalbers received money to his institution, Netherlands Cancer Institute Amsterdam, by Covidien*

2325 POSTER

Primary anastomosis, defunctioning stoma or end-colostomy; outcomes of mid rectal cancer surgery

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Background: Low anterior resection is the cornerstone of treatment for patients with mid rectal cancer. Surgical options consist of a primary anastomosis, anastomosis with a defunctioning stoma or end-colostomy. The aim of this study is to describe short-term and one-year outcomes of these three surgical strategies.
Material and Methods: This retrospective study with one year follow up was conducted in 7 hospitals in the Netherlands. All patients undergoing colorectal resection for mid rectal cancer were included. Patients with a T4 tumour were excluded. Short term endpoints were postoperative complications, re-interventions, prolonged hospital stay and postoperative mortality. One year outcomes were unplanned readmissions and re-interventions, hospital stay, presence of stoma and mortality.
Results: 388 patients undergoing low anterior resection for mid rectal cancer between the 1st January 2009 and 31st of June 2011 were included. From all included patients 72 obtained a primary anastomosis, 214 an anastomosis with defunctioning stoma and 102 patients had an end-colostomy. Short term outcomes showed postoperative complications in one third of all patients. Anastomotic leakage occurred in 10% of patients with a primary anastomosis and 7% in the defunctioning stoma group. No differences were found in re-intervention rate, prolonged hospital stay or mortality. One year outcomes showed, compared to patients with a primary anastomosis, more readmissions and re-interventions in patients with a defunctioning stoma or end-colostomy, with as main cause anastomotic leakage and stoma or abscess problems respectively. In the first year postoperative there was a 30% increase in percentage of patients with an end-colostomy (Table 1).
Conclusions: Many patients obtained a defunctioning stoma, which was associated with significant long term morbidity including anastomotic leakage. An end-colostomy may be a safe alternative in high risk patients, but long-term stoma complications should be taken into account.
No conflict of interest.

Table 1. One-year outcomes. Numbers in bold were statistically significant compared to the anastomosis group ($p < 0.05$).

	Anastomosis		Anastomosis with defunctioning stoma		End-colostomy	
	N	%	N	%	N	%
Readmissions	3	5%	**38**	**18%**	**20**	**17%**
Anastomotic leakage	1	2%	24	11%	0	0%
Ileus	0	0%	3	1%	3	3%
Stoma problems	0	0%	5	2%	12	10%
Re-interventions	1	2%	**26**	**12%**	**14**	**12%**
Revision stoma			5	2%	8	7%
Disconnect anastomosis + construction stoma	1	2%	11	5%	0	0%
Drainage			10	5%	6	5%
1-year mortality	2	3%	7	3%	**22**	**19%**
Total (after one year)	230		25		133	

2326 POSTER

Colon cancer surgery increases levels of vascular endothelial growth factor open more than laparoscopic approach: Results of a randomised controlled trial

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Background: Elevations of plasma vascular endothelial growth factor (VEGF) have been noted early after colorectal resection. Because VEGF is a potent promoter of angiogenesis, which is critical to tumor growth, a sustained increase in blood VEGF levels after surgery may stimulate the growth of residual metastases early after surgery. This preliminary report aimed to determine VEGF levels after different colorectal resection.
Methods: This prospective randomised trial included 56 patients with nonmetastatic colorectal cancer. 28 were assigned to laparoscopic surgery group and other 28 patients underwent open colorectal resection. Demographic, perioperative, pathologic, and complication data were collected. Plasma samples were obtained for all patients preoperatively and postoparative (POD) day 1, POD 3, POD 5, POD 7 for all patients and POD 30 for most patients. Levels of VEGF were determined via enzyme-linked immunoassay (ELISA) and compared using Wilcoxon's matched pairs test.
Results: The median plasma value was not significately correlated with age, sex, tumor stage and nodal status. The serum VEGF levels were not significantly different between the laparoscopic and open group at baseline (312 vs 389 pg/ml). A statistical difference was noted regarding the surgical approach. (laparoscopic versus open) VEGF levels were POD 1 (and 300 vs 453 pg/ml) POD 3 (412 vs 600 pg/ml) POD 5 (423 vs 844 pg/ml) POD 7 (414 vs 615) respectively. ($p = 0.003$). The correlation between serum VEGF levels and inflammatory factors, such as white blood cell (WBC) and C-reactive protein (CRP) demonstred a statistically significative correlation in POD5 between WBC and CRP and VEGF ($p = 0.006$ and $p = 0.007$) respectively.
Conclusion: This preliminary report demonstrates that after colorectal resection for cancer with open surgery median VEGF levels are significatively more elevated as after laparoscopic colorectal surgery. The clinical impact from increased blood levels of VEGF is uncertain. It is possible that the growth of residual tumor deposits may be stimulated early after surgery. These results warrant a larger study as well as endothelial cell in vitro assays to determine whether postoperative plasma stimulates proliferation and invasion.
No conflict of interest.

2327 POSTER

Colorectal surgery in octogenarians: Age is the sole relevant risk factor

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Background: Colorectal carcinoma (CRC) is the most common malignancy in the elderly. Published data regarding postoperative survival of this specific patient category are not available. The aim of this study is to analyze survival after CRC surgery in octogenarians and to identify predictors of an impaired survival.
Material and Method: Between 2008 and 2011 113 patients aged 80 years and older underwent a colectomy for primary CRC in our hospital. We collected data on the oncological status, pre-existent comorbidities and relevant postoperative parameters.
Results: Patients' mean age was 83.4 years (range 80−94), the mean and median duration of follow up were 22 months. We observed a total mortality of 48 patients (42.5%). 30-day mortality was 7.1% and mortality after one year was 20.4%.
Emergency versus elective surgery and higher ASA class did not influence the overall survival in a Logrank test. Incomplete tumor removal, increased cancer stage, and occurrence of postoperative complications did.
We observed in multivariate analysis that age per adjusted life year is a strong independent predictor of survival in octogenarians (HR 1.17, 95-CI 1.06–1.28, P<0.001).
Conclusions: For patients 80 and older, age per se is the single most important risk factor for influencing survival, besides obvious impairing conditions. In patients aged 80 and older each extra life year increases the risk of death risk 1.16 per annum. So that a patient at 90 years of age at time of surgery has an a baseline risk of dying 4.61 times greater compared to an 80 year old patient.
In the older population age alone is a strong predictor of mortality and as such it exceeds significantly the effect of comorbidities. We therefore conclude that age should get a more important role in risk stratification and decision making in elderly patients with colorectal carcinoma.
No conflict of interest.

2328 POSTER

Bilateral colorectal liver metastases: Towards the end of the two-stage hepatectomy?

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Introduction: Surgical treatment of colorectal bilateral liver metastases (LM) is essentially based on a two-stage hepatectomy strategy. However, technical progress in local ablation could afford to treat all the LM in a single surgery. The aim of this study was to analyze the immediate postoperative course and the long-term outcome of patients operated on for bilateral LM in a one stage-hepatectomy.

Patients and Methods: In a prospective database, patients operated on for bilateral LM in a one-stage hepatectomy, were selected. Patients, who underwent a right hepatectomy extended to segment IV, without further action, were excluded from the study.
Results: From January 2000 to December 2010, 174 patients were operated on for bilateral LM. Among them, 155 patients (89%), with a mean age of 57±9 years, underwent resection in one-stage hepatectomy. The median number of LM was 7 [3−42]. A major hepatectomy was performed in 63 patients (41%), minor in 31 (20%) and multiple limited resections in 55 (35%). At least one radiofrequency ablation (RFA) was associated in 131 (85%) patients with a median number per patient of 3 [1−16]. Three patients died postoperatively, and the rates of overall and specific complications were 57% and 20%, respectively. After a median follow-up of 47 [IC95% 40−62] months, overall and recurrence-free survivals at 3 years were 57 % [IC95% 48.1–66.2] and 12.3 [IC95% 7.6–20.2]. The T3 or T4 status of the primary tumor ($p = 0.001$) and the absence of postoperative chemotherapy ($p = 0.0005$) were the only independent factor of poor prognosis.
Conclusion: A surgical strategy combining hepatectomy and local ablation in one-stage is feasible, safe and achieves long-term survivals. This one-stage strategy could increase the prognosis of such patients, compared to the two-stage hepatectomy, by avoiding the tumor progression between the two-stage, reported in 20 to 30% of the patients, and appears to have a less cost-effectiveness.
No conflict of interest.

2329 POSTER

The incidence of nodal involvement after chemoradiation for locally advanced rectal cancer: who might benefit from local excision? Results from a pooled analysis of 2026 patients

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Background: For locally advanced rectal cancer preoperative (chemo)-radiotherapy facilitates radical resection and improves locoregional control. If there is a good response to neoadjuvant treatment local excision and even a wait and see policy in case of complete clinical response are currently being explored. For early rectal cancer local excision without preoperative treatment is a good option, provided that lymph node metastasis are ruled out. Data on the correlation between bowel wall involvement and the risk of node metastases are rather consistent in the literature, which helps to select patients that are candidates for local excision. For patients with advanced disease that requires preoperative chemoradiation, there are few data on this issue. In the current study we investigated the correlation between ypT and ypN stage for patients with locally advanced rectal cancer who are treated with chemoradiation and total mesorectal excision.
Material and Methods: Patients were selected from a pooled data set that consisted of 10 published studies. Proportions of patients with positive ypN stage according to ypT stage after chemoradiation were derived from the individual studies. Pooled proportions with 95% confidence intervals were calculated using a random effects model. The analyses were performed with STATA (version 11.0).
Results: Of the 2026 analyzed patients 95% was diagnosed with cT3/4 disease. 66% was clinically node positive whereas only 26% had N+ disease at pathological examination. ypTstage was distributed as follows: ypT0 16.8%, ypT1 5.7%. ypT2 28.9%, ypT3 44.8% and ypT4 3.9%. The pooled proportion of ypN+ disease per ypT-stage was 6.6%, 12.6%, 17.1%, 40.0% and 45.7%, respectively.
Conclusions: The incidence of nodal involvement per ypT stage after chemoradiation is only slightly lower than in patients who are not treated preoperatively. As for early disease, local excision after chemoradiation has a substantial risk of leaving lymph node metastases untreated. Only patients with favourable pathological characteristics of the primary tumour who are clinically node negative prior to neoadjuvant treatment are possibly candidates for local excision.
No conflict of interest.

2330 POSTER

The importance of the minimal resection margin in locally recurrent rectal cancer

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Background: Curative surgical treatment of locally recurrent rectal cancer (LRRC) is possible, but the outcome strongly depends on whether a radical resection can be performed. In contrast to primary rectal cancer, the importance of a minimal resection margin in radical resections of LRRC is not well defined. We examined the association between the minimal resection margin and long-term outcome after curative surgical treatment of LRRC.
Methods: All surgically treated patients with LRRC between 1990 and 2013 were retrospectively analyzed. Based on final pathology reports, patients were divided into 4 groups: A, radical resections with margins >2 mm; B, radical resections with margins >0−2 mm, C, microscopic irradical resections and D, macroscopic irradical resections. Kaplan–Meier curves were generated and factors affecting local control and survival were assessed by univariate and multivariate analysis.
Results: A total of 161 patients underwent curative surgery for LRRC. The resection margin was unknown in 14 patients and 9 patients had a complete pathological response, leaving 138 patients eligible for analysis. Five-year local control in patients with resection margins >2 mm (n = 32) was 86% compared to 58% for the 35 patients with margins >0−2 mm ($p = 0.02$). Patients with microscopic (n = 51) or macroscopic irradical resections (n = 20) had 5-year local control rates of 25% and 0%, respectively. These were both significantly worse than those of patients with resection margins >2 mm or 0−2 mm ($p < 0.05$).
There was a significant difference in 5-year overall survival in favor of patients with resection margins >2 mm compared to those with margins >0−2 mm (56 vs. 48%, $p = 0.02$). Patients with a microscopic or macroscopic irradical resection had 5-year overall survival rates of 16% and 5%, respectively. These were both significantly worse than those with resection margins >2 mm ($p < 0.05$), but the overall survival of patients with microscopic irradical resections did not significantly differ from those with resection margins >0−2 mm ($p = 0.11$). Multivariate analysis confirmed that the minimal resection margin was an independent prognostic factor for local control and overall survival.
Conclusion: The resection margin status is an independent prognostic factor after curative surgical treatment of LRRC. Patients with radical resection margins >2 mm have a significantly higher local control rate than patients with radical margins $\leqslant$2 mm and patients with irradical resections. Patients with a margin >2 mm also have a longer overall survival than patients with radical resections margins $\leqslant$2 mm.
No conflict of interest.

2331 POSTER

The utility of PET scanning in colorectal cancer liver metastases being considered for surgery

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Background: Liver resection remains the only potentially curative option for a subset of patients with colorectal cancer liver metastases (CRCLM). Preoperative imaging used to determine resectability includes contrast enhanced computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET). The objective of this study was to determine the utility of PET scanning for potentially resectable metastatic CRC to liver.
Material and Methods: We retrospectively reviewed a prospectively maintained database for all patients considered for resection of CRCLM from July 2010 to January 2013 in two specialist colorectal/hepatobiliary cancer centres. We extracted and analyzed data with respect to preoperative staging imaging and definitive treatment performed on completion of staging.
Results: We identified 114 patients who underwent preoperative staging investigations for potentially resectable CRCLM. The imaging techniques performed included: CT (n = 113, 99%), MRI liver (n = 89, 78%), PET (n = 105, 92%). In 22 (22/105, 21%) patients PET scanning added to the preoperative cross sectional staging information, identifying local

recurrence (n = 3, 2.8%), confirming liver metastases following an inconclusive CT/MRI (n = 2, 1.9%), outruling liver metastases (n = 1, 0.9%) and identifying extrahepatic sites suspicious for disease (n = 16, 15.2%). The extrahepatic sites included either lung (n = 6), bone (n = 2), peritoneum (n = 1) or lymph nodes (n = 7). There were 2 false positive results. One patient with FDG-avid mediastinal lymph nodes had no cancer on endobronchial biopsy. One patient with FDG avidity at the primary anastomosis had no evidence of disease at colonoscopy. PET scanning definitively changed the therapeutic strategy in 16 patients (16/105, 15.2%): precluding liver resection in 10 patients (10/105, 9.5%), leading to resection of extrahepatic disease in 4 patients (4/105, 3.8%), resection of local recurrence in 1 patient (1/105, 0.9%) and resection of hepatic metastases in one patient (1/105, 0.9%).
Conclusion: In this small retrospective cohort the addition of metabolic imaging altered the management in 15.2% of patients with potentially resectable CRCLM. There is a need for randomized evidence to support the routine use of PET in addition to cross-sectional imaging in this setting.
No conflict of interest.

2332 POSTER

Surgical resection of metastases and survival outcomes in patients with metastatic colorectal cancer (mCRC) treated with cetuximab (CTX) in the EREBUS cohort of real-life use

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Background: CTX has demonstrated improved survival outcomes in mCRC. Surgical resection of metastases has become an option in the multidisciplinary management of unresectable mCRC, but few data are available concerning its benefit in real-life practice.
Methods: EREBUS is a French multicentre (n = 65) cohort that included patients with unresectable wt KRAS mCRC in whom 1st-line CTX-based therapy was initiated in 2009–2010. Patients were followed for 12 months. A committee of experts validated baseline resectability and resection results. Resection rates and survival outcomes were described according to metastatic sites: liver-only, liver-not exclusively, other. Overall and progression-free survival (OS and PFS) were analysed using Kaplan–Meier method.
Results: 389 patients were included: 37.8% liver-only metastases, 38.3% liver-not exclusively, 23.9% other. Among these, 97 patients (24.9%, 95% CI [20.6–29.2]) underwhent resection; rates for liver-only: 36.7% [28.9–44.5], liver-not exclusively: 20.8% [14.3–27.3], other: 12.9% [6.9–21.5]. Baseline characteristics of these 97 operated patients: median age 62 years, 67.0% male, 91.8% ECOG=0−1, 62.9% primary tumour resection, 64.9% single metastatic site, and 55.7% only liver. Combined chemotherapy regimens included irinotecan (53.6%), oxaliplatin (40.2%), or irinotecan+oxaliplatin (5.2%). Median duration of CTX use was 6.3 months and chemotherapy use 7.9 months. The median interval from initiation of 1st-line to 1st surgery was 6.1 months; mainly one-stage operative procedures were performed (69.1%). There was 63.5% radical resection with R0/R1/radiofrequency (liver-only: 77.8% and liver-not exclusively: 35.5%), 9.4% missing metastases (liver-only: 7.4% and liver-not exclusively: 9.7%) and 27.1% had R2 resection (liver-only: 14.8% and liver-not exclusively: 54.8%). 52.6% had post-operative complications (20.6% infection, 9.3% thromboembolic event, 8.2% other cardiovascular event, 3.1% death). The 1-year OS probability for operated patients was 94.8% [87.8–97.8] and the 1-year PFS probability was 59.0% [48.4–68.1]. Median OS and PFS were not reached.
Conclusion: Metastases resection rate was very close to that found in RCTs of CTX even though real-life patients are more heterogeneous. There was a higher rate of resection among patients with liver-only metastases as compared to other more rarely studied mCRC patients (liver-not exclusively and other metastases). Survival outcomes and recurrence at 36 months follow-up will be investigated.
Conflict of interest: *Advisory board: Sanofi, Merck-Serono. Corporate-sponsored research: Merck-Serono*

2333 POSTER

Impact of postoperative complications on long-term survival after resection for rectal cancer

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Background: The relevance of type and severity of postoperative complications after curative resection for rectal cancer on survival and recurrence rates is a matter of controversy. The aim of this study was to investigate the impact of postoperative complications on long-term outcome after resection for rectal cancer.
Materials and Methods: Between January 1984 and October 2008, 811 patients with rectal cancer underwent curative resection. Patients who experienced postoperative complications were divided into a minor complication group (grade I and II) and a major complication group (grade III and IV) according to the Clavien classification. The influence of several pathological and clinical factors including complications in terms of overall and disease-free survival was tested and compared in univariate and multivariate analyses.
Results: Curative resection was performed in 811 patients, median age was 65 years. The Kaplan–Meier estimates ($\pm$ the standard error) for five- and ten-year overall cumulative survival were 70.3% $\pm$ 1.8% and 54.5% $\pm$ 2.4%; Kaplan–Meier estimates for five- and ten-year disease-free survival were 64.0% $\pm$ 1.8% and 50.9% $\pm$ 2.3%. Some 165 patients (20.3%) had minor complications and 103 patients (12.7%) had major complications. Twelve patients (1.48%) died within 30 days after surgery. There was no significant difference between patients with no complications, patients with minor and patients with major complications in terms of overall (p = 0.41) or disease-free survival (p = 0.32).
Conclusions: Following resection for rectal cancer, severity of post-operative complications (minor or major) according to a standardised classification system does not demonstrate a statistically significant effect on either overall or disease-free survival.
No conflict of interest.

2334 POSTER

No association between volume and outcome after colorectal cancer surgery in southern Netherlands

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Background: Uncertainty remains whether hospital resection volume is associated with surgical outcome and survival in colorectal cancer.
Methods: Patients who underwent resection for primary colorectal cancer diagnosed between 2008 and 2011 in the southern Netherlands were included (n = 5655). Hospitals performing <130 resections per year were classified as low volume; hospitals performing $\geqslant$130 resections per year were classified as high volume. Differences in surgical approach, circumferential resection margins, anastomotic leakage and 30-day mortality between high volume and low volume hospitals were analysed using Chi^2 tests. Expected proportions of anastomotic leakage and 30-day mortality were calculated using multivariable logistic regression. Crude 5-year overall survival was calculated using Kaplan–Meier curves. Cox regression analyses were used to discriminate independent risk factors for death.
Results: 5 hospitals were classified as high volume and 5 hospitals as low volume. 23% of patients with locally advanced rectal cancer (LARC) diagnosed in a low volume center was referred to a high volume center. Patients with colon cancer underwent less laparoscopic surgery and less urgent surgery in low volume hospitals compared to high volume hospitals (10% versus 32%, p < 0.0001, and 8% versus 11%, p = 0.003, respectively). For rectal cancer, rates of abdominoperineal resections versus low anterior resections, and circumferential resection margins were not associated with hospital volume. Crude and adjusted rates of anastomotic leakage, 30-day mortality, and long-term survival after resection for CRC did not differ between low volume and high volume hospitals.
Conclusion: In the southern Netherlands, low volume hospitals deliver similar high quality surgical colorectal cancer care as high volume hospitals in terms of circumferential resection margins, anastomotic leakage, 30-day mortality and survival, also after adjustment for casemix. However, this excludes patients with locally advanced rectal cancer since a substantial proportion was referred from low volume to high volume hospitals.
No conflict of interest.

2335 POSTER

Higher risk for recurrences in colon cancer patients with postoperative complications

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Background: Colorectal cancer is a major health problem, with a high recurrence rate. This study aimed to describe the incidence of loco-regional and distant recurrence among patients with colorectal cancer in the Netherlands and to identify prognostic factors for recurrences.
Material and Methods: All 646 patients operated with curative intent for stage I−III colorectal cancer between January 1, 2006 and December 31, 2008 in one university and two teaching hospitals in the western region of the Netherlands were analysed. Cumulative incidences of loco-regional and distant recurrence were computed with death as competing risk. To identify prognostic factors, Cox's proportion hazards regression model was used.
Results: For colon cancer, the 1-year and 3-year cumulative incidences were 3.1% and 8.0% for loco-regional recurrence and 8.6% and 15.1% for distant recurrence. For rectal cancer, these percentages were 2.1% and 5.6% for loco-regional recurrence and 4.8% and 13.4% for distant recurrence. The risk of developing a recurrence was highest between 0.5−2 years after surgery. Prognostic factors for loco-regional and distant recurrences for colon cancer were complications requiring readmission, T3 -T4 tumours and positive lymph nodes. Emergency surgery was only a prognostic factor for loco-regional recurrence. For rectal cancer, T3 -T4 and N2 tumours were prognostic factors for distant recurrences.
Conclusions: Colorectal cancer recurrences continue to be a serious concern with an incidence up to 15% in 3 years. Next to known prognostic factors, complicated operations seem to have an impact on the rate of recurrences. Clearly, operative complications have long term detrimental effects on colorectal cancer outcome and reducing operative complications may improve recurrence rates.
No conflict of interest.

2336 POSTER

Laparoscopic TME: Short and long-term results in a single institutional series including 516 patients

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Background: To assess short and long-term oncologic outcome after laparoscopic total mesorectal excision (TME) for rectal cancer in a single Institution series including 516 patients.
Methods: We reviewed the prospective database of 516 unselected consecutive patients with histologically proven cancer of the mid and distal rectum undergoing laparoscopic TME between January 2000 and January 2012. Those with T3-T4 or N+ received long course preoperative radiochemiotherapy. Surgical technique and follow-up were standardized. Data evaluated included short and long-term results with survival outcomes calculated using the Kaplan-Meyer method.
Results: Some 516 patients underwent laparoscopic TME. Conversion to open surgery was required in 4.8% of patients. Adjuvant treatment was given in 60.5% (312/516) of the patients. A Sphincter-preserving surgery was performed in 484 patients, while an abdominoperineal resection of the rectum was necessary in 32 cases. The overall postoperative mortality rate was 1.7%. The overall morbidity rate was 30.9%.
Clinical anastomotic leak occurred in 17% (82/484) of the patients. The reoperation rate was 11%. With respect to short-term oncological variables, mean (SO) distal resection margin was 2.9 (2) centimetres and the mean (SO) number of lymph nodes intraoperatively collected was 15.5 (9.3). A RO resection rate was obtained in 95.9% (495/516) of the patients. Mean (range) follow-up period was 72 (10–156) months.
Overall and disease free survival rate were 71.3% and 63.4%, respectively. There was no case of trocar site recurrence. The local recurrence rate occurred in 5.3% of the patients after curative resection.
Conclusions: The results of these study with large number of patients over a long follow-up period suggested that laparoscopic TME is safe with a good oncological outcome.
No conflict of interest.

2337 POSTER

An interim analysis of a single arm, open-label, multicenter phase II study of capecitabine plus oxaliplatin (XELOX) as the perioperative treatment of patients with potentially resectable liver-only metastases from colorectal cancer (ML22298; NCT00997685)

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Background: The liver is the most common metastatic site of colorectal cancer (CRC). Surgical resection is currently considered a standard of carefor all resectable colorectal liver metastases (CLMs). Therefore,it is importantto convert unresectable CLM to resectable CLM to improve survival rate of CRC patients. The purpose of this studyis to investigatethe efficacy and safety of capecitabine plus oxaliplatin(XELOX)in the perioperative treatment of patients with potentially resectable CLM.
Method: The interim analysis of this single arm, open-label, multicenter phase II trial assessed objective response rate (ORR) and R0 resection rate after perioperative chemotherapy of XELOX in patients with potentially resectable CLM.The primary endpoint of this study is progression-free survival(PFS);Secondary endpoints includeORR, R0 resection rate, overall survival (OS) and the safety profile of perioperative treatment of XELOX.Patients with CLM that wasdiagnosed as potentially resectable were treated with XELOX. After 6 weeks (2 cycles) of chemotherapy, tumor remission was assessed by CT scan. Resectability of CLM was assessed by CT after 12 weeks (4 cycles) of chemotherapy. If patient was diagnosed as not suitable for resection during or after neoadjuvant chemotherapy, alternative chemotherapy regime was used and corresponding patients were withdrawn from this study.After hepatectomy, adjuvant chemotherapy of XELOX was started based on patients' conditions (but not later than 8 weeks after surgery).
Results: 30 patients (17 males/13 females)were enrolled from 10 medical sitesbetween January 2010 and November 2011. The ORR was 33.3% (95% CI: 47.2%-82.7%). The conversion rate from unresectable to resectablewas 36.7% (11/30). Amongthese 11 patients,10 (90.9%) had R0 resection. There were 4 (4/30)patients with post-operation complications of ascites and/orhydrothorax.3 cases of SAE were reported due to leukopenia, hepatotoxicity (elevated serumalanine transaminase&γ-glutamyltransferase levels)and diarrhea. Other AEs mainly were neutropenia, vomiting and intestinal obstruction.
Conclusion: Perioperative chemotherapyofXELOX in patients with potentially resectable CLM possesses high conversion rate and R0 resection rate, with manageable toxicities and post-operation complications.
No conflict of interest.

2338 POSTER

Improvement of the learning curve of cytoreduction and HIPEC in the Netherlands

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Introduction: The combination of cytoreduction (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has become the preferred treatment for many peritoneal surface malignancies. Experience with this procedure is needed to achieve a macroscopic complete resection with a low morbidity. In the Netherlands, new HIPEC centres are mentored by surgeons from experienced HIPEC centres to set up the treatment safely. In this study learning curves were analyzed of a pioneer institution and three institutions that started recently with CRS and HIPEC.
Methods: The first consecutive 100 CRS and HIPEC procedures of four institutions in the Netherlands were included, when available. Indications were peritoneal carcinomatosis (PC) from colorectal carcinoma and pseudomyxoma peritonei (PMP). Patient, tumour and treatment

characteristics were retrospectively obtained. Operation characteristics, morbidity and completeness of cytoreduction were the main outcome parameters for the learning curves. The learning curves of the pioneer institution were compared to the learning curves of the three later institutions together. Learning curves were determined by a regression model with the rank of the operation as a covariate.
Results: Three-hundred seventy-two cases were included in the four institutions. In total 167 procedures were performed for PC from colorectal carcinoma and 105 for PMP. The number of abdominal regions affected (0−7) was larger in the procedures of the pioneer hospital than in the other hospitals (mean abdominal region count 4.3 vs 3.2, $p < 0.001$). Grade III−V morbidity rates were 64% in the pioneer centre and 32% in the later centres. A macroscopic radical resection was reached in 66% of the cases in the pioneer centre and in 86% of the cases in the later centres. The rank of the operation (OR 1.02, 95% CI 1.011–1.03), treatment in the new centres (OR 2.50, 95% CI 1.33−4.9) and number of abdominal regions affected (OR 0.60, 95% CI 0.50–0.71) were predictors for a complete macroscopic resection in a multivariate logistic regression model.
Conclusions: Recently started HIPEC centres in the Netherlands showed improved learning curves compared to the pioneer institution with a better starting point for all main outcome parameters and a significant learning curve in the first 100 patients regarding complete cytoreduction, which is an indicator for survival. Patient selection was an important independent factor for this learning curve.
No conflict of interest.

2339 POSTER

Curative cytoreductive surgery followed by intraperitoneal chemotherapy in patients with colorectal peritoneal carcinomatosis and synchronous resectable liver metastases: A French monocentric experience

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Background: Cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC) increases overall survival in patients with peritoneal carcinomatosis (PC) from colorectal origin. However the optimal treatment both for PC and for resectable liver metastases (LMs) in the same surgical time remains controversial. The objective of our monocentric retrospective study was to describe the outcome of patients with LMs or not and to examine predictive factors after curative surgery combined with HIPEC.
Material and Methods: From 1999 to 2011, all patients with colorectal PC who underwent curative cytoreductive surgery followed by HIPEC in our institute were evaluated from a prospective database. Overall survival (OS) and disease free survival (DFS) in patients with PC and synchronous liver metastases were compared with PC only. Univariate and multivariate analyses were performed to evaluate variables predictive for OS.
Results: Fifty height patients were enrolled. 22 patients (first group) with colorectal PC and synchronous LMs of which 17 (77%) underwent a minor hepatic resection, were compared to 36 patients with PC only (second group). No significant difference was found between the two populations according to the following criteria: age, performance status, peritoneal cancer index (PCI), completness cytoreductive score (CCS) and post-operative comorbidity. The median OS were 36.1 months [95% CI: 20.9; 125.8] for the first group and 22.9 [95% CI: 14.8; 82.6] for the second ($p > 0.05$) with 38.2% and 40.4% as 5-years OS rates ($p > 0.05$). The median DFS were 8.4 [95% CI: 5.5; 12.0] and 7.9 months [95% CI: 4.6; 11.2] respectively ($p > 0.05$). Only CCS >0 [odds ratio (OR): 1.29, $p < 0.0001$] was identified as independent factor for poor OS in multivariate analysis.
Conclusions: In our experience, synchronous cytoreduction with peritonectomy and liver metastases resection plus HIPEC is a feasible therapeutic option. This process suggests an improvement to overall survival such as patient with PC only. This multimodal procedure would have to be performed in selected patients and in an experienced center for oncology.
No conflict of interest.

2340 POSTER

Laparoscopic colorectal surgery leads to increased overall survival when compared to a conventional open approach

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Introduction: Over the past decade laparoscopic surgery has become increasingly popular in the treatment for colorectal malignancies. Short-term results are equivocal and skepticism regarding safety is rapidly diminishing. To date however, not much is known about its effect on the long-term outcome. Therefore, we conducted this study to evaluate the impact of a laparoscopic approach on the survival of patients operated in our hospital.
Methods: We conducted a retrospective analysis of our prospectively collected colorectal cancer database, including all patients who underwent a resection between 2004 and 2011. Patients were divided into two groups based on surgical technique: an open versus a laparoscopic approach. Peri-operative data were collected as well as follow-up, recurrence rates and survival data.
Results: A total of 774 patients underwent a colorectal resection for a malignancy. The open approach was performed in 259 patients and the laparoscopic approach in 515 patients. Rectal cancer patients were also included, 60 abdominoperineal (APR) resections were performed and a total of 165 low anterior resections (LAR). These patients received preoperative (chemo)radiation according national guidelines. Groups showed an equal distribution for pre-operative characteristics. After a median follow-up of four years, multivariate analysis showed a resection performed by a laparoscopic approach as an independent prognostic factor for disease-free survival (hazard ratio [HR] 0.737; 95% CI 0.55-.099; $P = 0.046$) as well as for overall survival (HR 0.595; 95% CI 0.43−83; $P = 0.002$).
Conclusions: In our experience a laparoscopic approach is associated with both an increased disease-free survival as well as a longer overall survival in the multivariate analyses. Therefore, when there are no contra-indications for laparoscopic surgery, surgeons performing colorectal surgery should offer this approach to their patients as the technique of choice.
No conflict of interest.

2341 POSTER

Morbidity associated with colostomy reversal after cytoreductive surgery and HIPEC

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Background: Cytoreductive surgery (CRS) and Heated Intra-Operative Peritoneal Chemotherapy (HIPEC) has improved the survival in selected colorectal cancer patients with peritoneal metastases (PM). In some of these patients a low rectal anastomosis is avoided by placement of a stoma during CRS. Currently, the morbidity and mortality accompanying the reversal procedure of the colostomy in this population is unknown.
Methods: Our study involved two prospectively collected databases including all patients who underwent CRS and HIPEC. We identified all consecutive patients who had a colostomy and requested a reversal procedure. The distribution of clinical and treatment related factors are described in our cohort. The associations between four clinical and 10 treatment related factors with the outcome of the reversal procedure were determined by univariate analysis.
Results: Twenty-one patients of 336 (6.3%) with a median age of 50.8 years (SD 10.2) underwent reversal of their colostomy. Eleven patients had pseudomyxoma peritonei and ten had colorectal adenocarcinoma. One patient was classified as American Society of Anesthesiologists (ASA) grade III, six as ASA grade II and the remainder as ASA grade I. A median of 394 days (range 133–1194) elapsed between the initial CRS & HIPEC and the subsequent reversal procedure. No life threatening complications requiring intensive care management or mortality were observed after reversal. The reversal related morbidity was 67%. Infectious complications, including intra-abdominal abscess formation and enterocutaneous fistulization, were observed in seven patients (33%). Infectious complications after CRS & HIPEC, including development of a fistula, were negatively correlated with the ultimate restoration of bowel continuity *($P = 0.05$)*. The bowel-continuity was successfully restored in 76% of the patients.
Conclusions: Although the restoration of bowel continuity after CRS & HIPEC was successful in the majority of patients, it was associated with a relatively high complication rate. Particularly patients with infectious complications after HIPEC have a diminished chance of successful restoration of bowel continuity.
No conflict of interest.

2342 POSTER

Variation in circumferential resection margin: Reporting and positivity in the South-Netherlands

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Background: An involved circumferential resection margin (CRM) in rectal cancer surgery is a predictor of a higher local recurrence and distant metastases rate and decreased overall survival. In previous studies patients with distal tumors who underwent an Abdomino Perineal Resection (APR) had significantly higher rates of CRM positivity. However, since the introduction of the total mesorectal surgery and standard pathology results have dramatically improved. The aim of this study is to analyze reporting of CRM and to study predictive factors for CRM positivity.
Materials and Methods: 1136 consecutive patients who underwent a resection for rectal cancer in the Eindhoven Cancer Registry area in the period 2008–2010 were included. This area includes 10 hospitals where rectal cancer surgery is performed. The number of patients with missing CRM in the pathology report, and CRM positivity-rates were assessed.
Results: CRM was missing in 26.2% of the cases in 2008, in 2009 in 16.5% and in 2010 in 13.0%. CRM reporting varied between hospital and pathology departments, with missing cases ranging from 8.0% to 64.4% between hospitals and 8.6% to 64.4% pathology laboratories. CRM positivity after Low Anterior Resection (LAR) and APR was respectively 7.8% and 10.0%. The CRM positivity was stable over the years, around 9.1% (range 8.1%-10.1%). CRM reporting became more detailed in terms of reporting the number of mm versus 'positive' or 'negative' margin. The two most important factors associated with CRM positivity were high T-stage (32.7% CRM positivity in T4 rectal cancer) and absence of neoadjuvant (chemo)radiation treatment (CRM positivity of 16.9% in the group who underwent surgery only). No differences in sex, age, distance of the tumor to the anus and type of operation were found.
Conclusions: There is a high variation in reporting of CRM positivity in the South-Netherlands, although significant improvements are made during the last years. In contrast to the literature, CRM positivity is no longer dependent of the location of the tumor or the surgical procedure, but only on tumor stage and the use of neoadjuvant (chemo)radiation.
No conflict of interest.

2343 POSTER

Rectal cancer proctectomy in the elderly − The National Cancer Centre "G. Paolo II" experience

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Background and Aim: Rectal cancer shows a high incidence in older patients, however, only few reports focused exclusively on rectal cancer with the exclusion of the surgery of the colon. This retrospective study aimed to compare short-term and long-term outcomes for rectal cancer in patients more than 75 years old with that observed in younger patients.
Patients and Methods: Four hundred consecutive patients operated on for primary rectal adenocarcinoma at National Cancer Centre 'G. Paolo II' were collected in a prospective institutional database and divided into two groups: group 1 ($\geqslant$75 years, n = 98); group 2 (<75 years, n = 302). Restaurative proctectomy was the only procedure considered. Main clinical and pathological data, morbidity, clinical anastomotic leakage, reoperation rate, 30-day mortality, overall survival, and cancer-related survival were assessed and compared.
Results: Significant differences between the two groups were detected with regard to the the American Society of Anesthesiologists classification, comorbidities and the emergency presentation. Overall morbidity rate was 30.4% and 20.2% in group 1 and group 2, respectively. Clinical anastomotic leakage rate was 6.1% in group 1 while 10.9% in group 2. The reoperation rate was 7.1% and 9.9% respectively in group 1 and group 2, mainly related to anastomotic leakage. The operative mortality rate was 6.1% in group 1 and 1.3% in group 2. In patients operated on for cure the overall 5-year survival rate was 76 % in group 1, 84 % in group 2 ($P = 0.0223$). The cancer-specific 5-year survival rate was 86 % in group 1 while 91 % in group 2 ($P = 0.0179$).
Conclusions: In our experience advanced age itself is not a contraindication to surgery, although it is associated with higher morbidity and mortality. Overall survival is lower in patients over 75 age, but cancer-related survival is not different between the two groups.
No conflict of interest.

2344 POSTER

Cetuximab plus mFOLFOX-6 as first-line therapy for unresectable liver metastases from colorectal cancer: an open-label, non-randomized, multicenter phase II clinical trial (CLIME Study)

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Background: We designed this study to observe whether the addition of cetuximab to chemotherapy yields a high response and curative resection rates, long progression-free survival (PFS) and long-term overall survival (OS) in a patient population treated in a real life setting in China.
Methods: An open-label, multi-center, phase II study of cetuximab in combination with mFOLFOX-6 as first-line treatment in patients with KRAS wt, unresectable liver metastases of CRC. Patients received cetuximab (500 mg/m^2 q2w) plus mFOLFOX-6 including oxaliplatin 85 mg/m^2 plus CF 400 mg/m^2 and 5-FU as a 400 mg/m^2 bolus followed by 2400 mg/m^2 infusion over 46 hours on day 1, repeated every 2 weeks for maximum of nine cycles. The primary endpoint was R0 resection rate. Secondary endpoints included objective response rate (ORR), PFS, OS and safety.
Findings: Between Dec. 7th 2010 and Sep. 17th 2012, 194 patients were screened at 17 centers in China. Among them 126 were KRAS wild-type cases (65.0%) and 97 cases were enrolled. ORR was 81.3% (95% CI 69.5%, 90.0%) among 64 patients with efficacy assessment available. Of 31 patients undergoing surgical evaluation (finishing medication), 20 patients underwent R0 resection yielding an R0 resection rate of 31.3% (95% CI 20.2%, 40.1%). Among these 20 cases with R0 resection, the median interval between the first and last medication was 64.5 days and the median interval between the last medication and surgery was 29 days. Median PFS was 12.16 months among 67 evaluable patients (95% CI 10.78,-). Incidence of adverse events of any grade was 79.4%, mainly including rash and malaise.
Conclusion: Combination therapy with cetuximab and mFOLFOX-6 was well tolerated and provided ORR, R0 resection rates, PFS and less time between medication and surgery that compares well with data from other clinical trials.
Funding: This study was supported by Merck KGaA Darmstadt, Germany and Sanofi-aventis.
No conflict of interest.

2345 POSTER

Colorectal cancer in high-risk patients: Is laparoscopic surgery really suitable and effective?

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Background: Colorectal cancer (CRC) is a major cause of morbidity and mortality. Laparoscopic colorectal surgery (LCS) allows good short-term outcomes and provides oncologic results comparable to open surgery. However, often LCS is not suitable for high-risk patients (HRP) due to significant comorbidities. This study aims to evaluate the short-term results of LCS for CRC in HRP, assuming that there are no statistically significant differences compared to low-risk patients (LRP).
Methods: According to the current literature, HRP are defined as those>80 years, with ASA score$\geqslant$3, preoperative radiotherapy, T4 tumor or BMI$\geqslant$30 kg/m^2. We considered a consecutive unselected series of 215 patients who underwent elective LCS for CRC at our institution between January 2008 and December 2011. Of these patients 85 (39.6%) were HRP, and 130 (60.4%) LRP. Data on the patients' demographics, disease features, operative details and follow up were prospectively recorded in a specific database and retrospectively analyzed. Comorbidity was quantified by using the Charlson Comorbidity Index (CCI). All the procedures were performed by the same fully trained team (IS, ADL, FR), instrumentation and perioperative management were standardized. Right colectomies were performed until 2009 through a laparoscopic-assisted approach while we used a totally laparoscopic technique from then on, in left colectomies we made a Knight-Griffen anastomosis, a total mesorectal excision was always performed for rectal cancers, whereas a temporary loop ileostomy was created for tumors localized at middle and low rectum. The group 'others' collected laparoscopic transverse or splenic flexure resections, and Miles' procedures. Complications were classified using the Clavien–Dindo system (CDCS).

Results: We reviewed right colectomies (30.2%), left colectomies (44.2%), rectal resections (19.5%), and others (6.1%). There was no significant difference in sex ratio and type of surgical procedures between HRP and LRP, while, by definition, age, body mass index, American Society of Anesthesiology score and tumor stage were statistically different. An higher comorbidity according to CCI characterized HRP (4.6 vs 2.2; P < 0.1). Median operative time (235.6±97.6 vs 223.4±75.1 min; NS), estimated blood loss (52.2±72.7 vs 60.5±94.8 mL; NS), conversion rate (1.2% vs 1.5%; NS), and timing to canalization (4.4±1.4 vs 4.2±1.8dd; NS) were comparable in both groups. HRP was associated with a significantly longer length of hospital stay compared with LRP (10.6±8.6 vs 7.8±4.6dd; P < 0.1). There was no statistically significant difference in postoperative complications according to CDCS (27.0% vs 21.5%; NS), reoperations (1.2% vs 1.5%; NS), and 30-day mortality (0% vs 0.8%; NS).
Conclusions: LCS is safe and efficacious even in HRP. The risk variables considered do not significantly increase either operative time or postoperative complications and short-term outcome. We believe that HRP may have a greater benefit from a minimally invasive approach to CRC.
No conflict of interest.

2346 POSTER

Pelvic exenteration for locally advanced primary and recurrent rectal cancer

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Aim: A review of a single-centre experience of pelvic exenteration as a treatment modality for patients with locally advanced primary and recurrent rectal cancer. The perioperative outcomes, morbidity and long term oncological outcomes are reviewed.
Materials and Methods: Patients undergoing pelvic exenterations for recurrent and locally advanced rectal cancer between 1st January 2006 to 1st August 2012 were identified from a prospective database. All patients underwent pre-operative staging investigations with Computed Tomography (CT) scan of chest, abdomen and pelvis and pelvic Magnetic Resonance Imaging (MRI). Patients with locally advanced primary rectal cancer were counselled for pre-operative chemo-radiation. Pelvic exenteration is defined as en bloc removal of the pelvic organs to which the primary tumour was adherent to. Structures such as the urinary bladder, female reproductive organs were resected en-bloc where indicated with the lesion. Urological or plastic reconstructions were employed where indicated. Patients were followed up according to a standard protocol of colonoscopy, CEA measurements and imaging modalities CT/MRI/Positron Emission Tomography (PET). The primary outcome measured was overall survival (OS) and disease free survival (DFS) and secondary outcomes measured were time to local recurrence (LR) and systemic recurrence. DFS was examined by the Kaplan–Meier Method.
Results: Pelvic exenterations were performed in 13 patients with a median age of 59 (range 26−81). The rate of major postoperative complications was 8% (n = 1), where the patient had anastomotic leakage. There were no mortalities in the perioperative period. All patients were operated with curative intent and negative circumferential margins were achieved in 9 out of 13 patients (70%). With a median follow-up of 23 months, the DFS and OS were 19.4 and 22.5 months respectively.
Conclusion: An aggressive approach with en bloc resection of organs involved provides survival benefit to patients with locally advanced primary and recurrent rectal cancer. Overall survival benefits outweigh the morbidity of surgery.
No conflict of interest.

2347 POSTER

Strategies to minimize the influence of chemotherapy-induced liver injury before the resection of colorectal liver metastasis: Liver surgeons' suggestions

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Background: To minimize the influence of chemotherapy-induced liver injury on the patients undergoing a hepatectomy for colorectal liver metastases (CRLM), it is necessary to clarify preoperative risk factors for liver injury and adequate choice of operative procedure for impaired liver function.
Material and Methods: A total of 94 patients underwent a hepatectomy following oxaliplatin and/or irinotecan-based chemotherapy and were divided into 2 groups according to the indocyanine green retention rate at 15 minutes (ICGR15), (normal ICGR15, n = 24, ICGR15>10%, n = 60). Portal vein embolization (PVE) prior to hepatectomy was conducted when future remnant liver volume ratio was estimated to be less than 40% in the patients with a normal ICGR15 or less than 60% in patients with ICGR15>10%. Preoperative factors associated with ICGR15>10% were indentified in the multivariate analysis.
Results: Eighteen patients (19%) received PVE. Postoperative complications occurred in 45 (48%) and were more frequent in the patients who had ICGR15>10% and received PVE than the others(73% vs. 43%, p = 0.029). The occurrence of complications classified grade III or severer was comparable (6.7% vs. 5.1%, p = 0.81). An age of 60 years or older (odds ratio 2.72, P = 0.04) and 3 or more cycles of oxaliplatin-based chemotherapy without bevacizumab (odds ratio 2.82, P = 0.04) were significantly associated with ICGR15>10%.
Conclusions: Application of criteria based on the ICGR15 value including PVE and choice of chemotherapy, avoiding oxaliplatin-based chemotherapy without bevacizumab especially in the patients aged 60 years or older, can minimize postoperative complication of hepatectomy for CRLM.
No conflict of interest.

2348 POSTER

Synchronous colorectal liver metastases: Simultaneous vs delayed liver surgery in an Italian district community hospital

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Background: The optimal surgical strategy for the treatment of resectable synchronous colorectal liver metastases (CLMs) is still unclear.
According to literature, simultaneous resection seems to be safe and efficient, both avoiding a second major operation (with a positive impact on postoperative immunodepression, early instigation of adjuvant therapy and patient's discomfort) and reducing social costs. Nevertheless, it's related to negative impact on long term survival.
Moreover, to perform a simultaneous technique, two different specialized surgical equipes are needed (mainly for rectal and hepatic resection). That is not so easy to obtain in most community district hospitals.
Materials and Methods: Aim of the study is to compare simultaneous colorectal and hepatic resection (SR) with a delayed strategy (DR) in patients with synchronous CLMs. All patients, referring to our district community hospital in Savona, with synchronous CLMs who underwent hepatic resection between 1st October 1998 and 31st March 2013 were analyzed retrospectively. We excluded from the study 18 patients who underwent a two stage hepatectomy for multiple bilobar metastases. Short-term outcome and overall survival were compared in patients having SR and those treated by DR.
Results: Of 53 patients undergoing hepatectomy for synchronous CLMs, 43 (81%) had a SR and 10 (19%) had a DR. The 90 days mortality rate following hepatectomy was 4 (7.5%) in the two groups (7% versus 10% in SR and DR respectively). The mean survival rate was 39 months in the two groups (34.3 for SR group, 58.3 for DR group). Three and five-year overall survival rates were 50 and 33% (54 and 37% in the SR group; 56 and 44% in the DR group).
Conclusions: In this limited and low powered study, combined strategy seems to be safe in patients with synchronous CLMs without clear differences in terms of mortality and overall survival compared to a delayed procedure. Nevertheless, considering data regarding 90 days mortality, SR in elderly patients should be carefully considered.
No conflict of interest.

	Study Population (N = 53)		*P*
	SR (N = 43)	DR (N = 10)	
Mean Age [Yrs (S.D.)]	69(10)	68(7)	0.8304
Sex Ratio [M:F]	28:15	6:4	0.7615
Primary Tumor			
Colon (%)	30(69.8)	7(70)	0.9885
Rectum (%)	13(30.2)	3(30)	
Liver resection			
Up to 2 segments (%)	25(58.1)	8(80)	0.2127
More than 2 segments (%)	18(41.9)	2(20)	
90 Days Mortality (%)	3(7)	1(10)	
Actuarial 3 Yr Survival Rate	54	56	
Actuarial 5 Yr Survival Rate	37	44	

2349 POSTER

Total anorectal and pelvic floor reconstruction after Mile's resection: A special technique

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Background: Innovative techniques created to restore gastrointestinal perineal continuity after abdominoperineal resection in patients with anorectal cancer include pseudocontinent perineal colostomy, in which the colon is pulled to the perineum and wrapped with a sleeve of stretched colon segment to act as a new sphincter.
Objective: We investigated perineal reconstruction with a modified pseudocontinent perineal colostomy technique.
Design: Prospective cohort study.
Settings: Tertiary care university hospital in Egypt.
Patients: Patients with T2 or T3 anorectal cancer invading the sphincter who underwent Miles abdominoperineal resection and immediate total pelvic reconstruction between 2003 and 2007.
Intervention: Pelvic floor reconstruction by a vertical rectus abdominis myocutaneous flap with modified perineal colostomy pulled through the flap in order to add the high-pressure zone of the flap to that of the colostomy and to create a persistent new anorectal angle.
Main outcome measures: Early and late complications were recorded. Functional results were evaluated at regular intervals by questionnaire, physical examination, and balloon manometry. Continence was graded according to Kirwan. Satisfaction with continence was assessed by questionnaire.
Results: A total of 14 patients (3 women) were included. Tumors were adenocarcinoma (n = 11), squamous cell carcinoma (n = 2), and melanoma (n = 1).
Complete (R0) resection was achieved in all patients without perioperative deaths, major postoperative morbidity, or conversion to permanent iliac colostomy. Early postoperative complications (perineal wound infection, flap dehiscence, and partial perineal stoma necrosis) occurred in the first 4 patients. Late complications occurred in 7 patients, with mucosal prolapse in 3, stomal stricture in 4, and tumor recurrence in 1. Fecal continence progressed consistently with time, and by the end of the first year 8 patients (57%) had complete continence (grade A), 5 (36%) were continent with minor soiling (grade C), and 1 (7%) still had major soiling (grade D). After 6 months, 9 patients (64%) were satisfied with continence; after 1 year, 13 patients (93%) were satisfied. Regular enemas were necessary during the first year to improve soiling, and 8 patients (57%) were not in need after that. At 37 months median follow-up, 8 of 9 evaluable patients (89%) were satisfied with continence (grade A) without regular enemas.
Limitations: This was a preliminary observational study with no control group.
Conclusions: Total orthotopic pelvic reconstruction with autologous tissues transposition to rebuild the principle anorectal continence elements is feasible with minor complications and oncologically safe. This new technique offered high continence satisfaction independent of regular enemas and electrical stimulation.
No conflict of interest.

2350 POSTER

No change in disease free survival of node negative patients after improved nodal staging of colon cancer

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Background: Since July 2004 colorectal resection specimens in our hospital have been processed and fixated using modified Davidson Fixative (mDF). Earlier study showed that this technique improved nodal harvest and changed nodal staging in a substantial number of patients (stage migration). Primary aim of this study is to evaluate if the improved staging after the introduction of mDF affects disease free survival in the node negative group. Secondary aims were to investigate if the number and size of lymph nodes and metastases affect survival rates.
Patients and Methods: The specimens of 125 patients operated after July 2004 where fixated using mDF. The other 117 patients were operated before the introduction of mDF. Patients with rectal cancer, distant metastases (DM) or non-radical resection ($\geqslant$R1) were excluded. The size of the metastatic and non-metastatic lymph nodes was measured. Overall (OS) and disease free survival (DFS) between the groups were compared. Kaplan–Meier curves were used for univariate analysis.
Results: 215 patients were analyzed. The groups were similar for tumour and patient characteristics. Between the groups, differences were observed in the number of detected lymph nodes, node positive rate (no mDF 30%, mDF 41%), number of positive lymph nodes and size of metastatic lymph nodes. In 55 patients tumour recurred. The DFS and OS did not differ between groups. In univariate analysis for the total group, T-status, N-status, number of positive lymph nodes, size of nodal metastasis, adjuvant therapy and ASA 3 classification affected DFS, while fixation method and number of examined lymph nodes did not. Size of metastatic node almost reached significance. In the node negative group fixation method and number of nodes were not significant while T status was. In multivariate analysis, only T- and N-status remained significant factors for disease free survival.
Conclusion: mDF leads to a higher number of examined lymph nodes and nodal upstaging. However, improved nodal staging did not affect the DFS in node negative patients. Except for T- and N-status and number of nodal metastases, size of metastatic nodes may also play a pivotal role with a trend towards significance. Improved staging leads to detection of more and smaller metastatic nodes (stage migration/upstaging) with a change in treatment (adjuvant chemotherapy) for some patients who are upstaged from N0 to N+. Prospective studies on large numbers of patients are necessary to provide changes in survival rates.
No conflict of interest.

2351 POSTER

Association between bevacizumab administration and postoperative wound complications in patients who undergo surgery for liver metastasis of colorectal cancer

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Background: Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, is known to inhibit wound healing. For bevacizumab, the appropriate rest period between the last administration of chemotherapy and surgery (6−8 weeks) is decided on the basis of only on pharmacokinetics data. Our primary objective in this study was to investigate the adverse effect of bevacizumab on surgical wound healing and to clarify the appropriate rest period between the last administration of chemotherapy and surgery in terms of clinical outcome.
Materials and Methods: We retrospectively analyzed 373 surgical cases in 297 patients who underwent surgery for liver metastasis of colorectal cancer at our institution between February 2003 and September 2012. Differences in the distribution of the variables and odds ratio were evaluated using the chi-squared test or Fisher exact test, as appropriate.
Results: Before surgery, 35 patients (9.4%) underwent chemotherapy with bevacizumab (group A), 110 (29.5%) underwent chemotherapy without bevacizumab (group B), and 228 (61.1%) did not undergo chemotherapy (group C). The median time between the last administration of chemotherapy and surgery was 11.1 weeks (range, 2.7–86.1 weeks) in group A and 22.4 weeks (range, 2.1–401.6 weeks) in group B. A total of 90 patients (24.1%) had primary lesions and underwent synchronous colectomy. Postoperative wound complications occurred in 28 cases (7.5%): wound infection, 20 cases; wound dehiscence, 5 cases; ecchymoma, 2 cases; and skin flap necrosis, 1 case. The difference between groups was not associated with wound complications; only synchronous colectomy showed a strong correlation (20.0% vs 3.5%; odds ratio [OR], 6.83; 95% confidence interval [CI]; 3.02–15.43, P <0.001). In group A, the median time between the last administration of bevacizumab and surgery was 15.0 weeks (range, 5.4–86.1 weeks). The patients who were treated with bevacizumab less than 7 weeks before surgery had more frequent wound complications than those at 7 weeks or later (40.0% vs 3.4%; OR, 18.667; 95% CI, 1.28–272.12; P = 0.05). Only one patient underwent synchronous colectomy 7.6 weeks after the last administration of bevacizumab in group A. In contrast, in group B, the incidence of wound complications did not differ between patients who received chemotherapy less than 7 weeks before surgery and those who received chemotherapy more than or equal to 7 weeks before surgery (4.0% vs 4.7%; OR, 0.844; 95% CI, 0.09–7.91; P = 1.00).
Conclusions: In conclusion, this study demonstrated that preoperative chemotherapy or bevacizumab administration does not influence the risk of postoperative wound complications. For patients with a history of bevacizumab treatment, a rest period of 7 weeks between the last administration of chemotherapy and surgery seemed to be appropriate.
No conflict of interest.

2352 POSTER

Colorectal peritoneal carcinomatosis treated with cytoreductive Surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC): The experience of a tertiary Asian centre

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Background: Peritoneal metastases occur in up to 20% of colorectal cancers, and accounts for 40−70% of all recurrent disease. In 10−30% of these recurrences, the disease is confined to the peritoneum, with no distant metastases. In these patients, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have been shown to improve survival when compared to intravenous chemotherapy alone. We review our institutional experience with this group of patients, and evaluate their overall (OS) and disease-free survival (DFS) rates.
Method: Data was prospectively collected from all patients with colorectal peritoneal carcinomatosis treated by CRS and HIPEC at the National Cancer Centre Singapore between Jan 2001 and December 2012. Our primary end points were overall and disease-free survival.
Results: A total of 35 patients underwent CRS and HIPEC. The majority of the patients (89%) were of Chinese ethnicity. Median follow up duration was 24.7 months. The 1, 3- and 5- year disease-free survival was 43.8%, 22.3% and 22.3% respectively, and the overall survival was 83.7%, 38.2% and 19.1% respectively. Factors influencing OS were age at surgery, N stage, completeness of cytoreduction (CC) score, and disease-free interval (DFI); Age, CC score and DFI remained significant for DFS. The 30-day morbidity was 40% and there were no 30-day inpatient mortalities.
Conclusion: CRS and HIPEC can be safely carried out in Asian patients with colorectal peritoneal carcinomatosis, and confers significant disease-free and overall survivals. The age of the patient, DFI and nodal status, together with careful patient selection to ensure that optimal cytoreduction can be achieved is essential for the success of this procedure.
No conflict of interest.

2353 POSTER

Selective decontamination of the digestive tract in gastrointestinal surgery: A valuable addition to infection prevention? A systematic review

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Background: Gastrointestinal surgery is associated with high incidences of infectious complications. The most severe is anastomotic leakage, associated with considerable morbidity and mortality. The use of prophylactic antibiotics strongly reduces infectious complications. The aim of this systematic review was to evaluate effects of perioperative selective decontamination of the digestive tract (SDD), an antimicrobial prophylaxis regimen of oral nonabsorbable selective antibiotics eradicating gastrointestinal carriage of potentially pathogenic micro-organisms, on infectious complications after abdominal surgery.
Methods: Relevant studies were identified using computerised bibliographic searches of MEDLINE, EMBASE, and the Cochrane database (published between 1970 and November 2012) and a manual search of reference lists and the review of 'epub ahead of print' articles. A comprehensive search was performed using the search terms: gastrointestinal tract, gastrointestinal disease, antibiotic prophylaxis, decontamination. Additional keywords and further logical combinations were used to maximise sensitivity.
Results: Of the 1257 abstracts, 96 articles met the primary criteria and were identified for potential inclusion and reviewed in detail. After appliance of the secondary criteria, defined as studies investigating SDD in abdominal surgery, eight randomised controlled trials, one meta-analysis and one retrospective analysed case-controlled clinical trial were selected. One study explored SDD in oesophageal resections, one in gastrectomy and another study in both total gastrectomy and oesophagectomy patients. Three clinical trials investigated SDD in colorectal cancer and one meta-analysis and two studies in liver transplantation. SDD in pancreatic surgery was inquired in one study.
Discussion: The available evidence for the use of SDD in colorectal surgery indicates that SDD, in addition to intravenous antibiotics, reduces (surgical site) infections and the clinical anastomotic leakage rates. For oesophageal and gastric cancer surgery, results are encouraging but heterogeneous. Therefore SDD might be considered as a valuable adjuvant tool for perioperative infection prophylaxis in colorectal cancer surgery. We believe that these results provide a rationale for a large multicenter randomized clinical trail with SDD in colorectal cancer surgery to confirm these effects with sufficient level of evidence.
No conflict of interest.

2354 POSTER

One-stapler technique for right colectomy in colon cancer: A safe and fast technique

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Background: Right colectomy can be effectuated with various methods as far as anastomotic technique is required. One-stapler technique, although has been described almost 20 years ago, is becoming more and more popular among surgeons due to the significant advantages that presents.
Materials and Methods: From January 2012 until December 2012 eleven patients had been submitted to right colectomy due to colon cancer using one-stapler technique. Seven patients were male with an average age of 78 years and four patients were female with an average age of 69 years. Five patients were diagnosed with cancer of the cecum, four were diagnosed with cancer of ascending colon and one was diagnosed with cancer of hepatic flexure. All patients were treated by the same surgeon and one-stapler technique was applied with a subsequent latero-lateral ileocolic anastomosis. The patients in whom this technique was applied were chosen randomly.
Results: The parameters that were taken under consideration were the duration of anastomotic time and post-operative complications of this technique. Anastomotic time was calculate to have an average duration of eight minutes while post-operative complications included one male patient, 80 years old, who presented melena on the 1st post-operative day and was treated conservatively. Melena was attributed to a limited micro-bleeding in the anastomotic area. All the other patients had a normal post-operative course and on a follow-up of 3−11 months had not presented any complications.
Conclusions: One-stapler technique with a subsequent latero-lateral ileocolic anastomosis on the case of right colectomy for colon cancer is a fast technique that can contribute significantly to reducing surgical time. This fact is of major importance for patients submitted to this kind of operation, given their advanced age and the concomitant diseases that aggravate their situation. The fore-described technique is safe, time-saving and of minimal contamination risk, while risk of hemorrhage in the anastomotic area can be avoided by controlling thoroughly the stapling line intra-operatively and reinforcing the stapling line with absorbable sutures. Taking under consideration our experience from these patients, this technique has become our treatment of choice in case of cancer of right colon.
No conflict of interest.

2355 POSTER

Utility of preoperative colonoscopy in localization of colorectal cancer

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Background: Erroneous localization of colorectal carcinomas puts the patients at risk for inappropriate use of adjuvant therapy, inadequate operative approach, prolonged surgery or missing the lesion.
Material and Methods: A retrospective chart review was conducted on a total of 146 patients who had complete endoscopic and CT reports available and had undergone surgery for colon or rectal malignancies between January 2007 and January 2013. The purpose of this study was twofold: (a) to determine the accuracy of colonoscopy and CT scanning in localizing colorectal tumors and (b) to examine the utility of preoperative colonoscopy performed by surgeon.
Results: Tumor location was accurately determined via colonoscopy in 80.5% of cases and erroneously in 19.5% of cases. CT scan confirmed colonoscopic localization in 59.6% of cases, and did not detect known tumors in 40.4% of cases. Of the tumors erroneously located by colonoscopy, 2.7% were accurately localized by CT scan. 48.4% of the patients with undetected tumors on CT scans, underwent second (preoperative) colonoscopy, performed by surgeon. The location of the tumor as determined by preoperative colonoscopy differed from the location noted on referral colonoscopy in 14.6% of patients. Tumor localization was determined correctly in all patients with preoperative colonoscopy and the difference in the accuracy of tumor localization between the patients which underwent two colonoscopies and those which did not, was statistically

significant. The average size of the tumors not detected by CT was 2.98 cm. Large (>4 cm) tumors were rarely missed.
Conclusions: Identifying localization of colorectal tumors by two complementary methods is essential before resection is undertaken. Preoperative colonoscopy, performed by surgeon, would decrease the likelihood of mislocalization of the small lesions detected on the first colonoscopy.
No conflict of interest.

2356 POSTER

Surgical treatment of rectal cancer: A single center experience

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Background: Evaluation of the results of surgical treatment in patients with resectable rectal cancer based on multivariate analysis.
Methods: This study is based on the analysis of 680 consecutive resectable rectal cancer patients, which underwent radical surgical-only treatment during 1990–2010. Localization of rectal tumors ranged from 4 to 15 cm above the anal verge. 333 patients (49%) had upper rectal cancer, 170 patients (25%) − middle, 177 patients (26%) − low. 456 patients (67.1%) had anterior resection (AR), 97 (14.3%) had low anterior resection with coloanal anastomosis (LAR-CAA) and 127 (18.6%) had abdominoperineal resection (APR). Stage distribution was following: T1−2NoMo (Stage I) − in 145 patients (20.6%), T3−4NoMo (Stage II) − 341 (50.6%) and T2−3N1−2Mo (Stage III) in 194 (28.8%).
Results: Local recurrences rate was 11.8%: 9% after AR − 9% after LAR-CAA − 21.6%, after APR − 16.5%; depending on tumor localization: 9% for upper rectal cancer, 26.6% − middle, and 21.2%- low; depending on TNM stage: I − 9%, II − 10.4%,III − 23.5%. Overall 5-year survival rate was 63.8%, 5-year disease-free survival − 58.2%. Relapse rate during 1990–2000 was 18.6%, during 2000–2010 − 5.1%.
Conclusion: Based on our experience, learning curve is crucial factor influencing treatment outcome. Distal localization of rectal cancer is the most important prognostic factor for rectal cancer. Quality surgery allows to achieve local control in 95% of the patients.
No conflict of interest.

2357 POSTER

Significance of BMI over complications in laparoscopic colorectal cancer

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Background: Numerous studies have explored the association between outcomes and risk factors for surgical procedures. One recent study determined the most important predictors of complications that need to be included in models for adequate risk adjustment. The outcome of colorectal surgical procedures is influenced by a variety of factors, including the quality of care, patient characteristics, preoperative risk factors, and operative details. Obesity is a risk factor to develop complications.
Objective: To identify of significance of BMI (Body mass index) >30 iver complications in patients with laparoscopic colorectal cancer (LCC).
Patients: 90 patients with colorrectal laparoscopic surgery.
Results: Only 16 patients with >30 BMI (18%). Mean age: 53.31 years old, 15 are men, 81.3% have a biopsy of colorectal adenocarcinoma. ASA II was grade of the classification for anesthetic risk in 75.5%. In 17% an endoprosthesis was required in the evolution of disease. Surgical mean time was 243 minutes. In 68% patients the reconstruction was mechanical. Conversion to open surgery was necessary in 1 patient by tumoral adhesions. Some kind of complication (wound infection, urinary infection, etc) was identified in the 56.3%. One reoperation was realized for complications (fistulae). In one patient a double ureteral injury was identified (BMI >40). Surgical wound was complicated in 37.6%. A previous diagnosis of colorectal adenocarcinoma was made in 85.7%. Mean number of resected lymph nodes was 16 (11−56). Dukes (Modified Astler-Coller) more frequent was C2 with a 37.5%. Oral intake oral was begin in the first 24−48 hours after surgery in 64.2%. Only 18.8% patients presented a recurrence of initial tumor.
Conclusions: Obesity is known to lead to higher complication rates across a wide variety of surgical procedures. It is not sur-prising that, in our study, increasing BMI was associated with increased postoperative complication rates.
No conflict of interest.

2358 POSTER

Efficiency of multivisceral resection for T4 rectal cancer

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Background: Review a single-center experience of multivisceral resections (MVR) for rectal cancer to determine the accuracy of intraoperative prediction of potential curability and to examine the effect of surgical experience on short-term outcome and long-term results.
Material and Methods: A retrospective study was performed to analyze the data collected 278 patients who underwent a curative resection for $T_4N_{0-2}M_0$ primary rectal cancer (2000–2009). Chemoradiation was using a 3-field belly-board technique. The median total dose was 45 Gy (range 40−60). Estimated overall survival, overall recurrence and local recurrence were compared using the log rank method and Cox regression analysis.
Results: In 136 cases of 278, the patients had macroscopically direct invasion of adjacent organs and underwent a MVR (main group): $T_4N_0M_0$ − 86 (63.2%), $T_4N_{1-2}M_0$ − 50 (36.8%). A control group − 142 patients with T4 rectal cancer without either macro- or microscopic invasion into adjacent organs, who underwent standard surgery: $T_4N_0M_0$ − 99 (70%), $T_4N_{1-2}M_0$ − 43 (30%). Common resected organs were the uterus (45%), vagina (25%), prostate and bladder (23%). In the MVR group, tumor infiltration was confirmed histologically in 38% of the cases, and peritumorous adhesion had mimicked tumor invasion in 62%. Postoperative complications (class III Clavien − Dindo) occurred in 6% of the patients who underwent standard surgery vs. 12% of those who underwent a MVR ($P < 0.0001$). The survival rate of patients after a MVR was similar to that of patients after standard surgery (5-year survival rates: 44.4% vs. 52.8%; $P = 0.36$), thus a recurrence − free survival rate in both groups showed no statistical significance (30% vs. 36%; $P = 0.59$). On univariable analysis, the only factor associated with local recurrence was completeness of resection (local recurrence rate 16% vs 74% for R0 vs R1 resection; $P < 0.001$). On multivariable analysis, factors associated with overall survival were absence of metastatic disease and R0 resection.
Conclusion: MVR was associated with higher postoperative morbidity, but the long-term survival and disease − free survival is similar to that after a standard resection. MVR for T4 rectal cancer had good oncological outcomes when clear resection margins were achieved. Less advanced pathologic N-stage is a significantly favorable prognostic factor for disease-free and overall survival.
No conflict of interest.

2359 POSTER

Initial results of a new antibody-drug conjugate (ADC), IMMU-130 (labetuzumab-SN38), in patients with metastatic colorectal cancer (mCRC)

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Background: IMMU-130 is an ADC comprising labetuzumab (hMN-14) bound to the active metabolite of irinotecan, SN-38. hMN-14, a slowly-internalizing monoclonal antibody (mAb), binds CEACAM5 (CD66e), expressed in >80% CRC. In vitro, the Ab-drug linkage is cleaved in serum, with 50% of SN-38 released in ~1 d, suggesting that most SN38 is released at the tumor in enhanced concentration. Since irinotecan, a standard therapy of mCRC, can have major gastrointestinal (GI) and hematologic toxicity, conjugating insoluble SN-38 to this tumor-targeting mAb should improve the prodrug's therapeutic index. A safe starting dose of IMMU-130 was determined from preclinical toxicology studies showing no GI toxicity and transient mild myelosuppression. This single-arm, open-label, dose-escalation, phase I study was undertaken to define the MTD of IMMU-130 in mCRC pts.
Material and Methods: Eligible pts had received at least 1 prior irinotecan-containing regimen, and serum CEA >5 ng/mL. Permission for this study was obtained from the FDA and local IRB, and informed consent was given. IMMU-130 is administered biweekly, with a goal of 12 cycles in the absence of unacceptable toxicity or disease progression. Pt cohorts are treated at increasing dose levels. DLT is defined as Grade 4 neutropenia $\geqslant$5 d, $\geqslant$ Grade 3 thrombocytopenia, Grade 3 anemia, $\geqslant$ Grade 3 nausea, vomiting or diarrhea >48 h, or other $\geqslant$ Grade 3 non-hematological toxicity in the first 2 doses.
Results: To date, 11 pts have been treated at 2, 4, 8 and 16 mg/kg. The median number of doses given is 4.09, 7 pts received $\geqslant$3 doses. Of 5 pts having >2 doses of 16 mg/kg, one received 18 and achieved a PR after 8, which lasted 8 mos. One DLT was observed at 16 mg/kg: Grade 3 thrombocytopenia. The same pt, and another at the same dose, had Grade 4 neutropenia <5 d. Importantly, no Grade $\geqslant$2 drug-related GI

toxicities were observed. A single case of hypersensitivity occurred. No human anti-human antibodies (HAHA) have been detected. PK analysis shows the intact conjugate clears quicker than the Ig in the circulation, consistent with SN-38 being gradually released from the ADC.
Conclusion: This first-in-man study indicates that IMMU-130, an ADC comprising SN-38, is safe and reasonably well tolerated within a clinically effective dosage range. Dose escalation is continuing.
Conflict of interest: *Board of directors: David M. Goldenberg. Corporate-sponsored research: Neil H. Segal and Leonard B. Saltz. Other substantive relationships: Serengulam Govindan, Pius Maliakal, Robert M. Sharkey, William A. Wegener, and David M. Goldenberg are employees and shareholders of Immunomedics, Inc.*

2360 POSTER

Regorafenib dose modifications in patients with metastatic colorectal cancer in the phase III CORRECT study

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Background: CORRECT (NCT01103323) was a randomized, double-blind, placebo-controlled, phase III study that evaluated the multikinase inhibitor regorafenib (REG) in patients (pts) with metastatic colorectal cancer (mCRC) that had progressed on standard therapy. REG-treated pts showed a clinically significant improvement in overall and progression-free survival *vs* placebo (P). Adverse events (AEs), such as hand–foot skin reaction (HFSR), could be managed with dose interruptions or reductions. This abstract reports details of dose modifications in CORRECT.
Materials and Methods: The CORRECT study, sponsored by Bayer HealthCare, randomized pts to receive REG 160 mg or P once daily for weeks 1−3 of each 4-week cycle. AEs could be managed with interruption or a reduction in treatment dose by 40 mg. In addition, the study protocol provided specific dose modification recommendations for HFSR, hypertension and liver function abnormalities.
Results: 753 pts (500 REG, 253 P) received at least one dose of treatment (median 2 cycles in each group, mean 3.3 cycles of regorafenib, 2.3 cycles of placebo). Dose modifications were reported in 76% of REG-treated pts and 38% of P recipients. The number and duration of dose modifications is reported in the table. The most common AEs requiring dose reduction were HFSR (18% of REG-treated pts *vs* 0.4% of P recipients), diarrhea (4% *vs* 0%), hypertension (3% *vs* 0.4%), fatigue (3% *vs* 2%), and rash/desquamation (3% *vs* 0%). The most common AEs requiring dose interruption were HFSR (19% *vs* 0%), fatigue (6% *vs* 2%), diarrhea (6% *vs* 1%), rash/desquamation (5% *vs* 0%), and hypertension (3% *vs* 0.4%). AEs leading to permanent discontinuation were reported in 18% and 13% of pts in the REG and P groups, respectively.
Conclusion: Although significantly more REG-treated pts than P recipients had dose modifications due to AEs, the difference in the incidence of permanent treatment discontinuation was relatively small. This suggests that dose modifications are effective for managing AEs, and allow pts to continue REG treatment.

	P (n = 253)	REG (n = 500)
Dose reduction, % pts	3	20
Number of dose reductions, % pts		
1	3	16
2	0	3
3	0	1
Mean duration, days (SD)	5.6 (4.4)	11.7 (7.6)
Median duration, days	6.0	7.5
Dose interruption, % pts	38	70
Number of dose interruptions, % pts		
1	28	36
2	8	19
⩾3	2	16
Mean duration, days (SD)	5.8 (5.8)	6.9 (5.5)
Median duration, days	4.0	6.0

Conflict of interest: *Ownership: (stock ownership) Bayer Healthcare Pharmaceuticals. Advisory board: Amgen, Bayer, Roche, Merck, Sanofi-Aventis, Celgene, Genomic Health, Takeda. Board of directors: n/a. Corporate-sponsored research: Amgen, Bayer, Roche, Merck, Taiho, Daiichi-Sankyo, ImClone. Other substantive relationships: (employment) Bayer Healthcare Pharmaceuticals, Bayer Pharma AG*

2361 POSTER

Time to health status deterioration in regorafenib-treated patients with metastatic colorectal cancer (mCRC): A post-hoc analysis of the phase III CORRECT study

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Background: The phase III CORRECT study (NCT01103323) was a randomized, double-blind, placebo-controlled study sponsored by Bayer HealthCare. The study showed that the oral multikinase inhibitor regorafenib (REG) improved overall and progression-free survival in patients with mCRC refractory to standard therapy. This post-hoc analysis assessed time to deterioration (TTD) of health status in the CORRECT study.
Materials and Methods: Patients with mCRC progressing after all standard therapies were randomized to receive REG 160 mg (n = 505) or placebo (P; n = 255) once daily for weeks 1−3 of each 4-week cycle. TTD was analysed using three definitions of deterioration: a 3-component composite of ⩾10 point reduction in EORTC quality of life questionnaire (EORTC QLQ-C30) global health status (GHS) score, disease progression, or death; a 2-component composite of ⩾10 point reduction in GHS score or death; and ⩾10 point reduction in GHS score alone. Additional analyses assessed these endpoints using physical functioning (PF) score in place of GHS.
Results: REG was associated with significantly longer TTD *vs* P when assessed with the GHS-based 3-component endpoint (hazard ratio [HR] 0.77; 95% confidence interval [CI] 0.65–0.91; p < 0.01). TTD did not differ significantly in the REG group *vs* P using the 2-component composite and GHS only definitions (HR 0.91; 95% CI 0.75–1.09; p = 0.35 and HR 0.96; 95% CI 0.77–1.20; p = 0.80, respectively). Results for analyses performed with the PF-based endpoints were consistent with those for GHS, with HRs for the 3-component, 2-component, and PF-only endpoints of 0.74; 0.62–0.88; p < 0.01, 1.03; 0.84–1.25; p = 0.98, and 1.14; 0.90–1.44; p = 0.26, respectively. Patient censoring was high in the 1 and 2-component analyses, and was disproportionately greater in the P group.
Conclusion: REG is associated with a significantly longer median TTD than P when deterioration is measured using a 3-component composite endpoint, but not when deterioration is measured using a 2-component endpoint or GHS alone. This suggests that deterioration in health status in this patient group is driven by disease progression, not by quality of life. The 1 and 2-component analyses should be interpreted with caution due to high patient censoring.

Median TTD, weeks (95% CI)	P (n = 255)	REG (n = 505)	HR (95% CI)
3-component composite	7.0 (6.0−7.1)	7.0 (6.0−7.4)	0.77 (0.65–0.91)
2-component composite	8.1 (8.0−8.6)	8.1 (7.7−8.4)	0.91 (0.75–1.09)
GHS	8.1 (8.1−8.4)	8.0 (7.1−8.3)	0.96 (0.77–1.20)

Conflict of interest: *Ownership: n/a. Advisory board: Bayer, Amgen, Celgene, Genomic Health, Roche, Sanofi-Aventis, Merck, Takeda. Board of directors: n/a. Corporate-sponsored research: Amgen, Bayer, Roche, Merck, Taiho, Daiichi-Sankyo, ImClone. Other substantive relationships: (employment) Bayer Healthcare Pharmaceuticals, Bayer Pharma AG*

2362 POSTER

Efficacy and safety in elderly patients on adjuvant therapy with UFT+LV or S-1 for stage III colon cancer: ACTS-CC trial (TRICC0706)

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Background: The ACTS-CC trial (ClinicalTrials.gov:NCT00660894) is a randomized phase III trial designed to validate non-inferiority of S-1 to UFT/LV which is a standard adjuvant therapy for stage III colon cancer in Japan. Adverse events (AEs) and disease free survival (DFS) at 3 years (primary endpoint) were previously reported. To evaluate the efficacy and safety in elderly patients (pts), subgroup analysis was performed.
Patients and Methods: 20−80 aged pts with stage III colon cancer were randomly assigned to receive UFT/LV (UFT: 300 to 600 mg/day and, LV: 75 mg/day on days 1−28, followed by 7 days rest, 5 courses) or S-1 (80 to 120 mg/day on days 1−28, followed by 14 days rest, 4 courses). We compared AEs and DFS between group A (age $\leqslant$70) and group B (age 71−80).
Results: A total of 1518 pts (760 in S-1 arm, 758 in UFT/LV arm) were analyzed. The proportion of pts of group A and B were 69% (1043 pts) and 31% (475 pts), respectively, and there was no difference in stage distribution between the age groups. Pts with PS1 were more in group B than in group A (2.6% in group A vs. 8.7% in group B).
In S-1 treatment, incidences (any grades) of anemia (29% in group A vs. 40% in group B), decreased platelet count (11% vs.16%), anorexia (29% vs. 38%) and fatigue (25% vs. 33%) were higher in group B than in group A. In $\geqslant$ grade 3 AEs, anorexia (3% vs. 9%), nausea (1% vs. 3%) and fatigue (2% vs. 4%) were more frequent in group B.
In UFT/LV treatment, incidence (any grades) of anorexia (22% vs. 32%) and anemia (24% vs. 33%) were higher in group B, while that of elevation of AST (23% vs. 14%) and ALT (25% vs. 14%) were higher in group A. In $\geqslant$ grade 3 AEs, the difference between age groups was observed only in anorexia (3% vs. 6%).
Both in S-1 and UFT/LV treatment, there was no difference in the treatment completion rate between group A and B (78% and 74% in S-1, 75% and 71% in UFT/LV). The rate of discontinuation due to pts' request regarding AEs was higher in group B (4.3% vs. 8.8% in S-1, 4.4% vs. 8.2% in UFT/LV).
There was no difference in DFS between group A and B both in pts receiving S-1 (log-rank test: $p = 0.535$, 3-year DFS rate: 75% and 78%) and in pts receiving UFT/LV ($p = 0.315$, 73% and 69%).
Conclusions: Both S-1 and UFT/LV as adjuvant therapy for stage III colon cancer maintained their efficacy and feasibility in elderly pts (age 71−80).
Conflict of interest: *Ownership: None. Advisory board: MI and KS have a advisory relationship to Taiho Pharmaceutical Co. Ltd., Japan. Board of directors: None. Corporate-sponsored research: None. Other substantive relationships: MI, TI, HU and KS have honoraria from Taiho Pharmaceutical Co. Ltd., Japan.*

2363 POSTER

Hospital variation in type of adjuvant chemotherapy for patients with stage III colon cancer

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Purpose: To assess which factors determine whether or not platinum-based chemotherapy is administered to patients with stage III colon cancer.
Patients and Methods: 1113 patients who underwent resection for primary colon cancer stage III diagnosed in the Southern Netherlands between 2008–2011 were included. Differences in patient and tumour characteristics between patients receiving platinum-based chemotherapy, non-platinum-based chemotherapy or no chemotherapy were analysed using Chi^2 tests. After stratification by age group, crude and adjusted proportions of patients receiving platinum-based chemotherapy and non-platinum-based chemotherapy were calculated for each of 10 hospitals. Multivariable logistic regression analysis was conducted to assess the influence of several patient and tumour characteristics and hospital on the administration of platinum-based chemotherapy among the subgroup of patients treated in adjuvant setting.
Results: 87% of patients aged <70 years received adjuvant chemotherapy. In patients aged 70−74 years, 66% received adjuvant chemotherapy and among patients aged $\geqslant$75 years, this percentage was 24%. A large hospital variation in the addition of oxaliplatin could be noted, ranging from 73%-96% for patients aged <70 years, from 50%-100% for patients aged 70−74 years, and from 8%-100% for patients aged $\geqslant$75 years. Older patients and patients with T1 stage were less likely to receive platinum-based chemotherapy (adjusted $OR_{\geqslant 75 years\_vs\_<70 years}$ 0.02, 95% CI <0.001–0.58 and adjusted $OR_{T1\_vs\_T3}$ 0.17, 95% CI 0.05–0.62, respectively). Patients from two hospitals were less likely to receive platinum-based chemotherapy (adjusted $OR_{G\_vs\_C}$ 0.36, 95% CI 0.14–0.89 and adjusted $OR_{H\_vs\_C}$ 0.34, 95% CI 0.13–0.87, respectively).
Conclusion: The decision to withhold platinum-based chemotherapy does not only depend on predictable factors such as age and stage, but also on hospital. The impact of hospital variation in type of adjuvant chemotherapy on outcome is important but remains to be established in future research.
No conflict of interest.

2364 POSTER

Prospective analysis of UGT1A1 genotyping for predicting toxicities in advanced colorectal cancer (ACRC) treated with irinotecan (IRI)-based regimens: The development of nomogram predicting severe neutropenia

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Background: *UGT1A1*6* and *UGT1A1*28* are risk factors for severe IRI-related toxicities in Asians, and recommended IRI doses based on *UGT1A1* genotypes has not been established. We conducted a prospective analysis to examine the correlation between *UGT1A1* genotypes and safety/efficacy of IRI-based regimens in Japanese ACRC patients (pts), (NCT 01039506).
Methods: Pts who had histologically confirmed ACRC with PS of 0−2 and received IRI-based regimens (FOLFIRI, IRI+S-1, IRI monotherapy) were genotyped for *UGT1A1*. All pts provided written informed consent. *UGT1A1* polymorphisms were analyzed and categorized into 3 groups: wild (**1/*1*), hetero (**1/*6, *1/*28*), and homo (**6/*6, *6/*28, *28/*28*). Detailed toxicities in the first 3 months of treatment were prospectively recorded. For interim safety analysis, incidences of grade 3−4 (severe) toxicities were assessed among *UGT1A1* genotypes and a logistic regression model was used to determine the associated risk factors for severe toxicities. Then a nomogram for predicting severe toxicities was developed, and bootstrap validation was performed.
Results: We enrolled 1376 pts between October 2009 and March 2012. At the time of this abstract submission, toxicity data of 1062 pts were available. The prevalence of UGT1A1 polymorphisms, 47% wild, 42% hetero, and 11% homo, were similar to those previously published in Japanese population. FOLFIRI was administered to 63% pts, initial IRI doses (mean$\pm$SD mg/m^2) were 138.6$\pm$25.3 in wild, 137.4$\pm$27.7 in hetero, and 121.1$\pm$33.2 in homo. During the first 3 months of treatment, severe neutropenia developed in 32% pts: 25% in wild, 35% in hetero [Odds ratio (OR) to wild, 1.7; 95% CI, 1.3−2.2], and 51% in homo [OR to wild, 3.1; 95% CI, 2.0−4.8]. Severe diarrhea was 4% in wild, 4% in hetero [OR to wild, 1.0; 95% CI, 0.5−1.9], and 10% in homo [OR to wild, 3.3; 95% CI, 1.4−7.4]. We developed a nomogram for predicting severe neutropenia in the first treatment cycle using a multiple logistic regression model included regimen, initial IRI dose, gender, age, *UGT1A1* genotype, and PS. The resulting nomogram demonstrated good accuracy in predicting severe neutropenia, with a bootstrap-corrected concordance index of 0.7033.
Conclusions: *UGT1A1* genotype along with other clinical factors has been confirmed to be a critical risk factor for severe toxicities of IRI-based regimens. We will provide the final nomogram based on 1320 pts data and its additional validation results. This nomogram would help us to find the individual starting dose of IRI.
Conflict of interest: *Advisory board: Daiichi Sankyo. Corporate-sponsored research: Daiichi Sankyo. Other substantive relationships: Daiichi Sankyo*

2365 POSTER

The relevance of thymidine kinase 1 (TK1) expression to treatment efficacy of TAS-102 and prognosis in patients (pts) with metastatic colorectal cancer (mCRC)

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Background: TAS-102 is a novel oral nucleoside antitumor agent, consisting of trifluorothymidine (FTD) and thymidine phosphorylase inhibitor that prevents degradation of FTD. FTD is incorporated into DNA after phosphorylation by thymidine kinase 1 (TK1), and leading to antitumor effects. In addition, TK1 is believed to play an important role in the prognosis of various cancers. TAS-102 improved the prognosis of mCRC pts in Phase II study conducted in Japan. The first report of the relationship between TK1 and TAS-102 expression was already presented, and we performed further analysis to clarify the role of TK1 in mCRC and TAS-102 treatment.
Material and Methods: Immunohistochemical analysis of TK1 was performed in 150 (TAS-102: 99, placebo: 51) of 169 pts and TK1 expression in cytoplasm was blindly assessed at the central laboratory. The relationship between TK1 expression and efficacy of TAS-102 was retrospectively investigated with variable cut-off value which evaluates occupancy of TK1 positive cell in tumor cells. This study was supported by Taiho Pharmaceutical CO., LTD. (JAPIC Clinical Trials information Identifier: JapicCTI-090880.)
Results: The median OS of the population with a high TK1 expression tend to shorter than that of the population with a low TK1 expression in the placebo group, whereas TAS-102 reduced the risk of death at each cut-off point irrespective of TK1 expression. At a cut-off of 30%, the median OS of pts with high TK1 expression (n = 13) and low (n = 38) expression was 4.9 and 7.2 months in the placebo group. In contrast, the median OS of pts with high TK1 expression (n = 27) and low (n = 72) expression was 10.4 and 7.7 months (p = 0.04, HR = 0.51, 95% CI=0.27–0.97) in the TAS-102 group. TAS-102 is highly effective in prolonging the survival of pts with high TK1 expression. The hazard ratio for OS by TAS-102 was 0.14 (p = 0.0013, 95% CI=0.04–0.46) in pts with high TK1 expression and 0.62 (p = 0.044, 95% CI=0.39–0.99) in pts with low TK1 expression. The decrease in the risk of death was favored in the population for which the TK1 high expression cell revealed $\geqslant$30% occupancy. HR for OS adjusted by *KRAS* mutational status and the other background factors be significant from pre-planned multivariate analysis was 0.52 (p = 0.0019, 95% CI=0.35–0.79) and interaction between treatment effect and TK1 expression could be suggested (p = 0.083).
Conclusions: TK1 could be a prognostic factor of mCRC and TAS-102 could be more effective in pts with high TK1 population.
Conflict of interest: *Ownership: H.Baba: Ownership of Ohtsuka, that is parent company of TAIHO Pharmaceutical Co., Ltd. Advisory board: T. Yoshino: KRAS adviser (TAIHO Pharmaceutical Co., Ltd.). H. Baba and A. Ohtsu: A member of steering Committee (TAIHO Pharmaceutical Co., Ltd.). Board of directors: All authors is not on the board of directors. Corporate-sponsored research: Y. Komatsu, T. Yoshino, N. Mizunuma, K. Yamazaki, T. Nishina, H. Baba, A. Tsuji, K. Yamaguchi and K. Muro: This phase I clinical study is sponsored by TAIHO Pharmaceutical Co., Ltd. Other substantive relationships: H. Baba and A. Ohtsu: honoraria from TAIHO Pharmaceutical Co., Ltd.*

2366 POSTER

Liver resection in patients (pts) treated with 1st line chemotherapy (CT) for metastatic colorectal cancer (mCRC) from Japanese cross-sectional cohort study (EMERaLD study)

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Background: Complete resection of metastatic diseases can only result in cure with metastatic colorectal cancer (mCRC). We planned and conducted a large cross-sectional cohort study which investigates 1st line CT and metastasectomy in mCRC in Japan.
Methods: EMERaLD study evaluated the 6-month efficacy and safety data on 1,005 pts, recruited from 132 centers in Japan between October 2010 and September 2011, treated with 1st line CT including oxaliplatin and bevacizumab (BV) for mCRC. Among the total 1,005 pts, 627 pts has liver metastasis (mets) from colorectal cancer. We performed a sub-group analysis focused on 627 pts with liver mets from colorectal cancer.
Results: The background of 627 pts were the following; male/female, 411/216; median age of 64 (range, 27−89); ECOG PS 0/1/2/3, 534/86/6/1; site of primary tumor colon/rectum/others, 356/267/4; site of metastatic disease liver limited/with extrahepatic, 362/265; vascular invasion of liver mets with/without/unknown, 102/504/21; FOLFOX/ CapeOx/ others with BV, 285/324/18, KRAS-status wild/mutant/unknown, 138/113/376. Median number of liver mets was 5 (pts with the number of liver mets 1−4/$\geqslant$5/unknown, 296/321/10). Median maximum diameter of liver mets was 3.5 cm (range, 0.25−23). Among 627 pts, 106 pts (16.9%) received liver resection following 1st line CT. 90 pts (14.4%) had R0 liver resection. As a result of multivariate analysis, the following variables at baseline were associated to liver resection; age ($\geqslant$/<75 years old) (p = 0.0787; Odds Ratio (OR) = 1.844), extrahepatic diseases (p < 0.0001; OR = 0.194), the number of liver mets (p < 0.0001; OR = 0.812), peritoneal effusion (p = 0.034; OR = 0.265) and the response to 1st line CT (p < 0.0001; OR = 0.301). For the number of liver mets, Receiver Operating Characteristic analysis identified a cut-off value of 5 (1−5/$\geqslant$6) to distinguish between pts with or without liver resection.
Conclusions: Multivariate analysis showed liver resection of mCRC was associated to the following variables; no extrahepatic diseases, the number of liver mets of 1−5, no peritoneal effusion and the response to 1st line CT. We will further investigate and analyze the 2-year data including survival.
This study is sponsored by the Public Health Research Center Foundation CSPOR in Japan.
No conflict of interest.

2367 POSTER

First-line treatment with regorafenib (REG) in combination with mFOLFOX6 (folinic acid + 5-fluorouracil [5-FU] + oxaliplatin) for metastatic colorectal cancer (mCRC): A single-arm, open-label phase II clinical trial

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Background: 5-FU-containing chemotherapy is commonly used as first-line therapy for mCRC. Although response rates are high, most tumors eventually progress, indicating a need for agents that provide improved efficacy. REG is a novel oral multikinase inhibitor that blocks the activity of kinases involved in angiogenesis, oncogenesis, and tumor microenvironment signaling. A recent phase III trial demonstrated that REG monotherapy improved overall survival (OS) in patients (pts) with mCRC previously treated with other approved agents. The combination of REG and 5-FU-based chemotherapy showed acceptable tolerability in an earlier phase I trial. In the current phase II study (NCT01289821, sponsored by Bayer HealthCare) we evaluated REG in combination with mFOLFOX6 as first-line mCRC therapy.
Materials and Methods: Key inclusion criteria were mCRC that was not/unlikely to be resectable and an ECOG performance status of 0 or 1.

Exclusion criteria included prior systemic anticancer therapy for mCRC. Pts received REG 160 mg orally once daily on days 4−10 and 18−24 of each 28-day cycle, in combination with mFOLFOX6 on days 1 and 15 of each cycle. The primary endpoint was objective response rate (ORR), based on blinded central radiological review using RECIST v1.1. Additional endpoints included disease control rate (DCR), OS, progression-free survival (PFS), and safety.
Results: The study recruited 54 patients, all Caucasian (men n = 28, 51.9%; women n = 26, 48.1%), aged <65 (n = 33, 61.1%) or ⩾65 years (n = 21, 38.9%), with baseline ECOG scores of 0 (n = 35, 64.8%) or 1 (n = 19, 35.2%). 49 pts discontinued treatment, and five pts are still in the study. The median duration of REG treatment was 7 cycles (range 1−21). ORR was 43.9% (all partial responses); DCR was 85.4%. Median PFS was 8.5 months (95% CI 7.4–11.3). Median OS was not yet reached (range 0–19.9 months, including censored data). All pts experienced drug-related adverse events (AEs); four pts stopped treatment permanently because of AEs. The most common REG-related grade 3/4 AEs were increased lipase (n = 10, 19%), hypertension (n = 9, 17%), diarrhea (n = 7, 13%), and hypophosphatemia (n = 6, 11%). Among 24 pts who had mutational data available, nine tumors were *KRAS* wild type, eight were *KRAS* mutant, four were *PIK3CA* mutant, and three had other mutations.
Conclusion: The results of this study indicate that the combination of mFOLFOX6 with REG is feasible with a manageable safety profile in pts with mCRC.
Conflict of interest: *Ownership: n/a. Advisory board: Roche, Bayer, Sanofi Aventis, Merck, Amgen. Board of directors: n/a. Corporate-sponsored research: Bayer. Other substantive relationships: MERK (consultant), Bayer (consultant and employee)*

2368 POSTER

A phase 1B study of second-line therapy with panitumumab, irinotecan and everolimus (PIE) in metastatic colorectal cancer (mCRC) with KRAS wild type (WT)

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Background: The mammalian target of rapamycin (mTOR) is a key downstream protein activated via PI3K-AKT pathway,that regulates cell growth, proliferation, and survival. Inhibition of mTOR in addition to EGFR may overcome upstream resistance to EGFR inhibitors in CRC. This is a phase Ib study to determine the maximum tolerated dose (MTD) of the PIE combination.
Patients and Methods: Patients with *KRAS* WT mCRC following failure of first line fluoropyrimidine-based therapy received IV irinotecan and panitumumab every 2 weeks, and everolimus orally throughout a 14-day cycle. Dose finding used a standard 3+3 design with the MTD defined as the dose with dose limiting toxicity (DLT) in ⩽1/6 patients. A DLT is any of the following in the first 28 days: febrile neutropenia, G3/G4 neutropenia >14 days, any G4 thrombocytopenia, any non-haematologic event of G4 or of G3 for >7 days, or treatment delays of >14 days. Dose level 1; irinotecan 200 mg/m^2, panitumumab 6 mg/kg, everolimus 5 mg alternate days. Dose level 2; irinotecan 200 mg/m^2, panitumumab 6 mg/kg, and everolimus 5 mg daily.
Results: Of the 16 patients enrolled into the study, 2 withdrew prior to receiving any therapy. Five patients were enrolled at dose level 1. Two patients were not evaluable. Of the 3 evaluable patients there was no DLT. Three patients were then treated at dose level 2. Following one DLT (grade 3 mucositis >7 days), the cohort was expanded to 5 evaluable patients but suspended after a further DLT (grade 3 mucositis). Other grade 3 toxicities were anorexia, rash, vomiting, and hypersensitivity. There were no grade 4 toxicities. Dose level 1 was expanded by 4 to a total of 7 evaluable patients. Grade 3 toxicities were mucositis (14%), fatigue (14%), diarrhoea (29%), rash (14%), hypomagnesaemia (14%), and neutropenia (14%). There was no DLT. At dose level 1 the partial response rate was 29% and stable disease 43%.
Conclusions: Dose level 2 exceeded the MTD. Dose level 1 appears tolerable and warrants further investigation. The phase II component of the study is ongoing.
Conflict of interest: *Advisory board: TJ Price, N Tebbutt and C Karapetis all uncompensated members of Amgen advisory board. Corporate-sponsored research: Amgen and Novartis are supporting this study*

2369 POSTER

Phase II study of linifanib in KRAS mutated metastatic refractory colorectal cancer

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Background: Vascular endothelial growth factor (VEGF) pathway blockade has proven efficacy in metastatic colorectal cancer (mCRC). Linifanib is a potent tyrosine kinase inhibitor (TKI) of VEGF and platelet-derived growth factor receptors. NCT01365910 evaluated the efficacy of linifanib in patients with KRAS mutated refractory mCRC.
Methods: Patients with KRAS mutated mCRC refractory to 1−3 lines of chemotherapy were treated with linifanib at 17.5 mg orally daily per 28 day cycle. Disease evaluations were every 2 cycles. Primary endpoint was response rate (RR) in the intent to treat population with a target of at least 15% overall RR using RECIST 1.1. Simon two-stage design was used. Stage 1 enrolled 30 patients and required ⩾2 responses to proceed to stage 2, for a total of 52 patients. The design provided 80% statistical power to detect a difference of 10% (15% vs 5%) with a significance level <0.05 (type 1 error).
Results: 30 patients were accrued. One patient never started linifanib. Absolute decrease in tumor size was seen in 8 patients (26.7%), without any partial response (PR). Cavitary lesions as seen with some TKI's were seen without meeting RECIST response. 21 patients (70%) had stable disease (SD). 4 patients (13.3%) had progressive disease (PD). 5 patients (16.7%) were not evaluable secondary to early withdrawal and lack of post baseline imaging. Progression free survival (PFS) was 4.1 months (CI 3.6−5.5). Overall survival was 7.0 months (CI 4.3–10.9). All evaluable patients required ⩾1 dose reduction. 26 patients (86.7%) had a maximum grade 3 adverse event (AE) at least possibly related to study drug. Most common related grade 3 AEs were fatigue (43.3%), hypertension (36.7%), proteinuria (10%), oral pain (10%), thrombocytopenia (6.7%), and arthralgia (6.7%). One patient remained on study for 72 weeks.
Conclusions: Linifanib was intolerable at 17.5 mg daily in this population, with 16.7% of patients withdrawing prior to the first post baseline imaging from poor tolerability. Only 16 patients (53.3%) were removed for RECIST progression. With dose reduction, tumor control was seen in the majority of the patients, manifested as RECIST SD and a PFS similar to what has been seen in monotherapy trials of agents active in refractory mCRC. Nonetheless, this study was terminated as it did not meet criteria to proceed to stage 2.
This study was supported by AbbVie and by the Vanderbilt-Ingram Center Support Grant P30CA68485.
Conflict of interest: *Advisory board: Amgen: Emily Chan. Genentech: Emily Chan. Corporate-sponsored research: Study was an ITT awarded to Jordan Berlin. AbbVie provided research support for the study. I was the institutional PI on another AbbVie study but all the money went to the institution for the conduct of the study.*

2370 POSTER

Kinetics of CEA, CA19-9 and circulating tumor cells in patients treated with chemotherapy for a metastatic colorectal cancer

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Background: Clinical management of patients with cancer could be significantly improved through the development of a non-invasive method for the evaluation of treatment sensitivity or resistance. We have previously reported that CEA kinetic at the 0.05 threshold may be used as an accurate and non-invasive marker to predict chemotherapy (CT) efficiency in metastatic colorectal cancer (mCRC). The primary objective of this multicenter study was to validate prospectively the relevance of the CEA kinetic at the 0.05 threshold in an independent set of mCRC patients. The secondary objectives included the analysis of CA 19−9 and Circulating Tumor Cells (CTC) during the chemotherapy sequence.

Methods: From 11/2010 to 03/2013, 100 mCRC patients who started a CT regimen with an informative CEA and/or CA19-9 (⩾5 μg/L or ⩾30UI/mL, respectively) were included. For each patient, plasma was assessed at baseline and at the fourth cycle of CT for assay of CEA and CA19-9. CTC were analyzed using the ScreenCell® method at baseline, weeks 6 and 12. Response to CT based on RECIST criteria, progression-free survival (PFS) and overall survival (OS) were analyzed according to baseline value and kinetic of each marker.
Results: CEA kinetic at the 0.05 threshold was significantly associated with disease control (p = 0.003) with a positive and negative predictive value of 61% and 78%, respectively. The CA19-9 kinetic using the threshold of −0.07 determined by ROC curves (sensibility of 77% and specificity of 71%) was also significantly associated with disease control (p = 0.0004). CTC were detected in 53% and 63% of patients at baseline and weeks 6 respectively with a trend for disease progression for baseline value (p = 0.06) without impact on survival. In contrast, univariate analysis showed that CEA kinetic (p = 0.05), increased baseline CEA>25 μg/L (p = 0.01) and CA19-9 kinetic (p = 0.0009) were correlated with PFS. Moreover, baseline CEA>25 μg/L (p = 0.05) and CA19-9 kinetic (p = 0.05) were associated with OS.
Conclusions: In an independent series of mCRC patients treated with CT, our results confirm that CEA kinetic is a non-invasive marker associated with response to CT and PFS. CA19-9 kinetic is also clinically relevant in this setting whereas no conclusive results have been yet observed for CTC analysis.
Conflict of interest: *Corporate-sponsored research: Roche, Amgen et Merck-Serono*

2371 POSTER

Effect of adjusting the pH of oxaliplatin solution by mixing steroid on venous pain: Randomized phase II APOLLO study

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Background: Administration of oxaliplatin through peripheral vein can cause venous pain. The pH level of oxaliplatin solution is about 4.8 and that of buffered by steroid is around 7.0.
To assess the hypothesis that adjusting the pH of oxaliplatin solution by mixing steroid can reduce venous pain, we have conducted a randomized control study to compare pH adjusted oxaliplatin solution with unadjusted oxaliplatin solution.
Material and Methods: This was a single-blinded multicenter randomized phase II study. Colorectal cancer patients receiving oxaliplatin through peripheral vein were enrolled and randomly assigned to arm A (oxaliplatin 130 mg/m^2 with dexamethasone 1.65 mg) or arm B (the same, without dexamethasone). Venous pain was evaluated according to CTCAE criteria (ver. 4.0) and the verbal rating scale (VRS). Assessments were conducted every 3 weeks until cycle 4.

Venous pain	Arm A (%)	Arm B (%)	risk ratio
Grade >=2 (CTCAE ver.4.0)	33.3	58.3	0.57 [0.30–1.10]
Score >=3 (VRS)	12.5	37.5	0.33 [0.10–1.08]

Results: A total of 53 patients (38 men and 15 women; median age, 67 yr) were enrolled. Of these, 48 evaluable patients were randomized to either arm A (n = 24) or arm B (n = 24). Incidence of venous pain (grade>=2) was 33.3%(n = 8) in arm A and 58.3%(n = 14) in arm B (relative risk 0.57 [0.30–1.10]). Incidence of venous pain (VRS score>=3) was 12.5%(n = 3) in arm A and 37.5%(n = 9) in arm B (relative risk 0.33 [0.10–1.08]). Among 9 pts who received pH adjustment in the course of treatment, venous pain was slightly decreased in 5 pts. Response rate was 62.5% in arm A and 66.7% in arm B. No difference was observed in safety.
Conclusions: Mixing steroid reduced grade>=2 venous pain with unaffected efficacy or adverse events. When oxaliplatin is administered through peripheral vein, it is recommended that pH is adjusted by mixing steroid at the start of chemotherapy.
No conflict of interest.

2372 POSTER

Chemotherapy delivery and tolerability of FOLFOX vs FOLFIRI in a phase 3 trial of pegfilgrastim in patients with colorectal cancer (CRC)

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Background: The Pegfilgrastim Anti-VEGF Evaluation Study (PAVES) evaluated the efficacy of pegfilgrastim (Neulasta®) to reduce the incidence of grade 3/4 febrile neutropenia (FN) in 845 patients with CRC receiving first-line bevacizumab with FOLFOX or FOLFIRI. Here we describe the tolerability of FOLFOX vs FOLFIRI and low-dose regimens (LDR: FOLFOX4/FOLFIRI Douillard) vs high-dose regimens (HDR: FOLFOX6/mFOLFOX6/FOLFIRI).
Methods: This double-blind, placebo-controlled, phase 3 trial included patients ⩾18 years with measurable locally advanced (LA) or metastatic (m) CRC per RECIST 1.1. Patients were randomized 1:1 to chemotherapy plus bevacizumab and either placebo or 6 mg pegfilgrastim. Study treatment period: 4 Q2W cycles. Randomization stratification factors: North America/rest of world, LA/mCRC, and FOLFOX/FOLFIRI. Grade 3/4 FN: absolute neutrophil count (ANC) <1.0x10^9/L the same (±1) day as a temperature ⩾38.0ºC, sepsis, infection, or neutropenia-related hospitalization. Grade 3/4 neutropenia: ANC <1.0x10^9/L. Long-term follow-up of this Amgen-sponsored trial (NCT00911170) is ongoing.

	FOLFOX	FOLFIRI	LDR	HDR
Placebo	**N = 207**	**N = 216**	**N = 174**	**N = 249**
Mean RDI				
%	94.1	92.7	93.4	93.4
95% CI	92.8–95.5	91.4–94.0	92.0–94.9	92.1–94.6
Dose Delays >3 days				
%	21.3	27.8	27.0	22.9
95% CI	15.9–27.5	21.9–34.3	20.6–34.3	17.8–28.6
Dose Reductions >15%				
%	6.3	13.9	7.5	12.0
95% CI	3.4–10.5	9.6–19.2	4.0–12.4	8.3, 16.8
Grade ⩾3 Adverse Events[a]				
n	56	63	48	71
%	27.2	29.3	27.6	28.7
Fatal Events[a]				
n	6	5	5	6
%	2.9	2.3	2.9	2.4
Grade 3/4 FN				
%	6.3	5.1	4.0	6.8
95% CI	3.4–10.5	2.6−8.9	1.6−8.1	4.0–10.7
Grade 3/4 Neutropenia				
%	17.9	16.2	16.1	17.7
95% CI	12.9–23.8	11.6–21.8	11.0–22.4	13.1–23.0
Pegfilgrastim	**N = 207**	**N = 215**	**N = 160**	**N = 262**
Mean RDI				
%	94.4	93.6	94.8	93.5
95% CI	93.1–95.8	92.3–95.0	93.2–96.4	92.3–94.7
Dose Delays >3 days				
%	16.9	22.8	16.9	21.8
95% CI	12.1–22.7	17.4–29.0	11.4–23.6	16.9–27.2
Dose Reductions >15%				
%	7.7	9.8	6.9	9.9
95% CI	4.5–12.2	6.1–14.5	3.5–12.0	6.6–14.2
Grade ⩾3 Adverse Events[a]				
n	60	55	33	82
%	29.3	25.6	20.8	31.4
Fatal Events[a]				
n	5	5	4	6
%	2.4	2.3	2.5	2.3
Grade 3/4 FN				
%	1.0	3.7	1.9	2.7
95% CI	0.1−3.4	1.6−7.2	0.4−5.4	1.1−5.4
Grade 3/4 Neutropenia				
%	1.9	5.1	2.5	4.2

Results: The study met its primary endpoint: Pegfilgrastim significantly reduced overall incidence of grade 3/4 FN in the first 4 cycles (2.4% vs 5.7%; *P* = 0.014). See table for relative dose intensity (RDI) and tolerability of each chemotherapy regimen.
Conflict of interest: *Advisory board: SO has an advisory role with Amgen Inc. Corporate-sponsored research: SO has received research funding from Amgen Inc. Other substantive relationships: MM, EA, MC, and FDV are employees of and stockholders in Amgen Inc.*

2373 POSTER

S-1 and irinotecan versus 5-fluorouracil and leucovorin plus oxaliplatin with or without bevacizumab in metastatic colorectal cancer: a pooled analysis of 4 phase II studies

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Background: S-1, a novel oral prodrug of 5-fluorouracil (5-FU), and irinotecan with or without bevacizumab is known to be effective for metastatic colorectal cancer (mCRC). However, it is not clear whether S-1 and irinotecan confers benefit compared to 5-FU and leucovorin plus oxaliplatin (FOLFOX) in patients with mCRC.
Patients and Methods: We analyzed 187 patients with previously untreated mCRC who were enrolled in four phase II studies of SIR study (S-1 and irinotecan, n = 40), SIRB study (S-1 and irinotecan with bevacizumab, n = 51), FOLFOX study (5-FU and leucovorin plus oxaliplatin, n = 46), and STOX study (stop and go strategy of modified FOLFOX-6 with bevacizumab, n = 50). We evaluated efficacy and safety between SIR/SIRB group and FOLFOX/STOX group.
Results: Baseline characteristics were similar between two groups of SIR/SIRB (n = 91) and FOLFOX/STOX (n = 96). There was no significant difference in overall response rate between two groups (65% in SIR/SIRB group versus 52% in FOLFOX/STOX group, p = 0.125). Median progression-free survival was 10.9 months in SIR/SIRB group versus 12.1 months in FOLFOX/STOX group (p = 0.58). Median overall survival was 27.3 months in SIR/SIRB group versus 26.8 months in FOLFOX/STOX group (p = 0.97). The most common grade 3 or 4 adverse events in SIR/SIRB group versus FOLFOX/STOX group were neutropenia (24% versus 45%; p = 0.0036) and anorexia (12% versus 3%; p = 0.025). The multivariate analyses demonstrated that female (hazard ratio [HR], 1.70; 95% confidence interval [CI], 1.18–2.45) and synchronous metastases (HR 1.77; 95% CI, 1.19–2.63) were independent poor prognostic factors for patients received first-line 5-FU-based combination chemotherapies.
Conclusions: S-1 and irinotecan with or without bevacizumab was well tolerated and similar response rate and survival compared to FOLFOX with or without bevacizumab. This combination should be considered as an experimental first-line treatment for mCRC.
No conflict of interest.

2374 POSTER

Analysis of Köhne's prognostic index in KRAS wild type patients with metastatic colorectal cancer (mCRC) treated with salvage-line cetuximab-based regimen: HGCSG0901

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Background: In treatment for metastatic colorectal cancer, it is essential for understanding the prognosis of each individual patient. Köhne's prognostic index based on performance status, white blood cell count, alkaline phosphatase and number of metastatic sites has been previously proposed(Köhne CH, et al. Ann Oncol. 13:308−17, 2002). However, in the salvage setting, the validity of Köhne's classification has not been reported in patients treated by cetuximab-based chemotherapy.
Methods: 269 patients with mCRC treated by cetuximab contained chemotherapy were retrospectively registered from 27 centers in Japan (HGCSG 0901 study). Of these, the *KRAS* wild type patients that were refractory to or intolerant for 5-FU/ irinotecan/ oxaliplatin, and were never administered anti-EGFR-antibody, were included in this analysis. Univariate and multivariate analysis for overall survival were performed using patient characteristics. Survival analyses were performed with Kaplan–Meier method, log-rank test and Cox proportional hazards model.
Results: All data were available for prognostic categorization in 127 patients. Median survival was 9.8 months. The distribution and median survival for Köhne's prognostic groups were as follows: low risk (n = 40; 13.1 months), intermediate risk (n = 17; 9.6 months), and high risk (n = 70; 7.6 months). The survival difference was significant between low and high risk groups (p = 0.004), but not between intermediate and high risk groups (p = 0.213), and between low and intermediate risk groups (p = 0.321). In Cox multivariate analysis, Köhne's prognostic index had shown an independent prognostic impact (hazard ratio: 1.370, 95% CI: 1.078–1.742, p = 0.010).
Conclusions: It was shown that Köhne's prognostic index might provide valuable information in salvage treatment with cetuximab-based regimen. Moreover, the prospective evaluation is needed for the further validation.
Conflict of interest: *Advisory board: Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Yakult Honsha Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Merck Serono Co., Ltd., Bristol-Myers Squibb Co., Pfizer Japan Inc., Novartis Pharma K.K., Sawai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd. Corporate-sponsored research: Taiho Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Novartis Pharma K.K., Yakult Honsha Co., Ltd., Daiichi Sankyo Co., Ltd., Merck Serono Co., Ltd., Takeda Pharmaceutical Co., Ltd., Kureha Corporation. Other substantive relationships: Synergy International, Inc.*

2375 POSTER

Phase II trial of Irinotecan and S-1 (IRIS) combination chemotherapy as preoperative chemotherapy for operable advanced colorectal cancer (NCCSG03)

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Background: We found the patients diagnosed as the lymph node positively colorectal cancer (CRC) before the surgery a prognosis is worse than after the surgery by our retrospective investigation. Irinotecan plus S-1(IRIS) combination chemotherapy reported an active for metastatic colorectal cancer (mCRC) in the FIRIS study (Muro K et al. Lancet Oncol 2010;11:853–860). We planned a phase II trial to evaluate the efficacy and safety of IRIS as preoperative chemotherapy for patients with operable lymph node positively CRC.
Material and Methods: The study design was multicenter, single-arm, open-label phase II study. Eligible patients had to have operable advanced colorectal cancer confirmed diagnosis of adenocarcinoma, positive lymph nodes (⩾10 mm) and no radiologic evidence of metastatic disease on abdominal and pelvic computed tomography (CT) scans, no previous chemotherapy or radiotherapy, an age from 20 to 80 years, ECOG performance status (PS) of 0−1. S-1 80 mg/m^2 daily p.o. was given on days 1−14 and irinotecan 100 mg/m^2 was given on days 1 and 15 of a 28-day cycle. Surgery with curative intent was undertaken at least 4 weeks after completing 2 cycles of preoperative chemotherapy, followed by a further 24 weeks of postoperative chemotherapy. The primary endpoint was overall response rate (OR). The secondary endpoints included overall survival (OS), relapse free survival (RFS), completion of planned surgery rate, curative resection rate and safety.
Results: From 09/05 until 01/10, 35 patients were enrolled and investigated. Median age was 64 years (range, 40 to 79). Twenty-eight patients were male. All patients starting preoperative chemotherapy completed the 8-week course with two stopping early because of toxicity. The OR was 45.7% (16/35). Completion of planned surgery rate was 97.1% (34/35). Only one patient didn't undergo surgery, because of chemotherapy was continued by the clinician's choice. No patient had surgery delayed. Curative resection rate was 88.2% (30/34). 3-year RFS rate was 76.5% and 3-year OS rate was 93.3% in curative resected patients. On safety analysis, the incidence of grade 3 or 4 adverse reactions were as follows: anorexia, 17.1%; diarrhea, 11.4%; neutropenia, 8.6%; nausea, 5.7%; vomiting, 5.7%; leucopenia, 2.9%; anemia, 2.9%; fatigue, 2.9%. There was no treatment or surgery related death.
Conclusions: IRIS as preoperative chemotherapy for radiologically staged operable lymph node positively CRC is an active and well-tolerated.
No conflict of interest.

2376 POSTER

Chemotherapy as palliative treatment of peritoneal carcinomatosis of gastric origin

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Background: Peritoneal carcinomatosis (PC) is an important cause of morbidity and mortality among patients with gastric cancer, and can be treated by palliative systemic chemotherapy at most. The aim of the current population-based study was to evaluate trends in systemic treatment and survival of patients with peritoneal carcinomatosis of gastric origin.
Materials and Methods: All patients with an adenocarcinoma of the stomach diagnosed between 1995–2011 in the area of the Eindhoven Cancer Registry in the Netherlands were included.
Results: In total, 5,220 patients were diagnosed with gastric cancer of whom 706 patients (14%) were diagnosed with PC. Patients who were treated with chemotherapy were younger (40% of patients <60 years vs. 16% of patients 70−79 years), had less comorbidities (32% of patients without comorbidities vs. 18% of patients with >2 comorbidities), lower N-stage (35% of patients with N0 vs. 18% of patients with >N2) and were diagnosed more recently. In the period 1995–1998 11% of the patients with PC were treated with chemotherapy, compared to 42% in the most recent period (2007–2011), however, median survival did not increase (5.7 to 7.9 months, p=.310).
Conclusions: PC is a frequent condition in patients presenting with gastric cancer. Increased palliative systemic chemotherapy did not show an effect on survival on a population-based level. Therefore further efforts should be undertaken to further explore other strategies such as intra-peritoneal chemotherapy.
No conflict of interest.

2377 POSTER

Final results of the CONCERT cohort study with bevacizumab and chemotherapy in patients with mCRC and subgroup analysis of patients with resected or unresected primary tumor

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Background: CONCERT is a large, prospective, multicenter, cohort study conducted in patients (pts) with metastatic colorectal cancer (mCRC) starting a treatment with bevacizumab (Avastin®). Results at 12 and 24 months were already presented. We report final efficacy results (at a maximum of 36 months) and descriptive subgroup analyses in mCRC pts with synchronous metastases at diagnosis and resected/unresected primary tumor.
Methods: mCRC pts (n = 737 for efficacy, n = 760 for safety) treated for the first time with bevacizumab (Bv) and chemotherapy (CT), whatever the line, were eligible. They were followed-up for 36 months. Progression-free survival (PFS) was the primary endpoint. Secondary endpoints included overall survival (OS), safety (targeted and non-targeted adverse effects − AEs) and quality of life.
Results: As of February 2013, median follow-up was 17 months [0; 42], and median PFS was 10.4 months [95% CI: 9.6–11.3] in pts treated with 1st line Bv (n = 521), 8.5 months [95% CI: 7.0−9.2) in 2nd line (n = 154) and 6.3 months [95% CI: 4.5−8.9] in ⩾3rd line (n = 62). Median OS was 25.3 months [95% CI: 21.5–28.6] in 1st line Bv, 19.1 months [95% CI: 15.7–22.6] in 2nd line and 14.9 months [95% CI: 11.6–20.4] in ⩾3rd line.
In pts with synchronous metastases treated with 1st line Bv (n = 305), 121 (40%) had an unresected primary tumor and 184 (60%) were resected. Median PFS was 9.4 months [95% CI: 8.2–11.0] vs 11.5 months [95% CI: 10.4–13.8] and median OS was 17.5 months [95% CI: 14.8–20.4] vs 29.6 [95% CI: 23.9 − -], respectively.
AEs were reported in 57%, 67% and 48% of pts in 1st, 2nd and 3rd line or more. Grade 3/4 AEs were reported in 12% of pts overall. Most frequent grade 3/4 targeted AEs were venous thromboembolic events (2%) and hypertension (1%). Serious targeted AEs were venous thromboembolic events (1.7%), fistula (0.8%), bleeding (1.0%), gastro-intestinal (GI) perforation (0.8%).
In the 1st line Bv unresected/resected subgroups (n = 310), grade 3/4 bleeding was reported in 0.8%/2.2% pts (including GI bleeding in 0.8%/0%) and grade 3/4 GI perforation in 0.8%/0.6%.
Conclusion: Final efficacy and safety results of the CONCERT cohort study in mCRC pts initiating a treatment with Bv and CT in daily practice in France are consistent with the data of Bv already described. These results confirm data in the literature suggesting that resection of the primary could have a positive impact on overall survival in mCRC (stage IV) pts with synchronous metastases.
Conflict of interest: *Ownership: None. Advisory board: Roche (Andr*, Ducreux, Bennouna, Breysacher), Amgen (Ducreux), Merk (Ducreux, Phelip), Boeringher (Bennouna), Nordik (Bennouna), Sanofi (Breysacher). Board of directors: None. Corporate-sponsored research: Roche (Ducreux), Lilly (Phelip), Sanofi (Phelip). Other substantive relationships: Roche (Andr*, Ducreux, Phelip), Sanofi (Phelip), Ipsen (Phelip), Amgen (Phelip)*

2378 POSTER

FGFR3 and FGFR4 contribute to resistance in the therapy of colorectal cancer in vitro

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Colorectal Cancer is one of the leading causes of death worldwide. Although therapy has been improved, survival-rate for late-stage tumours is not significantly changed. Response to classical chemotherapy drugs as well as drugs targeting EGFR signalling fails to achieve the desired effect as resistance develops after some time. Mechanisms described in the literature suggest an important role of the FGF signalling, be it by the positive regulation of anti-apoptotic signals or triggering G1-arrest.
Using the colorectal cancer cell line SW480 and appropriate vectors, we created FGFR3-IIIb, FGFR3-IIIc and FGFR4^{arg} as well as FGFR4^{gly} overexpressing cells and performed dose-response curves for the chemotherapy drugs Oxaliplatin and Irinotecan, and, the EGFR/HER2 dual inhibitor Lapatinib as well as the FGFR3 inhibitor PD173074.
Here, we report a significantly decreased sensitivity to (1) Oxaliplatin in cells overexpressing FGFR3-IIIb (IC50=3.7μM) as well as FGFR3-IIIc (4μM) when compared to the control cell line (3μM). Significantly higher IC50 values were also observed when (2) Irinotecan was added to FGFR4^{arg} (18.4μM), R3-IIIb (41.5μM) and R3-IIIc (36.7μM) transfected cells when compared to control (11.3μM). Treating the cells with the R3 inhibitor PD173074 revealed a significantly higher sensitivity of FGFR4^{gly} overexpressing cells (14.8μM) than control cells (18.9μM) while R3-IIIb overexpressing cells were more resistant (22.8μM).
The presence of FGFR3 splice variants as well as the FGFR4 G388R polymorphism may lead to less cell damage and negatively affect response to chemotherapy drugs and EGFR targeting compounds. Based on these results, combination treatment with Oxaliplatin/Irinotecan and PD173074 as well as Lapatinib and PD173074 is currently being tested.
No conflict of interest.

2379 POSTER

Phase II study of first-line single-agent panitumumab in frail elderly patients with advanced wild type KRAS colorectal cancer with poor prognostic factors

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Background: Frail elderly patients (pts) with metastatic colorectal cancer are considered not candidates for chemotherapy due to functional status and associated comorbidities. Median survival for non-frail pts treated with 5-FU based therapy is 10.7 and 6.1 months for intermediate and high risk group according to the Köhne Prognostic Classification (KPC). Anti-EGFR monoclonal antibodies have shown activity as monotherapy and have few

toxic effects regarding organs and body systems and may be an option for selected frail pts.
Methods: This is a single-arm multicenter phase II clinical trial conducted in 14 Spanish centers. Pts ⩾70 years with metastatic wild type KRAS colorectal cancer, ECOG status <3, intermediate or high-risk group according to the KPC and one or more of the following criteria were included: a)dependence for one of the basic daily living activities (Katz Index); b)three or more comorbid conditions according to the Charlson scale plus dependence for one of the instrumental activities of daily living; c)presence of one or more of the following geriatric syndromes (age >85 years, fecal or urinary incontinence in the absence of stress, frequent falls, spontaneous bone fractures, neglect). Pts received Panitumumab 6 mg/kg every 2 weeks until progression or unacceptable toxicity. The primary endpoint was progression-free survival rate at 6 months.
Results: 33 pts were included. Median age was 81 years (range 73−89), 22 male and 11 female, ECOG 0/1/2: 6%/39%/55%. 22 pts (66.7%) underwent previous surgery for the primary tumor and only 2 (6.1%) had received previous neoadjuvant/adjuvant chemotherapy. KPC intermediate: 52%, high: 45%. Panitumumab-related grade 3 adverse events: skin toxicity 15%, hypocalcemia 3%, hypokalemia 3%, hypomagnesemia 3%. One pt required a dose-reduction and 7 pts dose delay of panitumumab due to adverse event (only in one case the adverse event was related to panitumumab). Seventeen pts (51.5%) died during the study due to disease progression (14 pts), intercurrent event not related (2 pts), or unknown reason (1 pt). There were 3 partial responses (9%) and 18 stable disease for an overall disease control of 54%. 12 patients (36%) were free of progression at 6 months. Median progression-free survival was 4.2 months and median overall survival 8.1 months.
Conclusions: Single-agent panitumumab is active and well tolerated and may be a therapeutic option for high risk wild-type KRAS tumors in selected frail elderly pts.
No conflict of interest.

2380 POSTER

Bevacizumab + capecitabine and oxaliplatin (XELOX) as first-line treatment for elderly patients with metastatic colorectal cancer (mCRC) suitable for combination chemotherapy: Efficacy and safety findings from the phase II BECOX study (GEMCAD Study Group)

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Background: Subgroup analyses of clinical studies have demonstrated that bevacizumab + XELOX is effective and tolerable in otherwise healthy elderly patients with mCRC. We undertook the BECOX study to investigate the efficacy and safety of bevacizumab + XELOX followed by bevacizumab + capecitabine in elderly patients with mCRC who were considered suitable for combination chemotherapy.
Materials and Methods: Patients aged ⩾70 years with Eastern Cooperative Oncology Group performance status (ECOG PS) of 0/1 and histologically or cytologically confirmed mCRC were included in this phase II study. Patients received capecitabine 1000 mg/m^2 po twice daily on days 1−14 plus oxaliplatin 130 mg/m^2 and bevacizumab 7.5 mg/kg on day 1 every 21 days; oxaliplatin was discontinued after 6 cycles. The primary endpoint was time to progression (TTP); secondary endpoints included overall survival (OS), progression-free survival (PFS), overall response rate (ORR) and adverse events (AEs). Clinicaltrials.gov number NCT01067053 (this trial was sponsored by the GEMCAD Group).
Results: Sixty-nine patients were recruited, one of whom received no treatment. The intent-to-treat population comprised 68 patients (65% male, median age 76 years, ECOG PS 0/1 in 47%/53% of patients). Treatment was associated with good response and survival outcomes (see table). Grade 3/4 AEs occurred in 45 patients (66%); the most common grade 3/4 AEs were hand–foot syndrome (grade 3/4 in 7%/0%), diarrhoea (16%/2%), nausea (9%/2%), mucositis (13%/3%) and asthenia (16%/0%). Grade 3/4 AEs of special interest for bevacizumab included proteinuria (2%/0%), deep-vein thrombosis (6%/0%) and pulmonary embolism (3%/2%). There were no grade 5 AEs.
Conclusion: The combination of bevacizumab and XELOX was effective and well tolerated in elderly patients in the BECOX study. The AE profile was similar to that seen in younger patients and no new safety concerns were identified. Elderly patients with mCRC should therefore be considered candidates for treatment with bevacizumab plus combination chemotherapy.
No conflict of interest.

Outcome	N = 68
Median TTP, months (95% CI)	11.0 (8.1–14.1)
Median PFS, months (95% CI)	10.6 (8.3–12.8)
Median OS, months (95% CI)	20.4 (13.2–27.6)
Response, n (%)	
Complete response	2 (3)
Partial response	29 (43)
Stable disease	23 (34)
Progressive disease	14 (21)
ORR, % (95% CI)	45.6 (33.6–58.1)

2381 POSTER

Further efficacy and safety analyses from AVEX, a randomized phase 3 trial of bevacizumab with capecitabine in elderly patients with metastatic colorectal cancer

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Background: The open-label, multinational, randomized phase 3 trial AVEX (NCT00484939) evaluated first-line bevacizumab (BEV) + capecitabine (cape) in elderly patients (pts) with metastatic colorectal cancer.
Material and Methods: AVEX (sponsored by F. Hoffmann-La Roche, Ltd.) was completed on Dec 14, 2012. 280 pts aged ⩾70 y for whom doublet chemotherapy was not appropriate were randomized to first-line BEV (7.5 mg/kg) + cape (1000 mg/m^2 bid d1−14; n = 140) or cape (n = 140) q3w. The primary endpoint was progression-free survival (PFS). A post hoc analysis assessed treatment (tx) duration, dose intensity (% of expected dose received), on-tx PFS (time from enrollment to disease progression [PD] or death from any cause in pts receiving tx at PD or stopping tx ⩽28 d before PD; pts stopping tx >28 d before PD were censored), and adverse events (AEs) in pts with or without baseline hypertension (HTN).
Results: Median age was 76 y (range, 70−87) and pt characteristics were balanced between tx arms. Comorbidities were common; HTN was the most frequent (52%). BEV + cape significantly prolonged PFS compared with cape (hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.41–0.69; P<.001). The majority of pts continued tx to PD or stopped tx ⩽28 d before PD (Table 1). On-tx PFS was significantly prolonged with BEV + cape vs cape (77 pts vs 102 pts had a PFS event on tx) (HR, 0.46; 95% CI, 0.34–0.62; P<.001; median 10.5 vs 5.0 mo), consistent with overall PFS. Mean cape dose intensity was similar in the BEV + cape (85.2% [standard deviation (SD), 20.1]) vs cape arms (89.6% [SD, 17.2]); mean BEV dose intensity was 99.1% (SD, 4.4). 96% of pts in each arm had an AE on study. Incidence of AEs in pts with or without baseline HTN are shown (Table 2).
Conclusions: Most of the pts received tx to PD or ⩽28 d before PD. On-tx PFS was consistent with the overall PFS analysis. Baseline HTN did not increase overall rates of AEs; however, pts without baseline HTN receiving BEV + cape had more epistaxis and on-tx HTN, whereas pts with baseline HTN had more proteinuria.

Table 1.

	BEV + Cape (n = 140)	Cape (n = 140)
Pts with PD, n	113	127
Cape or BEV, %		
Treated to PD	34.5	36.2
Stopped tx ⩽28 d before PD	33.6	44.1
Stopped tx >28 d before PD	31.9	19.7

Table 2. Adverse events

AE	Percentage of patients			
	BEV + Cape (n = 134)		Cape (n = 136)	
	HTN (n = 78)	No HTN (n = 56)	HTN (n = 67)	No HTN (n = 69)
Any AE	94.9	96.4	94.0	97.1
On-tx HTN	17.9	21.4	7.5	2.9
Epistaxis	11.5	25.0	4.5	2.9
Proteinuria	11.5	1.8	0	1.4
Any AE leading to tx discontinuation	28.2	21.4	16.4	11.6
Any serious AE	23.1	41.1	34.3	30.4
Any AE with outcome of death	5.1	12.5	16.4	7.2

Conflict of interest: *Corporate-sponsored research: DC has received research funding from Roche, Merck KgaA, Novartis, Celgene, Amgen, and AstraZeneca. Other substantive relationships: JO has received honoraria from Merck and Roche. SO is an employee of F. Hoffmann-La Roche, Ltd., ML is an employee of, and holds stock in F. Hoffmann-La Roche, Ltd.*

2382 POSTER

Impact of the 12-gene colon cancer recurrence score assay on clinical decision-making for adjuvant therapy in stage II colon cancer patients in Israel

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Purpose: The 12-gene Recurrence Score (Onco*type* DX® Colon Cancer) assay has been clinically validated as a predictor of recurrence risk in stage II colon cancer patients following surgery and has been reimbursed by Clalit Health Services (CHS) in Israel since January 2011. The impact of the 12-gene assay on treatment decision-making for T3N0 MMR-P stage II colon cancer patients within CHS was evaluated.
Patients and Methods: CHS prospectively collected treatment recommendations before Recurrence Score testing and actual treatment received following receipt of test results. Change in treatment intensity was defined as: increased if change from observation to any chemotherapy or from 5FU to 5FU + Oxaliplatin, no change, or decreased if any change from 5FU + Oxaliplatin or from 5FU to observation.
Results: 273 stage II colon cancer patients with T3 MMR-P tumors had assay testing from Jan 2011 to May 2012; one sample did not yield a valid score (0.3%) and 3 patients (1%) had no pre-assay recommendation resulting in 269 evaluable patients. Median age was 68 (IQR: 60−75), 85% had 12+ lymph nodes examined, 7% high grade. Median assay result was 28 (IQR: 22−34) with 58% and 10% of patients in low and high Recurrence Score groups, respectively. Pre-assay treatment recommendation differed from post-assay treatment delivered in 102 (38%) of 269 patients, with less treatment delivered for 76 (28%) and more for 26 (10%). Pre-assay, 121 (45%) patients received recommendation for chemotherapy; post-assay, 75 (28%) received chemotherapy. Changes in treatment intensity were generally consistent with the Recurrence Score results with increased treatment intensity observed more often at higher scores and decreased intensity at lower scores.
Conclusion: We observed a 38% change in pre-assay treatment recommendation to post-assay actual treatment delivered for T3 MMR-P stage II colon cancer patients, consistent with previous US studies. The use of the 12-gene colon cancer assay impacted treatment decision-making in Israel in this study where overall net reduction of recommended chemotherapy use was observed, from 45% planned for treatment to 28% actually receiving it.
Conflict of interest: *Advisory board: R. Geva served on the Genomic Health Advisory Board. Other substantive relationships: M. Lopatin is an employee of Genomic Health and owns Genomic Health stock M. Lee is an employee of Genomic Health and owns Genomic Health stock*

2383 POSTER

Survival outcomes and prognostic factors in real-life practice after treatment with cetuximab in 1st-line metastatic colorectal cancer in the EREBUS cohort

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Background: Cetuximab (CTX) has demonstrated improved survival outcomes in unresectable metastatic colorectal cancer (mCRC) patients but data from real-life use are sparse.
Methods: EREBUS, a French multicentre (n = 65) cohort, included patients with unresectable wild-type KRAS mCRC in whom CTX-based 1st-line therapy was initiated in 2009–2010. Patients were followed for 12 months. Clinical data, treatment, response, and survival were collected from medical files. Overall and progression-free survival (OS and PFS) were analysed using Kaplan–Meier method. Factors associated with death and progression were identified using Cox proportional hazards models.
Results: A total of 389 patients were included. Baseline characteristics were: median age 64 years, 67.4% male, 77.9% ECOG=0−1, 55.5% primary tumour resection, 53.0% single metastatic site. Combined chemotherapy regimens included irinotecan (56.6%) and oxaliplatin (38.2%). The 1-year OS rate was 71.3%, 95% CI [66.4–75.6]. In multivariate Cox analysis, death was less likely in responders with resection (HR = 0.26 [0.08–0.90]) or without resection (HR = 0.37 [0.21–0.63]) and in patients with primary tumour resection before initiation of 1st-line (HR = 0.48 [0.32–0.72]). Death was also associated with a poor performance status at baseline (ECOG score $\geqslant$2: HR = 4.50 [2.59–7.84]) and poor tolerance (grade 3−4 adverse events during 1st-line: HR = 1.54 [1.03–2.30]). For the whole cohort, median PFS was 9.5 months (95% CI [8.6–10.1]). In multivariate Cox analysis, compared to patients with liver-only metastases, progression was more likely in patients with metastasis sites other than liver (HR = 1.85 [1.32–2.61]) and in patients with not exclusively liver metastases (HR = 1.41 [1.03–1.94]). Progression was also associated with poor performance status at baseline (ECOG score $\geqslant$2: HR = 2.63 [1.84–3.77]).
Conclusions: Median PFS and 1-year OS rate were comparable with those obtained in clinical trials with 1st-line CTX-based chemotherapy. Treatment response was associated with better survival in all patients irrespective of resection. Disease progression was more frequent in those with non-exclusively liver metastases.
Conflict of interest: *Advisory board: Sanofi, Merck-Serono. Corporate-sponsored research: Merck-Serono*

2384 POSTER

Single centre experience of drug use for metastatic colorectal cancer before and after the English Cancer Drugs Fund implementation

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Background: The Cancer Drugs Fund (CDF) was established in April 2011 in England to 'enable patients to access the drugs their doctors think will help them'. With reference to metastatic colorectal cancer, two drugs have been available within our locality since that date (Bevacizumab in the second line setting and Cetuximab in the third line setting). Our aim was to review practice within our centre before and after the CDF implementation and assess impact on patient outcomes.
Materials and Methods: All patients accessing Bevacizumab and Cetuximab via the CDF between April 2011 and April 2012 at the Queen's Centre for Oncology were identified. A separate cohort of metastatic colorectal cancer patients treated with palliative chemotherapy between April 2008 and April 2011 were randomly selected. A retrospective review of clinical records was conducted to include: date of diagnosis of metastatic disease, lines of treatment, dates of progression and date of death. Data was analysed using SPSS 19. Median follow-up was 19 months (range 2−72 months).
Results: A total of 100 patient records were reviewed; 51 patients in the Pre-CDF time period and 49 patients in the year after the CDF became available (Post-CDF group). Prior to the CDF implementation access to monoclonal antibodies was low at 6% for Bevacizumab and 12 % for

Cetuximab. The median overall survival in the pre-CDF group was 16 months (95% CI 12.1–19.9 months) and in the post CDF group was 25 months (95% CI 20.3–29.7 months). Log rank test showed this difference to be statistically significant (p = 0.008).

Table: Comparison of patients undergoing treatment for metastatic colorectal cancer before and after CDF implementation

	Pre-CDF	Post-CDF
N	51	49
Mean age (range), years	66 (31−85)	65 (26−83)
M:F	1.7:1	1.6:1
Median overall survival (95% CI), months	16 (12.1–19.9)	25 (20.3–29.7)

Conclusion: This data suggests there has been an improvement in overall survival in patient's undergoing treatment for Metastatic Colorectal cancer following the implementation of the Cancer drugs fund. The marked differences in overall survival may relate to increased access to newer monoclonal antibodies. However, this is a small data set and groups have not been matched for other variables including differences in disease volume or performance status.
No conflict of interest.

2385 POSTER

A first combination phase I study of TAS-102 and irinotecan (Iri) in Japanese patients (pts) with metastatic colorectal cancer (mCRC) refractory to fluoropyrimidine (FU) and oxaliplatin (Ox)

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Background: TAS-102 is a novel oral nucleoside antitumor agent that consists of trifluridine and tipiracil hydrochloride. In a randomized phase II study for mCRC, TAS-102 monotherapy significantly improved overall survival (OS) compared with placebo (Takayuki Yoshino, et al. Lancet Oncol. 2012;13:993–1001.), and currently, a phase III study (RECOURSE) is being conducted in the world. In addition, preclinical studies demonstrated TAS-102 additively enhanced the antitumor effect of Iri.
Material and Methods: We conducted a first combination phase I study of TAS-102 and Iri in Japanese pts with mCRC refractory to FU and Ox. The primary objectives were to assess the safety and maximum tolerated dose (MTD), using a modified 3 + 3 design. Secondary objectives included the evaluation of efficacy and pharmacokinetics (PK). TAS-102 was administered at the starting dosage of 25 mg/m^2 BID in a 28-day cycle (2-week cycle of 5 days of treatment followed by a 2-day rest period, and then a 14-day rest period), with a fixed-dose of Iri (150 mg/m^2) q2wks. Dose-limiting toxicity (DLT) was evaluated during the 1st cycle. This study treatment was continued until disease progression or intolerability was observed.
Results: A total of 10 pts were enrolled in the study, and 9 pts were evaluable for DLTs (dose levels: [DL1] 25 mg/m^2 BID, n = 6; [DL2] 30 mg/m^2 BID, n = 3). One pt was not evaluable for DLT because of pt withdrawal. The median age 61 years (range, 31−72 years); 6 male; ECOG PS 0/1 (8/1). The median number of cycles was 3 (range, 1−29). The treatment of 8 pts was discontinued because of PD. One pt in DL1 and 2 pts in DL2 developed DLTs, including Gr 4 neutropenia and Gr 3 febrile neutropenia (FN). Thus, MTD was confirmed to be 30 mg/m^2 BID of TAS-102. The most common Gr 3/4 adverse events were neutropenia (10), leukopenia (7) and FN (3). Administration of Iri on day 15 was omitted because of hematological toxicities (89%), and the relative dose intensity (RDI) during treatment period was 82% for TAS-102 and 62% for Iri. PK drug–drug interactions were not observed between TAS-102 and Iri. There were 2 PR (22%) and 3 SD (33%). Median progression-free survival and OS were 2.3 and 15.6 months, respectively.
Conclusions: The combination therapy of TAS-102 and Iri was manageable up to 30 mg/m^2 BID in pts with mCRC, resulting in the promising antitumor activities. However, because the RDI of Iri was low, further studies with schedule modifications are warranted.
Conflict of interest: *Advisory board: Atsushi Ohtsu: Steering Committee (TAIHO Pharmaceutical Co., Ltd.). Corporate-sponsored research: Kentaro Yamazaki: This phase I clinical study is sponsored by TAIHO Pharmaceutical Co., Ltd. Toshihiko Doi: This phase I clinical study is sponsored by TAIHO Pharmaceutical Co., Ltd. Narikazu Boku: This phase I clinical study is sponsored by TAIHO Pharmaceutical Co., Ltd. Wasaburo Koizumi: This phase I clinical study is sponsored by TAIHO Pharmaceutical Co., Ltd. Ken Shimada: This phase I clinical study is sponsored by TAIHO Pharmaceutical Co., Ltd. Yasutaka Takinishi: This phase I clinical study is sponsored by TAIHO Pharmaceutical Co., Ltd. Other substantive relationships: Nozomu Fuse: Honoraria (TAIHO Pharmaceutical Co., Ltd.), Research funding (TAIHO Pharmaceutical Co., Ltd., Daiichi-Sankyo Co., Ltd., YakultHonsha Co., Ltd.). Narikazu Boku: Honoraria (TAIHO Pharmaceutical Co., Ltd.). Atsushi Ohtsu: Honoraria (TAIHO Pharmaceutical Co., Ltd.).*

2386 POSTER

Updated results of a phase II study of neoadjuvant chemotherapy with mFOLFOX6 + bevacizumab for the synchronous liver metastases from colorectal cancer

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Background: The synchronous liver metastases (SLM) from colorectal cancer (CRC) have a poor prognosis, though treatment results can be improved with the advent of new agents. Therefore, our group, the Miyagi Hepato-biliary pancreatic clinical oncology group (Miyagi-HBPCOG), conducted a phase II study of neoadjuvant chemotherapy for SLM to determine the appropriate initial treatment. Here, we assessed the effectiveness of bevacizumab (BV) combined with mFOLFOX6 and report updated results including survival.
Patients and Methods: The main inclusion criteria of SLM were within 10 nodules and measurable disease. The primary endpoint was the response rate (RR). Between June 2008 and November 2010, 47 patients (pts) were enrolled from 17 centers. These pts were enrolled after R0-resection of the primary CRC and received 8 courses of mFOLFOX6 with BV (the first and last courses were mFOLFOX6 alone). After this 'neoadjuvant' chemotherapy pts underwent resection of liver metastases within 4−8 weeks.
Results: The mean age was 60.8 years. The median number of metastases was 2 nodules, and the maximum diameter of tumors was 12.9 cm. Three pts were excluded from evaluation of RR because they did not receive any scheduled chemotherapy. The overall RR was 70.5% (2 complete and 29 partial responses). Eleven pts (25%) showed stable disease and 2 pt (4.5%) had progressive disease. The liver resection rate was 93.2% (41 pts) and the R0-resection rate was 88.6% (39pts). The histological tumor response (HR) was assessed on the basis of the tumor regression grade (TRG). Twenty-two pts (55.0%) achieved TRG 1−2 (major HR), 13 pts (32.5%) had TRG 3 (partial HR), and 5 pts (12.5%) had TRG 4−5 (no HR). With a median follow-up of 35 months, the 1- and 2-year progression-free survival (PFS) rates were 45.1% and 27.3%, respectively, and the 1- and 2-year overall survival (OS) rates were 95.4% and 88.4%, respectively. Grade 3 and 4 adverse events (AEs) occurred in 21 pts with the most common being neutropenia (28.9%) and leucopenia (11.1%). There were 3 Grade 4 AEs: 1 case of renal failure and 2 cases of neutropenia.
Conclusions: Neoadjuvant chemotherapy with BV combined with mFOLFOX6 for liver metastases is effective and well tolerated. The benefit of this therapy as the initial treatment of SLM might need to be evaluated further by comparison with adjuvant therapy.
This trial is on University hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR); UMIN000001568.
No conflict of interest.

2387 POSTER

Updated survival results and analysis according to the prognostic factor in the BASIC trial of bevacizumab and S-1 in elderly metastatic colorectal cancer patients

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Background: We previously reported short term results of a phase II to evaluate the efficacy and safety of combined therapy with S-1 and bevacizumab in elderly patients who had advanced or recurrent colorectal cancer. The median progression-free survival (PFS) was 9.9 months (95% CI, 7.6–11.0) with median follow-up time 18.6 months (Takahari et al, ESMO 2011).
Methods: Study subjects comprised diagnosis of elderly patients 65 years or older who had a histologically confirmed advanced or recurrent colorectal cancer and were scheduled to receive first-line chemotherapy. As for the treatment regimen, bevacizumab (5 mg/kg) was given intravenously on days 1, 15, and 29, and S-1 (80 to 120 mg/day according to body-surface area in two divided doses daily, after meals) was administered orally on days 1 to 28 of a 42-day cycle, which was repeated until progression or unacceptable toxicity. We updated overall survival (OS) results with 34.6 months of median follow-up and analyzed them to classify according to a general prediction model reported by Kohne et al.
Results: From October 2007 through March 2010, a total of 56 patients were enrolled.
Their median age was 75 years. The median OS was 25.0 months (95% CI, 19.4 to 31.6). In high-risk (n = 14), intermediate-risk (n = 19), and low-risk (n = 23) patients, the median OS was 14.4 months (95% CI: 7.5–25.0), 28.5 months (95% CI: 18.5–32.3), and 35.3 months (95% CI: 22.3–Not Reached) (P = 0.0011), respectively. The hazard ratio for OS between the risk groups was 2.58 (95% CI: 1.17–5.69, P = 0.019) between high risk and intermediate risk, 4.21 (95% CI: 1.83–9.91, P<0.001) between high risk and low risk, and 1.63 (95% CI: 0.72–3.76, P = 0.237) between intermediate risk and low risk.
Conclusions: S-1 plus bevacizumab therapy is therapeutically effective and safe for elderly patients with metastatic colorectal cancer. The analysis with Kohne model suggested that it is useful to predict OS in elderly colorectal cancer patients treated with S-1 and bevacizumab.
No conflict of interest.

2388 POSTER

NK-EGFR01: Feasibility of allogenic natural killer cell (NK) adoptive transfer by intra-arterial injection in combination to cetuximab − a phase I clinical trial in EGFR+ gastrointestinal adenocarcinoma

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Background: NK cells are components of innate immunity recognizing and killing tumor or virus-infected cells. Major advances in NK cell alloreactivity biology resulted in the successful introduction of NK-based cellular therapy in the treatment of myeloid leukemia (Velardi A, *et al.* Science 2001 and Miller J, *et al.* Blood 2005). Our pre-clinical experiments confirmed the ability of activated alloreactive NK cells to recognize the chemoresistant colorectal cancer cell line HT29. The use of cetuximab improved NK cell cytotoxicity in this setting and prompted us to combine NK cell alloreactivity and Antibody-Dependent Cell-mediated Cytotoxicity (ADCC).
Materials and Method: Patients with liver metastases of colorectal or pancreatic cancers were included. Main inclusion criteria were: a positive expression of EGFR on tumor cells by immunohistochemistry, the absence of a specific Killer cell Immunoglobulin-like Receptors (KIR) ligand, a performance status of 0 or 1, an age below 75 years, the absence of an important extra-hepatic disease, and absence of standard therapeutic options. Patients were treated with a lymphodepleting chemotherapy (d-6 to J-2: fludarabine 25 mg/m^2 and d-6 cyclophosphamide 60 mg/kg) before adoptive transfer of NK by the liver artery (day 0). Cetuximab was administered at d-1 and every week for 7 weeks. Three dose levels were performed (3×10^6 NK/kg, 6×10^6 NK/kg, 12×10^6 NK/kg). Injections of interleukin 2 were performed after the adoptive transfer, every 3 days for 6 injections.
Results: Three patients were included at each dose level. The production of allogenic NK was possible for all patients. NK cells were cultured overnight in Xvivo 15 medium complemented with 10% of serum and 1000UI of interleukin 2/mL. Lymphodepleting chemotherapy was feasible in all selected patients. Main non-hematological toxicities included grade 3 chills and fever after IL-2 injections in 6 patients, grade 3 asthenia in 5 patients and grade 2 alopecia in 6 patients. Grade 4 neutropenia and lymphopenia were observed in all patients. The mean time of lymphopenia <100/mm^3 was 14 days. No dose limiting toxicity was reported. We could observe one partial objective response in CT-scan and PET-scan. The time of disease control was 4 months in this patient. Two additional disease stabilizations were achieved.
Conclusion: Allogenic NK cell adoptive transfer by injection in the liver artery is feasible.
No conflict of interest.

2389 POSTER

Analysis of cumulative neurotoxicity improvement by withdrawal of L-OHP (Subset analysis of T-CORE0901 Japan-Modified CONcePT trial)

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Background: The CONcePT trial revealed that intentional withdrawal of L-OHP administration of Bevacizumab (BV) + FOLFOX7 is effective and safe in view of deterioration of cumulative neurotoxicity against mCRC. However it is unknown of appropriable period of withdrawal of L-OHP. We carried out subset analysis of Japan-Modified CONcePT trial that withdrawal of L-OHP improved cumulative neurotoxicity before re-administration L-OHP in Japanese pts.
Material and Method: Japan-Modified CONcePT trial is a phase II trial to evaluate the efficacy and safety of intermittent L-OHP administration of first-line BV + mFOLFOX6 or CapeOX therapies. Six cycles of bi-weekly BV + mFOLFOX6 regimen is followed by 6 cycles of bi-weekly BV + sLV5FU2 or 4 cycles of tri-weekly BV + CapeOX regimen is followed by 4 cycles of tri-weekly BV + capecitabine regimen. Primary endpoint is to evaluate median progression free survival (PFS). Safety is one of secondary endpoints and cumulative neurotoxicity is evaluated by DEB-NTC.
Results: Sixty eight pts were enrolled and median PFS was 347 days (95% CI 286–462 days) and TTF was 229 days (95% CI 187–263 days). Thirty seven pts were re-administrated L-OHP after 12 weeks of withdrawal. The cumulative neurotoxicity was observed in 26 pts just before withdrawal L-OHP and 11 pts feels improvement of cumulative neurotoxicity. However 8 pts feels deterioration of cumulative neurotoxicity.
Conclusions: The intentional withdrawals of L-OHP administration of BV + mFOLFOX6 or CapeOX therapies were effective for Japanese mCRC pts. However 12 weeks of withdrawal of L-OHP is not enough for improvement of cumulative neurotoxicity.
No conflict of interest.

2390 POSTER

A randomized Phase II study of tegafur/uracil (UFT), oral Leucovorin and irinotecan, combination therapy (TEGAFIRI)+bevacizumab versus FOLFIRI+bevacizumab for the first-line treatment of patients with metastatic colorectal cancer

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Background: CPT-11 base chemotherapy plus bevacizumab (Bmab) is one of the first line standard therapies for metastatic colorectal cancer (mCRC). TEGAFIRI (UFT/LV+CPT-11) is new CPT-11 base chemotherapy. There has been no clinical data regarding TEGAFIRI+Bmab to date. We previously reported the results of a phase I study using TEGAFIRI, and the recommendation dose of CPT-11 (Cancer Chemother Pharmacol 2009). This study was designed to evaluate the efficacy and safety of TEGAFIRI+Bmab in mCRC patients.
Material and Methods: The study design was multicenter randomized phase II.The major inclusion criteria were previously untreated mCRC (age 20−75, PS 0−1). Patients were randomized to receive either TEGAFIRI+Bmab[UFT(300 mg/m^2/day) & LV(75 mg/day) orally for three weeks and CPT-11(150 mg/m^2) and Bmab(5 mg/kg)on day 1 and 15, every 4 weeks] (Group A) or FOLFIRI+Bmab (Group B). The primary endpoint was progression free survival (PFS).
Results: From 2007 to 2010, 72 patients (36 Group A and 36 group B) were randomized. Median PFS for Group A and Group B was 15.7 months and 9.6 months. The most common Grade3/4 adverse events were stomatitis(5.2% GroupA, 9.5% Group B), anorexia (0% and 4.8%), nausea(0% and 9.5%), diarrhea (5.3% and 4.8%), fatigue (0% and 4.8%). Post treatments with bevacizumab were performed in 10 patients (4 Group A and 6 Group B), and median overall survival was 25.1 months.
Conclusions: It was demonstrated that the first-line treatment of TEGAFIRI+Bev was effective and tolerable, and could be an additional option for first-line treatment.
No conflict of interest.

2391 POSTER

A phase II study of cetuximab in combination with irinotecan plus S-1 as first-line treatment in patients with KRAS wild-type metastatic colorectal cancer: CIRIS study

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Background: The CRYSTAL study demonstrated that the addition of cetuximab (Cmab) to FOLFIRI as first-line treatment improved the clinical benefit in patients (pts) with KRAS wild-type (wt) metastatic colorectal cancer (mCRC). Because the FIRIS study demonstrated the non-inferiority of irinotecan plus S-1 (IRIS) to FOLFIRI for mCRC, we conducted a phase II study to evaluate the efficacy and safety of Cmab in combination with IRIS as first-line treatment in pts with KRAS wt mCRC (clinical trial information: UMIN000004580).
Methods: Eligibility criteria included histologically confirmed colorectal cancer; KRAS wt; no previous chemotherapy; ECOG performance status (PS) 0−1 and adequate organ function. S-1 was administered at 80 mg/m^2 on days 1−14 and irinotecan at 100 mg/m^2 on days 1 and 15 every 28 days. Cmab was administered at a loading dose of 400 mg/m^2, followed by weekly infusions of 250 mg/m^2. The primary endpoint was response rate (RR), and the secondary endpoints were progression-free survival, overall survival, rate of tumor shrinkage and safety. The sample size calculation was carried out to reject a 37% response rate in favor of a target response rate of 60%, with a significance level of 0.05 and a statistical power of 80%.
Results: Between November 2010 and January 2013, 31 pts were enrolled. One patient was ineligible with inadequate renal function. The characteristics of the pts were as follows; median age: 65.5 (range: 38−79), male/female: 20/10, ECOG PS 0/1: 24/6, colon/rectum: 22/8, unresectable/recurrent: 21/9. The RR was 70% [95% confidence interval (CI): 52.1–83.3%] with complete response: 2, partial response: 19, stable disease: 9 and progressive disease: 0. With a median follow-up time of 13.1 months, the median PFS was 13.1 months (95% CI: 7.7–18.5 months). The most common grade 3−4 adverse events were leukopenia (22.6%), neutropenia (41.9%), febrile neutropenia (9.7%), anemia (9.7%), hypoalbuminemia (16.1%), anorexia (16.1%), diarrhea (9.7%), mucositis (9.7%), acne-like rush (9.7%), dry skin (19.4%) and paronychia (9.7%). There were no treatment-related deaths.
Conclusions: Cmab in combination with IRIS as first-line treatment was considered one of the promising options and showed manageable toxicities in pts with KRAS wt mCRC.
No conflict of interest.

2392 POSTER

Long term outcomes after neoadjuvant hyperfractionated short-course chemoradiotherapy for rectal cancer

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Background: Short course radiotherapy has advantages of less acute toxicity and less cost than long-term radiotherapy. One of the disadvantages is downsizing of the primary tumor cannot occur, because preoperative short-course radiation standard timing of surgery is day 7−9. But delayed surgery has been shown downsizing of the tumor recently. The aim of this study is to evaluate long term outcomes after neoadjuvant hyperfractionated short-course radiotherapy (NAHSRT) for rectal cancer.
Material and Methods: Between March 2008 and May 2012, 140 patients with rectal cancer were treated with NAHSRT. NAHSRT was performed with a dose of 2.5 Gy twice daily with an interval of 6 hours between fractions, up to a total dose of 25 Gy with chemotherapy (S-1 80 mg/m^2 day 1−10). Surgery was performed within 3−4 weeks following the end of the NAHSRT.
Results: 140 patients included 98 men and 42 women. The median age was 65.2±11.0. The median follow-up term was 45.2 months. 54 patients has tumor shrinkage (36.0 percent). No patients showed grade 4 toxicities. Sphincter preserving surgery was performed in 94.2 percent. The overall cumulative five-year survival rate was 81.5 percent. The local recurrence free survival rate was 90.3 percent. The disease free survival rate was 68.5 percent.
Conclusions: We presented long term outcomes after neoadjuvant hyperfractionated short-course chemoradiotherapy for rectal cancer. NAHSRT was considered feasible option and produced excellent long-term outcomes.
No conflict of interest.

2393 POSTER

Biweekly cetuximab in combination with FOLFOX-4 in the first-line treatment of KRAS wild-type metastatic colorectal cancer: Final results of a phase II open-label clinical trial

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Background: The addition of weekly cetuximab to FOLFOX-4 as first-line treatment of metastatic colorectal cancer (mCRC) improves the overall response rate (ORR) and reduces the risk of disease progression in patients with KRAS wild-type tumours. Seeking to increase convenience for patients and health care providers, the objective of this phase II study was to evaluate the efficacy and safety of biweekly cetuximab in combination with FOLFOX-4.
Methods: Previously untreated patients with KRAS wild-type tumours received biweekly cetuximab (500 mg/m^2 on day 1) plus FOLFOX-4 (oxaliplatin 85 mg/m^2 on day 1, leucovorin 200 mg/m^2 on days 1 and 2, and fluorouracil as a 400 mg/m^2 bolus followed by a 600 mg/m^2 infusion during 22 hours on days 1 and 2). Treatment was continued until disease progression, onset of unacceptable drug toxicities or patient/physician request to discontinue. The primary endpoint of the study was ORR. Secondary endpoints included progression-free survival (PFS) and overall survival (OS).
Results: A total of 99 patients were included in the intention-to-treat population, mean age was 63.9 (±9.2) years. The ORR was 60.6% (95% CI, 50.3% to 70.3%). Median PFS was 10.1 months. With a short median follow-up of 17.8 months, the OS was 20.8 months. Metastases from colorectal cancer were surgically resected in 26 (26.3%) patients, with complete surgical resection achieved in 18 (69.2%) patients. Median relapse free survival in patients undergoing resection of metastases was 12.6 months. The most common grade 3−4 toxicities were neutropenia (32.3%), acne-like rash (15.2%) and diarrhoea (11.1%).
Conclusions: The efficacy of biweekly combination of cetuximab with FOLFOX in patients with KRAS wild-type tumours is similar to what has been reported for the weekly administration of cetuximab. Reported toxicity

was also consistent with the known toxicity profile of weekly cetuximab. Our results support the administration of cetuximab in a dosing regimen more convenient for patients and health care providers.
Conflict of interest: *Other substantive relationships: This study was supported by Merck, S.L.*

2394 POSTER

Japanese cross-sectional cohort study of 1st line chemotherapy (CT) for metastatic colorectal cancer (mCRC) (EMERaLD study)

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Background: An observational cohort study plays a crucial role to establish a database to assess clinical status of patients (pts). There is no database which shows the current status including treatments of mCRC pts in Japan.
Methods: We planned and conducted a large cross-sectional cohort study which investigates 1st line CT in mCRC to establish a database to improve future clinical practice in Japan.
Data from the following pts are eligible to the study: treated with 1st line CT including oxaliplatin and bevacizumab (BV) for mCRC; started treatment in or after January 2010. The primary objectives are to evaluate overall survival (OS), liver resection rate, R0 liver resection rate; the secondary objectives are to evaluate response rate (RR), progression-free survival (PFS). We performed a preplanned interim analysis of 6-month efficacy and safety data after the 1,000th registration.
Results: A total of 1,353 pts were recruited from 132 centers in Japan between October 2010 and September 2011, and we analyzed data on 1,005 pts of them. The background of 1,005 pts were the following; male/female, 614/391; median age of 65 (range, 27−89); ECOG PS 0/1/2/3, 854/139/10/2; site of primary tumor colon/rectum/others, 549/451/5; and site of metastatic disease liver/lung/others, 627/308/421; FOLFOX/ CapeOx/ others with BV, 437/540/28, KRAS-status wild/mutant/ unknown, 225/168/612. Six-month efficacy data were the following; liver resection rate 10.5%, R0 liver resection rate 8.9%, RR 51.6%, PFS 83.9%. Six-month grade 3/4 (CTC-AEv3.0) adverse events related to BV were hypertension 2.4%, proteinuria 0.2%, thromboembolism 1.1%, bleeding 0.6%, and gastrointestinal perforation 1.5%. We also performed a subgroup analysis by ages, primary tumor sites, regimens, and KRAS-status.
Conclusions: We performed a preplanned interim analysis on 1,005 pts and this could be a large database to investigate 1st line CT in clinical practice of mCRC pts in Japan. We will further investigate and analyze the 2-year data including survival on all 1,353 pts.
This study is sponsored by the Public Health Research Center Foundation CSPOR in Japan.
No conflict of interest.

2395 POSTER

Chemotherapy in elderly patients with metastatic colorectal cancer: relation to co-morbidities and functional abilities

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Background: We aimed to study the management of elderly patients with metastatic colorectal cancer (mCRC) in relation to their co-morbidities and functional abilities.
Material and Methods: An observational study of a cohort of mCRC patients (65 years or older) treated by our oncology team between April 2010 until December 2012. There were 4 groups of patients according to the first line chemotherapy regimens they received; XELOX (oxaliplatin and capecitabine), capecitabine, FOLFIRI (Irinotecan and modified Degramont) and raltitrexed. Cumulative Illness Rating Scale for Geriatric (CIRS-G) and Lawton Instrumental Activity of Daily Living (IADL) (table 1) as well as response to chemotherapy were studied.
Results: There were 43 patients in this study. Thirteen patients were treated with XELOX regimen. They had CIRS-G score of 0−3, IADL score of 8 and performance status (PS) of 0−1. Three patients had dose reduction for co-morbidities and 7 for chemotherapy toxicities. Partial response (PR) of 61.5% and stable disease (SD) of 30.8% were achieved. The median progression free survival (PFS) and overall survival (OS) durations were 10 and 16 months respectively.
Ten patients had oral capecitabine. They had CIRS-G score of 0−3, IADL score of 4−8 and PS 2. Dose reduction was required in 7 patients for either co-morbidities (4 patients) or toxicities (3). Two had PR (20%) and 6 SD (60%). The median PFS and OS were 11 and 12 months respectively.
Five patients were treated with FOLFIRI (Irinotecan and modified Degramont) regimen. They had CIRS-G 1−3, PS 1 and Lawton IADL of 5−8. Dose reduction was required in 2 patients due to toxicities. Two patients had PR (40%) and 1 (20%) SD. Median PFS and OS were 9 months and 14 months respectively.
Fifteen patients with ischaemic heart diseases were treated with Raltitrexed. They had CIRS-G score of 2−3, IADL score of 4−8 and PS $\leqslant$2. Three patients had dose reduction due to mild renal impairment (1 patient) or significant side effects (2 patients). PR and SD rates were 35.7% each. Median PFS and OS were 7 and 10 months respectively.

Table 1.

Instrument	Score
Cumulative Illness Rating Scale for Geriatric (Miller MD, et al 1992)	
No problem	0
Current mild problem or past significant problem	1
Moderate disability or morbidity requiring first line therapy	2
Severe/constant significant disability/un-controllable chronic problems	3
Extremely severe/end organ failure	4
A total score is then calculated with particular focus on level 3 or 4 co-morbidities.	
Lawton Instrumental Activity of Daily Living (Lawton et al 1969)	
Ability to use telephone	0/1
Food preparation	0/1
House keeping	0/1
Laundry	0/1
Responsibility for own medications	0/1
Mode of transportation	0/1
Shopping	0/1
Ability to handle finances	0/1
A score of either 0 or 1 is assigned for each of the 8 patient's functional abilities. A summary score ranges from 0 (dependent) to 8 (independent).	

Conclusions: Elderly patients with mCRC can cope with chemotherapy but with occosional need for dose reduction. CIRS-G score, IADL and PS are quite helpful tools in assessing them prior to chemotherapy.
No conflict of interest.

2396 POSTER

Comparison of cetuximab with panitumumab in salvage-line monotherapy against KRAS wild type patients with metastatic colorectal cancer: Analysis of HGCSG0901 and HGCSG1002

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Background: Monoclonal antibodies targeting the epidermal growth factor receptor (EGFR) such as cetuximab and panitumumab have antitumor activity and acceptable safety profiles in patients with metastatic colorectal cancer (mCRC). Although monotherapy with cetuximab or panitumumab has demonstrated the effectiveness in salvage-line, there are no trials comparing these antibodies directly.
Methods: Data of 31 patients (pts) with mCRC treated by cetuximab (HGCSG 0901 study) and 51 pts treated by panitumumab (HGCSG 1002 study) registered from 27 institutions in Japan were retrospectively analyzed. All patients with *KRAS* wild type were refractory to or intolerant for 5-FU/ irinotecan/ oxaliplatin and also were never administered anti-EGFR-antibodies. Survival analyses were performed with Kaplan–Meier method and log-rank test.
Results: Patient characteristics were as below (cetuximab vs. panitumumab); male/female 20/11 vs. 27/24, median age (range) 65(44−76) vs. 64.5(44−81), PS 0−1/2−3 21/10 vs. 46/5, number of metastatic sites 1−2/3−22/9 vs. 25/16, prior bevacizumab administration 81% vs. 86%. Skin toxicity was common adverse events and was generally similar in two groups. The median overall survival was 8.4 months in the cetuximab group, as compared with 8.1 months in the panitumumab ($p = 0.32$). The median progression-free survival was 3.8 months in the cetuximab, as compared with 3.1 months in the panitumumab ($p = 0.60$); the corresponding response rate was 19.4 percent and 13.7 percent ($p = 0.54$).

Conclusions: In this retrospective comparison of two studies, there were no significant difference in efficacy between cetuximab and panitumumab in the salvage-line treatment of patients with mCRC. As there are no known predictive factors for anti-EGFR-antibodies in mCRC, anti-EGFR-antibodies should be chosen based on preferred treatment interval.
Conflict of interest: *Advisory board: Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Yakult Honsha Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Merck Serono Co., Ltd., Bristol-Myers Squibb Co., Pfizer Japan Inc., Novartis Pharma K.K., Sawai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd. Board of directors: Taiho Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Novartis Pharma K.K., Yakult Honsha Co., Ltd., Daiichi Sankyo Co., Ltd., Merck Serono Co., Ltd., Takeda Pharmaceutical Co., Ltd., Kureha Corporation. Corporate-sponsored research: Synergy International, Inc.*

2397 POSTER

Randomized phase II study of oxaliplatin reintroduction and biweekly XELOX in previously treated patients with metastatic colorectal cancer (mCRC): ORION study

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Background: Reintroduction of oxaliplatin is shown to be of benefit in patients with mCRC who have failed standard treatment. The aim of this study is to assess the efficacy and safety of oxaliplatin reintroduction as two different regimens of XELOX.
Methods: Patients with mCRC who have previously received both oxaliplatin and irinotecan therapy were randomly allocated to Arm A (tri-weekly XELOX; oxaliplatin 130 mg/m^2 on day 1 followed by capecitabine 1,000 mg/m^2 twice daily from days 1 to 14, q3w) or Arm B (bi-weekly XELOX; oxaliplatin 85 mg/m^2 on day 1 followed by capecitabine 1,000 mg/m^2 twice daily from days 1 to 7, q2w). Primary endpoint was time to treatment failure (TTF). The secondary endpoints include relative dose intensity (RDI), overall response rate (ORR), progression-free survival (PFS), overall survival (OS) and safety.
Results: Between December 2010 to April 2011, a total of 46 patients were randomized. The median age was 65 (range: 40−80). Major grade 3/4 toxicities were fatigue 17.7%/16.2%, HFS 3.2%/2.7%, allergic reaction 4.8%/5.4%, neuropathy 3.2%/5.4% in arm A and B respectively. TTF was 105 days (arm A: 122 days, arm B: 86 days) Disease control rate(DCR) was 60%(12 SD) in arm A and 65.2%(1 PR, 14SD) in arm B.
Conclusions: Reintroduction of oxaliplatin can be administered safely and effectively. We found no obvious difference between two different regimens of XELOX.
No conflict of interest.

2398 POSTER

Bi-weekly XELOX (capecitabine/oxaliplatin) plus bevacizumab as first-line treatment of metastatic colorectal cancer (mCRC): PHOENiX trial

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Background: The aim of this phase II study was to assess the efficacy and toxicity of an intermittent weekly capecitabine regimen in combination with oxaliplatin plus bevacizumab.
Methods: Fifty-one Japanese patients (pts) with measurable metastatic colorectal cancer (mCRC) who were conducted for the first line chemo-therapy were enrolled on to this disease-oriented multicenter Phase II trial. Pts with mCRC were required to have ECOG of 0 to 1, to be age of >20 years, and to have adequate organ function. Primary endpoint was progression-free survival (PFS). Secondary endpoints included response rate (ORR), overall survival (OS), time to progression (TTP), relative dose intensity (RDI) and safety. Capecitabine dose was 2000 mg/m^2/day on days 1−7 (n = 47) and was increased to 2500 mg/m^2/day (n = 4) in combination with oxaliplatin (85 mg/m^2) and bevacizumab (5 mg/kg), repeated every 2 weeks.
Results: 51 pts have been enrolled from 14 institutions by 12/2011 from 06/2012 and started a median of 11 (range 1−21) cycles. The median age was 66 (range: 38−85), colon 29(56.9%) and rectum 22(43.1%) in this study. Pertinent grade 3/4 toxicities seen were leukopenia (7.8%), neutropenia (7.8%), allergy (5.9%), hypertention (13.7%), hand–foot syndrome (2%), and peripheral neuro pathy (7.8%). Response rate (RR) was 51% (1 CR and 25 PRs). Median PFS was 13.1 months (95% CI, 7.5–14.4) and Median TTF was 6.5 months (95% CI, 4.9−7.3). Median OS has not yet been reached. Mean relative dose intensities (RDI) in this trial were 100% for oxaliplatin, bevacizumab and capecitabine.
Conclusion: The first-line treatment of mCRC using a bi-weekly combination of XELOX plus bevacizumab can also be administered safely and effectively in Japan. It is suggested that this regimen is one of the appropriate option for chemotherapy.
No conflict of interest.

2399 POSTER

Candidate genes associated with primary resistance to panitumumab (Pmab) in a phase II biomarker study of patients with KRAS wild-type (wt) metastatic colorectal cancer (mCRC)

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Background: Pmab monotherapy targeting the Epidermal Growth Factor Receptor (EGFR) results in improved Progression Free Survival in previously treated *KRAS* wt mCRC, but not all patients benefit from therapy. In this phase II study, we sought to identify genes differentially expressed with early resistance to Pmab therapy.
Material and Methods: Patients with measurable *KRAS* wt mCRC were treated until progression with q2weekly Pmab 6 mg/kg IV and response was assessed q2monthly by RECIST criteria. Pathologist-guided tissue macrodissection and RNA isolation was performed on formalin-fixed paraffin-embedded archival tissue of primary tumor and paired metastatic lesions, when available. Gene expression profiles of 100 knowledge-based selected genes, associated with *BRAF* mutation and cetuximab response in mCRC, were done using the Nanostring nCounter® system. Unsupervised hierarchical clustering of these 100 genes was used to test whether *KRAS* wt tumors formed biased clusters from 220 CRC tumors from The Cancer Genome Atlas (TCGA). Two-class Significance Analysis of Microarrays (SAM) compared expression profiles of tumors with a best response of progressive disease (PD) to those with stable disease (SD) or partial response (PR) to Pmab. Genes with a false discovery rate (FDR) $\leqslant$ 20% were analyzed with Database for Annotation, Visualization and Integrated Discovery (DAVID) to identify enrichment for specific pathways and chromosomes.
Results: Best response to Pmab therapy among 37 enrolled patients was PD in 12 (median # of cycles = 4), SD in 17 (median # of cycles = 12), and PR in 8 (median # of cycles = 15.5). Clustering analysis showed 9/12 paired primary and metastatic tumors were tightly grouped together, indicating the 100-gene expression profiles were conserved within pairs. There was no statistically significant clustering, indicative of an expression bias, of the *KRAS* wt tumors within the TCGA dataset. Using SAM at a FDR $\leqslant$ 11%, patients with PD had significant upregulation of *ERBB2*, but not *EGFR*, and *RAD51*, identified by DAVID analysis to be significantly involved (p = 0.0012) in the ErbB signaling pathway and DNA damage repair, respectively. Patients with PD also displayed marked upregulation of *MLPH*, *KLK6*, *MYRF*, and downregulation of *KLK10* and *TM4SF4*.
Conclusions: In this phase II biomarker study, early progression as best response to Pmab was documented in 32% of cases and was associated with distinct expression of 7 genes, including *ERBB2* and *RAD51*, as possible markers of inherent resistance to EGFR therapy.
No conflict of interest.

2400 POSTER

Novel molecular assay system for accurate lymph node staging in colorectal cancer patients: Results of prospective multicenter study in Japan (Japanese OSNA® Colorectal Cancer Study Group)

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Background: Occult metastases detected in node-negative patients point to lower survival rates. To improve patients' prognosis, treatment is required based on more accurate lymph node (LN) staging than provided by the standard histopathological method. The one-step nucleic acid amplification (OSNA®) assay is a novel molecular testing system for detecting LN metastases of colorectal, breast and gastric cancer. This OSNA assay allows assessing the metastases of a whole lymph node by homogenizing LN and detecting clinically relevant metastases quantified based on CK-19 mRNA copy number. In this study we investigated whether routinely classified patients can be upstaged by using OSNA assay results.
Patients and Methods: 3359 LNs from 159 clinically N0 and N1 colorectal cancer patients were collected from 11 institutes: Osaka Univ., Hyogo College of Medicine, Suita Municipal Hospital, Surugadai Nihon Univ. Hospital, Oita Univ., Mino City Hospital, Sapporo Medical Univ., Tochigi Cancer Center, Tokyo Women's Medical Univ., Kansai Rosai Hospital, and Osaka Medical Center for Cancer and Cardiovascular Diseases. All LNs were examined by one-slice H&E staining histopathology and staged according to the Japanese guideline (7th edition, Japanese Society for Cancer of the Colon and Rectum). In addition, when the LN was larger than 3 mm, it was sliced and half of it was examined by OSNA assay. We investigated the upstaging rate for stageI, II, and IIIa patients, and also characterized upstaged patients by stageII high-risk factors (T size, lympho-vascular invasion, and number of detected LNs).
Results: 2 to 25 (mean; 9.1) LNs per patient were examined by OSNA (total 1439 LNs). In total, 12.5% (18/159) were upstaged with OSNA results. 3.1% (1/32) of stageI and 18.3% (11/60) of stageII were upstaged to stageIIIa, and 12.8% (6/47) of stageIIIa were upstaged to stageIIIb. All upstaged histology stageII patients have at least one high-risk factor, and 45% (5/11) of them have more than two.
Conclusion: OSNA assay is a novel molecular system for detecting colorectal cancer LN metastases. This study confirmed that OSNA provides more accurate lymph node staging than standard histopathology. Future follow-up studies of the upstaged patients in this study will reveal the clinical benefit of the OSNA assay for colorectal cancer patients.
No conflict of interest.

2401 POSTER

Effects of intraluminal chemotherapy on colorectal cancer − study in an orthotopic murine model

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Introduction: Previously, intraluminal chemotherapy was used as an adjunct to surgery to decrease tumour micro metastasis. Theoretically, transanal chemotherapy offers benefits over conventional chemotherapy as it acts directly on the mucosal surface where the tumour transformation takes place. The purpose of our study was to evaluate the effects of transanal chemotherapy in a true orthotopic colorectal cancer murine model for subsequent potential application in humans.
Material and Methods: An intraluminal-mucosal orthotopic colon cancer murine model was made by doing transanal low dose mucosal coagulation, using a specially designed electrode, 2 cm inside the anus. Followed by transanal instillation of LS174T human colon cancer cells($1x10^6$) in NOG mice. Control, 5FU, Irinotecan and Oxaliplatin groups had 10 mice each. Treatment groups underwent weight adjusted 3 doses of alternate day transanal drug instillation after intraluminal tumour was confirmed by Coloview-mouse colonoscope.
Results: Control group showed a mean survival of 3.5wks, tumour size of 14±4 mm with widespread metastasis. 5FU group had an increased mean survival of 12wks, disappearance of primary tumour in 7 mice and mean tumour size of 0±3 mm with decreased metastasis. The Irinotecan and Oxaliplatin groups showed increased survival of 5wks and 6.5wks with tumour sizes of 5±2 mm and 3±2 mm respectively.
Conclusions: Transanal chemotherapy shows promising effects on colonic tumour with considerably decreased primary tumour size and increased survival. This treatment option could be applied to patients with colonic dysplasia, rectal tumours and obstructing colonic tumours as a bridge to surgery. This is the first report of effects of transanal chemotherapeutic agents in a true orthotopic colorectal cancer model.
No conflict of interest.

2402 POSTER

Identification of novel driver genes for colorectal cancer

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Background: Using our *Sleeping Beauty (SB*) model system we have been able to effectively identify more than 100 low penetrance common insertion site (CIS) drivers of colorectal cancer (CRC), confirming transformation phenotypes for many of these CIS genes when disrupted *in vitro* in 2D and 3D cell culture; *in vivo* in mouse models; and in human CRC. Here, we present studies of two novel classes of CRC driver genes. *First,* the *ion channel* genes *KCNQ1* and *CFTR*, high frequency CIS genes identified in multiple *SB* screens. *Second*, *fusion oncogenes*, a class of mutations that include three CIS genes, *RSPO2*, *RSPO3,* and *PTPRK* that form fusion genes in up to ~10% of human CRCs. We extend our previous work by identifying more than 400 new fusions in stage IV CRC.
Materials and Methods: *Ion Channel Genes:* Knockout (KO) alleles of *Kcnq1* and *Cftr* were introgressed into the Apc^{Min} model, followed by extensive tumour and tissue phenotyping, plus *in vitro* studies employing intestinal organoid cultures. Gene expression studies employing Illumina Bead Arrays were conducted and results confirmed by qRT-PCR. Pathways were analysed by Ingenuity Pathway Analysis and Gene Set Enrichment Analysis. The role of *KCNQ1* and *CFTR* in human CRCs was examined by Immunohistochemisty.
Fusion Oncogenes: Twenty stage IV CRC liver metastases (plus matching normal tissue, and primary cancer) samples were analysed by RNA Seq and deFuse. Confirmation of expression was confirmed by Nanostring counting and qRT-PCR, followed by functional validation of fusions *in vitro*.
Results: (I) Ablation of either *KCNQ1* or *CFTR* caused a significant enhancement in mouse tumour phenotypes, including a significant increase in intestinal tumour multiplicity, the development of adenocarcinomas in the proximal small intestine, inflammation in the rectum, stomach tumours, and pancreatic abnormalities. Gene expression studies and pathway analyses identified a large number of genes regulated by *KCNQ1* and *CFTR,* including many genes involved in immune responses and inflammation. Importantly, there was significant overlap between *KCNQ1* and *CFTR* target genes. Notably, loss of expression of KCNQ1 was associated with a reduction in median overall survival of 23 months in CRC patients following hepatic resection.
(II) More than 400 fusion genes were identified, including one fusion transcript that was found in 25% of the samples. Data will be presented to confirm whether this high frequency fusion is a driver of CRC metastasis.
Conclusions: The ion channel tumour suppressor genes *KCNQ1* and *CFTR*, along with high frequency fusion oncogenes identified in CRC liver metastases offer novel prognostic predictors and therapeutic targets for patients with advanced CRC.
No conflict of interest.

2403 POSTER

CD163 gene expression correlates with thymidine phosphorylase expression in colorectal cancer

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Background: Tumour-associated macrophages (TAMs) are macrophages with an M2-polarization, which differs from the regular M1-polarization associated with pro-inflammatory cytokines and microbicidal/tumouricidal activity. M2 macrophages instead have tumour promoting properties and promote tissue remodelling and angiogenesis. They secrete several growth factors and release anti-inflammatory cytokines. CD163 is a scavenger receptor expressed by M2, but not by M1, macrophages. The aim of this study was to correlate CD163 expression to clinical and pathological parameters. We also wanted to evaluate the relation between CD163 and thymidine phosphorylase (TP) which is an enzyme predominantly expressed in macrophages. We have previously reported that high TP gene expression relate to high number of positive nodes and a worse N stage, indicating a prognostic value.
Material and Methods: CD163 gene expression was analysed by real-time quantitative polymerase chain reaction in 254 tumour samples. All patients underwent radical surgery for colon (n = 139) or rectal (n = 115) adenocarcinoma in stage III. Tumour TP gene expression values were available from a previous study.
Results: The median age of the patients was 64 (interquartile range 57−75) years with an even gender distribution. The mean ± standard deviation of the relative CD163 gene expression was 0.29±0.52. No difference in

CD163 gene expression was seen according to age, gender or tumour location. T stage was not related to CD163 expression. CD163 expression in tumours correlated with lymph node staging, with higher expression relating to a higher number of positive nodes ($r = 0.15$, $p < 0.05$) and a worse N-stage ($p < 0.01$). The CD163 expression in rectal tumours of patients subjected to preoperative radiotherapy was significantly higher compared to tumours of non-irradiated patients ($p < 0.01$). There was a positive correlation between CD163 and TP gene expression ($r = 0.25$, $p < 0.01$).
Conclusions: Higher intratumoural CD163 expression was related to worse N stage and tumour grade and thereby associated with a worse prognosis. These findings are in line with results found in other cancer types. There was a positive correlation between CD163 and TP gene expression indicating that TP expression in a tumour microenviroment is partly generated by M2 macrophages.
No conflict of interest.

2404 POSTER

Establishing a diagnostic algorithm for HER2 amplification in colorectal cancer: The HERACLES-DGX study

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Background: We have identified the amplification of *HER2* occurring in 3−5% of genetically unselected colorectal cancer (CRC) as a potential onco-driver and marker of *de novo* resistance to anti-EGFR therapy in patients for whom other known genetic alterations conferring resistance to cetuximab were excluded. We have also shown that HER2-positive patient-derived CRC xenografts are impressively sensitive to anti-HER2 combinations (Bertotti et al., Cancer Discov 2011). Accurate HER2 assessment is crucial for patient selection for anti-HER2 therapy. Since the same scoring criteria for HER2 testing are not automatically applicable to different cancer types, as learned from breast and gastric cancer, we launched a retrospective study to establish a specific HER2 scoring in CRC.
Methods: CRC samples were centrally evaluated for HER2 expression using Ventana 4B5 antibody (V) and Dako HercepTest (D) HER2 immunohistochemistry (IHC) assays. Samples were scored positive if a moderate or intense basolateral or complete membrane staining was present. *HER2* gene amplification was tested by Ventana Inform Platform silver *in situ* hybridisation (SISH) using normal colon tissue as internal negative control. Samples with a *HER2*:CEP17 ratio >2.0 were considered amplified. Twenty samples were also tested by fluorescence ISH (FISH) (Abbott).
Results: 348 formalin-fixed, paraffin-embedded samples from 293 patients were centrally analysed and reviewed by a consensus panel (CP) of independent pathologists (MG, FP-L, GV). V yielded an 11.3% positivity (2+/3+, n = 33/293), of which 39.4% was amplified by SISH (n = 13/33). D staining bore a positivity rate of 5.5% with an 81.3% SISH confirmation (n = 16/293 and n = 13/16, respectively). Overall *HER2* amplification was detected in 5.1% of KRAS-WT and in none of the KRAS-mutated patients, suggesting mutual exclusion of the two mutations. SISH/FISH concordance was 100% (N = 20).
Conclusions: The CP defined HER2-positivity as: IHC 3+ and/or SISH/FISH amplification in more than 50% of cells, with central SISH re-testing in equivocal cases (IHC 2+ or heterogeneous 3+ cases; IHC 0 and 1+ cases were excluded). This practical algorithm is currently used for selecting HER2-positive cases for the HERACLES Phase II trial assessing the efficacy of the combination of lapatinib and trastuzumab in chemotherapy- and cetuximab-resistant patients.
Conflict of interest: *Advisory board: Roche, Dako, GSK, Merck*

2405 POSTER

Next generation sequencing reveals high concordance for recurrent somatic mutations in primary and matched metastasis from patients with colorectal cancer

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Background: Characterization of the genomic changes that drive an individual patient's disease is critical in the management of many cancers, including colorectal cancer (CRC). Spatial and temporal heterogeneity in mutational status can represent a major issue for personalized medicine. We undertook the present study to determine, using next generation sequencing (NGS) technology, the extent of molecular variability between primary tumors and matched metastasis for CRC with a special focus on known recurrent somatic mutations with established role in the pathogenesis of CRC.
Material and Methods: Surgical samples from primary and matched metastatic tumor pairs plus adjacent normal tissue from patients (pts) with metastatic CRC were analyzed using a targeted NGS assay in a CLIA laboratory (Foundation Medicine). Genomic libraries were captured for 3,230 exons in 182 cancer-related genes plus 37 introns from 14 genes often rearranged in cancer and sequenced to an average median depth of 778X with 99% of bases covered >100X.
Results: 13 pts were included, 11 had received chemotherapy between primary and metastasis surgery, either as adjuvant treatment or as first line chemotherapy at relapse, including anti-angiogenic agent for 2 pts. Among the 26 samples, 191 somatic alterations were identified including mutations in genes previously characterized to be altered in CRC (recurrent mutations) such as APC (13 pts), TP53 (11 pts), KRAS (7 pts), SMAD4 (3 pts). The total number of alterations between primaries (95) and metastasis (96) was remarkably similar. Primary and metastatic tumors from the same patient demonstrated 77% global concordance for mutations. The concordance rate was 86% for 12 known recurrent mutations in CRC. No discrepancies in KRAS status were in particular observed between primary tumor and metastasis.
Conclusions: These results suggest that genomic profiles of primary tumor can identify the key somatic alterations present in matched CRC metastases and therefore is a suitable specimen for clinical decision making in the majority of cases. Our data does not support the routine need for a new biopsy upon first recurrence since variability in recurrent mutations is low.
Conflict of interest: *Other substantive relationships: GF, RY, VM and PS are employees of Foundation Medicine and all receive stock compensation*

2406 POSTER

Exploitation of colorectal carcinoma microenvironment shows a central anti-cancer role for FcgRIII+ macrophage and CD8+ cells and auxiliary role for natural killer cells

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Background: Convincing evidence suggests that T lymphocytes infiltration in the CRC microenvironment improves survival in colorectal carcinoma (CRC) patients (pts). Conversely, the importance of innate immune cell inflammation in the CRC milieu is unclear.
Materials and Methods: We investigated the clinical impact of macrophage and NK cell based inflammation in CRC pts utilizing a tissue microarray composed of 1420, clinically well documented, CRC lesions by immunohistochemistry. Innate and NK cell infiltration were studied utilizing flow cytometry analysis of freshly removed CRC lesions.
Results: We found homogeneous infiltrations of CRC lesions by CD8+ and CD4+ T lymphocytes as well as CD68+ tumor associated macrophages (TAMs). Further phenotypic analysis showed that TAMs were composed of 2 distinct populations: CD16+HLA-DR−CD33+ but negative for NK cell markers and CD16−CD33+HLA-DR+/−. Notably, NK cells slightly infiltrated CRC lesions. We found NK cell infiltration only in 132 of 423 CRC lesions evaluable for CD56+ cell infiltration. Then, we investigated the clinical impact of T and innate cell infiltration in the CRC milieu. As expected, pts with >10 positive cells per lesion survived significantly longer ($P = 0.0002$) than CRC pts with $\leqslant$10 positive T cells. Similarly, only pts with an infiltration of CD16+ TAMs >30 cells survived significantly longer ($P = 0.0005$) than pts with CD16+ TAMs infiltration less than 30 cells and CD16− TAMs regardless their level of infiltration. CD16+ TAMs infiltration resulted to be a positive,

independent prognostic factor in CRC pts. In contrast, NK cells regardless their level of CRC infiltration did not affect CRC pts survival. To test the hypothesis whether NK cells could mediate an indirect clinicopathological effect in the development of CRC, perhaps potentiating the beneficial effect of CD3+ T cells, we compared the clinical outcome of CD8+, CD3+, or CD4+ cell infiltration in the presence or absence of NK cells on CRC pts survival. In univariate analysis, within 5 years follow-up, only CRC pts with NK and CD8+ T cell infiltration had the longest overall survival (P = 0.007), which declined after 5 years (P = 0.03), suggesting that NK cells specifically increased the anti-CRC effects of CD8+ T cells.
Conclusions: This study, for the first time, provides evidence that NK cell based inflammation in the CRC microenvironment improves the anti-CRC effects of CD8+ T cell based inflammation in CRC pts at clinical level.
No conflict of interest.

2407 POSTER

Molecular biomarkers for a prognostic stratification of K-RAS wild type colorectal cancer patients receiving irinotecan–cetuximab: Preliminary results of a prospective study

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Background: Translational research identified numerous putative markers for a 'beyond-k-ras' selection of colorectal cancer patients receiving cetuximab, but none of these entered clinical practice mainly because prospective validation is lacking.
The aim of our study was to evaluate whether a panel of biomarkers, prospectively analysed may be able to predict patients' clinical outcome more accurately than K-RAS status alone.
Material and Methods: Metastatic, K-RAS wild type colorectal cancer patients, candidate to receive second/third-line cetuximab with chemotherapy have been prospectively allocated, after informed consent, into 2 groups on the basis of their genetic profile: favourable (BRAF and PIK3CA exon 20 wild type, EGFR GCN $\geqslant$2.6, HER-3 Rajkumar score $\leqslant$8, IGF-1 immunostaining <2) and unfavourable (any of the previous markers altered or mutated). All patients received cetuximab treatment as planned by treating physician who was unaware of biomarkers results. To detect a difference in terms of response rate (RR) among patients with an unfavourable profile (estimated around 25%) and patients with a favourable profile (estimated around 60%), assuming a probability alpha of 0.05 and beta of 0.05, required sample size will be 46 patients.
Results: Thirty-one patients have been enrolled, most patients (27, 86%) received cetuximab as third-line. Eleven patients (35%) were allocated to the favourable profile and 20 patients (75%) to the unfavourable profile. Patients with the unfavourable profile showed 1 BRAF mutation, 2 PIK3CA exon 20 mutations, 12 cases of EGFR GCN <2.6, 13 cases of HER-3 and 11 cases of IGF-1 overexpression respectively. RR in the favourable and unfavourable group was 7/11 (64%) and 1/20 (5%) (p = 0.008) respectively. The favourable group also showed an improved median TTP (8 months vs. 2.6 months, p = 0.0007) and OS (16 months vs. 6 months, p = 0.0002).
Conclusions: Our results suggest that prospective selection of candidates for cetuximab may be able to improve clinical outcome in patients with a favourable profile. This approach, if confirmed, may also allow an early switch to alternative treatment in patients with an unfavourable profile.
No conflict of interest.

2408 POSTER

Transcript profiling of patient-derived (PD) colorectal cancer (CRC) xenografts for the identification of biomarkers for regorafenib (REG; BAY 73-4506)

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Background: REG is an oral multi-kinase inhibitor approved in the USA for treatment of metastatic CRC after failure of other standard therapies.
REG targets oncogenesis, tumor angiogenesis and maintenance of tumor microenvironment signalling by inhibiting multiple protein kinases, eg, VEGFR 1−3, TIE2, KIT, RET, PDGFR and FGFR. In preclinical studies, REG inhibited the growth of PD CRC xenografts and prolonged time to tumor progression in a mouse model of CRC liver metastases. Anti-tumor activity did not correlate with mutational status of known oncogenes associated with CRC (eg, *KRAS*, *APC* and *CTNNB1*).
The objective of this study (sponsored by Bayer HealthCare) was to try to identify biomarkers for REG by looking at genes possibly involved in resistance to treatment.
Materials and Methods: Transcript profiles − generated from RNA isolated from xenografts grown subcutaneously in mice and hybridized to human Affymetrix Gene 1.0 ST Arrays in quintuplicate − of 6 PD CRC models were compared: 1 from a mucinous CRC and not responsive to REG (Co8541); 5 REG-sensitive models.
For a transcript to be considered significantly differentially expressed, a p-value of <0.01, a false discovery rate (FDR) of <0.05 and a >5 fold change was needed in up- or down-regulation in all comparisons of non-responsive *vs* individual responsive tumor samples.
Gene ontology term enrichment and pathway analysis was done comparing resistant and sensitive groups respectively.
Results: The expression profile and clustering behaviour of Co8541 differed substantially from the other 5 models, with 15 genes significantly differentially expressed. Gene ontology term enrichment and pathway analysis showed several enriched processes and pathways related to inflammation in the insensitive *vs* sensitive models. Selective overexpression of the *COX2* gene, previously associated with colon tumorigenesis, was seen in the non-responsive model (p=1E-13, FDR=1E-10; fold change=10.3). Selective overexpression of the *MUC2* gene, implicated in resistance to anticancer drugs, in the non-responsive model was also detected, which is consistent with histological characterisation of this model and with published immunohistochemical analyses of mucinous CRC samples.
Conclusion: *MUC2* and *COX2* may play a role in resistance of mucinous CRC to REG. To further correlate these genes with resistance to REG, profile analyses of additional PD CRC models and confirmatory immunohistochemical analyses are in progress. Results will be presented.
Conflict of interest: *Ownership: (stock ownership) Bayer, EPO, Signature Diagnostics. Advisory board: n/a. Board of directors: n/a. Corporate-sponsored research: n/a. Other substantive relationships: (employee) Bayer Pharma AG, EPO-Berlin-Buch GmbH, Signature Diagnostics*

2409 POSTER

Upstaging from histopathology lymph node negative into lymph node positive colon carcinomas by one-step nucleic acid amplification (OSNA): Results of a European, multicenter study

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Background: Approximately 20% of colon carcinoma patients classified as lymph node negative by standard histopathology will suffer from recurrence, possibly due to undetected lymph node metastases. A new diagnostic semi-automated system, One Step Nucleic Acid Amplification (OSNA), detects cytokeratin (CK) 19 mRNA in lymph node metastases. The objective of this prospective, European, multicenter study was to assess whether histopathological pN0 patients can be upstaged to stage UICC III by OSNA.
Material and Methods: From patients who were classified as lymph node negative after standard histopathology (single haematoxylin & eosin (H&E) slice), the lymph nodes were subjected to OSNA analysis. An OSNA result revealing a CK19 mRNA copy number exceeding 250 was regarded as positive for lymph node metastases based on previous threshold investigations.
Results: In total, 1594 pN0 lymph nodes from 103 colon carcinomas (median lymph node/patient: 14, range: 1−46) were analyzed with OSNA. From 103 pN0 patients 26 had OSNA positive lymph nodes, resulting in an upstaging rate of 25.2%. Hereunder were 6/37 (16.2%) stage UICC I and 20/66 (30.3%) stage UICC II. Overall, 38 lymph nodes were OSNA positive: nineteen patients had 1, three had 2, three had 3, and one patient had 4 OSNA positive lymph nodes.
Conclusion: OSNA resulted in an upstaging of over 25% of initially lymph node negative patients after H&E analysis. OSNA is a standardized, observer-independent technique and may be more sensitive due to allowing the analysis of the whole lymph node. Therefore, the use of OSNA avoids

sampling bias due to not investigated lymph node tissue and could result in a more accurate staging in colon carcinoma patients.
Conflict of interest: *Advisory board: Company of Sysmex*

2410 POSTER

Hsa-miR-31-3p expression in FFPE tumor samples as a predictor of anti-EGFR response in patients with metastatic colorectal cancer (mCRC)

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Background: In mCRC, KRAS mutations are associated with anti-EGFR antibodies resistance. Expression level of miR-31-3p was associated with the progression free survival (PFS) on frozen tumor of KRAS wild type (WT) mCRC patients treated with anti-EGFR. To explore the role of miR-31-3p,we studied and validated the association of miR-31-3p expression level with PFS on formalin fixed paraffin embedded (FFPE) tumor samples and identified some target genes of miR-31-3p in a CRC context.
Material and Methods: Association between PFS and miR-31-3p expression level on FFPE samples was performed on two series of patients 1/35 KRAS WT patients treated with cetuximab or panitumumab (PMB) based chemotherapy, 2/39 KRAS WT patients treated with PMB and irinotecan as third-line from a phase II clinical trial. Identification of miR-31-3p target genes was conducted on Caco-2, Colo205 and Colo320HSR cell lines which were transfected with miR-31-3p mimic or control mimic. Total RNA was extracted for an expression array analysis using linear models for micro-arrays analysis. A miRNA predictive target database including 6 available databases was created. Identified target genes were validated on tumors sample of the second series of 39 patients.
Results: Correlation between miR-31-3p expression value of 15 frozen and the corresponding FFPE samples was done and a linear regression was determined with r^2=0.98. We built a nomogram allowing to calculate a risk score of progression based on miR-31-3p expression based on RNA extracted from paraffin embedded tissues. A significant link between survival and the expression of the miR-31-3p was established in both independent FFPE series by a Cox model. Using expression array and miR prediction databases we identified 25 direct putative target genes and 27 genes up-regulated in miR-31-3p overexpressing cells. 45 out of these 52 genes were validated with RT qPCR on tumor samples of PMB treated patients. Expression level of 2 putative direct target genes was anti-correlated with miR-31-3p expression level and was associated with PFS.
Conclusions: MiR-31-3p expression level is associated with PFS in mCRC patients in frozen and FFPE samples. The nomogram described is the first tool to select individuals with a WT KRAS tumor for anti-EGFR therapy. Furthermore, this study identified 2 new genes of interest in mCRC.
Conflict of interest: *Advisory board: INTEGRAGEN SA, AMGEN. Other substantive relationships: MERCK Serono*

2411 POSTER

VEGF and eNOS gene polymorphisms as predictors of efficacy of bevacizumab-based chemotherapy in patients with metastatic colorectal cancer

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Background: Bevacizumab (B) + chemotherapy (CT) is a widely used therapeutic option for the first-line treatment of metastatic colorectal cancer (mCRC). However, molecular predictors of B efficacy have not yet been identified. We verified the role of specific VEGF and eNOS polymorphisms as predictive markers of B efficacy in mCRC patients.
Methods: 149 patients enrolled onto the phase III prospective multicentric randomized ITACA (Italian Trial in Advanced Colorectal Cancer) trial were considered for this study. 74 patients received either FOLFIRI or FOLFOX plus B, while 75 patients received CT only. A peripheral blood sample was collected from each patient for genomic DNA extraction. Five VEGF and two eNOS polymorphisms (VEGF −2578 C/A, −1498 C/T, −1154 G/A, −634 G/C, +936 C/T, eNOS 894 G/T and eNOS VNTR 27bp 4a/b) were analyzed by direct sequencing, and one eNOS polymorphism (eNOS 786 C/T) was assessed by a Real Time PCR method. All the candidate genotypes were evaluated to identify a potential correlation with progression-free survival (PFS), overall survival (OS) (log-rank test) and objective response rate (ORR) (Chi-square test).
Results: In B-treated patients the presence of VEGF −634 GC genotype was associated with shorter PFS and worse ORR than the other genotypes. The presence of eNOS 894 GT genotype was associated with both shorter PFS and OS and with worse ORR, while the presence of eNOS 27bp 4ab genotype was correlated with shorter PFS and OS.

	Median PFS (95% CI)	Median OS (95% CI)	ORR (CR or PR/No. patients)
VEGF-634			
GC	8.6 (6.8–10.6)	17.8 (11.6-nr)	38.5% (10/26)
GG/CC	12.4 (9.6–14.1)	30.4 (21.8–36.7)	73.9% (34/46)
	p = 0.040	p = 0.118	p = 0.005
eNOS 894			
GT	9.1 (4.5–10.9)	17.8 (10.3–30.4)	42.96% (12/28)
TT/GG	12.6 (9.6–18.5)	31.6 (21.0–47.1)	72.7% (32/44)
	p = 0.024	p = 0.009	p = 0.013
eNOS VNTR 27bp			
4ab	8.4 (4.5–10.0)	21.0 (8.2–26.2)	50% (12/24)
4bb	12.3 (9.7–16.0)	30.4 (20.9–36.7)	66.7% (32/48)
	p = 0.023	p = 0.054	p = 0.174

No differences in terms of PFS, OS and ORR were observed in patients treated with chemotherapy only. Interaction testing between eNOS 894 G/T variants and treatment effect suggested that the association of eNOS 894 GT genotype with shorter PFS (p = 0.044), shorter OS (p = 0.025) and worse ORR (p = 0.047) was caused by the effect of B. Other investigated polymorphisms did not affect outcome.
Conclusions: VEGF −634 GC, eNOS VNTR 27bp 4ab and, in particular, eNOS 894 GT genotypes seem to be potentially negative predictive markers for B-based CT in mCRC patients.
No conflict of interest.

2412 POSTER

SLCO1B1 and SLC19A1 gene variants and irinotecan-induced rapid response and survival: A prospective multicenter pharmacogenetics study of metastatic colorectal cancer

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Background: Rapid response to chemotherapy in metastatic colorectal cancer (mCRC) patients (response within 12 weeks of chemotherapy) may increase the chance of complete resection and improved survival. Few molecular markers predict irinotecan-induced rapid response and survival. Single-nucleotide polymorphisms (SNPs) in solute carrier genes are reported to correlate with the variable pharmacokinetics of irinotecan and folate in cancer patients. This study aims to evaluate the predictive role of 3 SNPs in mCRC patients treated with irinotecan and fluoropyrimidine-containing regimens.
Material and Methods: Three SNPs were selected and genotyped in 137 mCRC patients from a Chinese prospective multicenter trial (NCT01282658). The chi-squared test, multivariable logistic regression model, and receiver operating characteristic analysis were used to evaluate correlations between the genotypes and rapid response. Kaplan–Meier survival analysis and Cox proportional hazard models were used to evaluate the associations between genotypes and survival outcomes.
Results: Genotype GA/AA **of** SNP rs2306283 of the gene *SLCO1B1* and genotype GG of SNP rs1051266 of the gene *SLC19A1* were associated with a higher rapid response rate (odds ratio [OR] =3.583 and

3.521, 95% CI =1.301–9.871 and 1.271–9.804, $p = 0.011$ and p = 0.013, respectively). The response rate was 70% in patients with both genotypes, compared with only 19.7% in the remaining patients (OR = 9.489, 95% CI = 2.191–41.093, Fisher's exact test $p = 0.002$). The rs2306283 GA/AA genotype was also an independent prognostic factor of longer progression-free survival (PFS) (hazard ratio = 0.400, 95% CI = 0.183–0.873, p=0.021). None of the SNPs predicted overall survival.

Conclusions: Polymorphisms of solute carriers' may be useful to predict rapid response to irinotecan plus fluoropyrimidine and PFS in mCRC patients.

No conflict of interest.

Table 1. Polymorphisms' association with RRR, PFS and OS

Genotype	n	RRR (%)	P	Median PFS (days)	P	Median OS (days)	P
rs2306283							
GG	51	8 (15.7)		104		501	
GA/AA	35	14 (40.0)	0.011*	124	0.014*	410	0.641
rs1051266							
GG	24	11 (45.8)		89		528	
GA/AA	62	12 (19.4)	0.013*	114	0.583	501	0.411
rs4149056							
TT	67	18 (26.9)		120		402	
CT/CC	20	5 (25.0)	0.868	89	0.498	501	0.293
rs2306283 (GA/AA) + rs4149056 (GG)	10	7 (70)		89		410	
others	76	15(19.7)	0.002*	111	0.736	501	0.840

RRR, rapid response rate; PFS, progression-free survival; OS, overall survival.
*Retained its significant association in multivariate analysis.

2413 POSTER

Prognostic significance of VEGFR-2 and 18F-FDG PET/CT SUVmax relative percentage co-reduction in patients with locally advanced rectal cancer treated with neoadjuvant therapy

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Background: Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2), Epidermal Growth Factor Receptor-1 (EGFR) and Cyclooxygenase-2 (Cox-2) stimulate key processes involved in tumor progression and are important targets for cancer therapeutics. 18F-fluorodeoxyglucose (18F-FDG)-positron emission tomography (PET)-computed tomography (CT) maximum standardized uptake value (SUVmax) is a marker of tumor metabolic activity. The purpose of this study was to measure SUVmax (ΔSUVmax%), VEGFR-2 (ΔVEGFR-2%), EGFR (ΔEGFR%) and COX-2 (ΔCOX-2%) percentage reduction after preoperative treatment for locally advanced rectal cancer (LARC) patients, and to correlate response with pathologic response [Tumor Regression Grade Rödel's scale (TRG)] and long-term clinical outcome.

Methods: VEGFR-2, EGFR and COX-2 was measured using a quantitative and qualitative compound immunohistochemistry analysis [Immunoreactive score (IRS score)] in the pretreatment endoscopic biopsy and definitive surgical specimen. A composite index using ΔSUVmax% and the 3 molecules was developed in order to stratify patients with metabolic and molecular response from non-responders. Cox proportional hazards models were used to explore associations between the tumor markers, disease-free survival (DFS) and overall survival (OS).

Results: Thirty-eight patients with a median follow-up of 69.3 months (range, 4.5−92) were analyzed.

Using the ΔVEGFR-2%/ ΔSUVmax% index, pathologic responders (TRG 3−4) and non-responders (TRG 0−2) were correctly identified in 13 of 19 (1 of these 6 non-responders died of disease progression), and 17 of 19 [Sensitivity 68%, specificity 89%, accuracy 79%, positive predictive value (PPV) 87%, negative predictive value (NPV) 74%]. On multivariate analysis, only ΔVEGFR-2%/ ΔSUVmax% responder index was associated with DFS (HR 0.15, p = 0.04) and OS (HR 0.19, p = 0.05).

Conclusions: LARC patients with a ΔVEGFR-2%/ ΔSUVmax% responder index are associated with improved overall outcomes. Determination of the optimal diagnostic cut-off level for this novel biomarker association should be explored. Evaluation within a clinical trial is required to determine whether selected patients could benefit from an VEGFR targeted therapeutic agent.

No conflict of interest.

2414 POSTER

Tumour infiltrating lymphocytes levels within colorectal liver metastases correlate with oncological outcomes

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Introduction: The study of tumour infiltrating lymphocytes (TIL) within resected colorectal cancer has been shown to offer new individualised prognostic information independent to standard radiological and histopathological staging systems. TIL within metastatic tissue has not been investigated but is highly relevant as case numbers and experience of surgically resecting colorectal liver metastases (CRLM) is increasing. This purpose of this study was to see if reported TIL findings were applicable to metastatic tissue.

Methods: A single centre, prospective, observational cohort study of consecutive patients undergoing CRLM resection with curative intent was performed. All patients were managed by a specialist multi-disciplinary team. Tissue microarrays were created in triplicate with 1 mm cores from matched primary (centre of tumour and invasive margin) and secondary tissue from each patient. $CD8^+$ and $CD45RO^+$ immunohistochemistry was performed in using standard practices. Samples were manually quantified and divided into TIL high and low groups using the overall mean TIL count. Overall and disease free survival was calculated using Kaplan–Meier analysis.

Results: 59 patients were recruited, 33 (56%) had liver metastases on presentation. All had undergone prior colorectal R0 resection with curative intent. Mean follow up from colorectal and metastasis resection was 66 and 42 months respectively. Three year overall and disease free survival following CRLM resection in the High vs. Low TIL groups was 69% vs. 22% and 62% vs. 18% respectively (p < 0.001). Five year overall and disease free survival was 58% vs. 0% and 41% vs. 0% (p < 0.001). In those that relapsed (69%), time to recurrence was double in the high group (12.3 vs. 5.5 months, p = 0.02). Mean TIL counts were double in overall and disease free survivors (310 vs. 164, p = 0.02; 351 vs. 174, p = 0.036). Positive correlation was seen in TIL counts in primary and CRLM tissues (p = 0.024) but no redundancy between CD8 and CD45RO markers was seen.

Conclusion: CD8+ and CD45RO TIL analysis within CRLM gives clinically useful prognostic information that correlates with oncological outcomes and is not available through current practice. High TIL counts are associated with improved overall and disease free survival and longer time to recurrence. This easily obtainable information may lead to individualisation of post operative prognosis, follow up and adjuvant treatment strategies.

No conflict of interest.

2415 POSTER

p38α: A key factor in CRC resistance

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Background: Targeted molecular therapies in addition to standard chemotherapeutic treatments have significantly improved patient survival rates. However, development of chemoresistance often makes treatments for colorectal cancer (CRC) ineffective. Identifying the cellular mechanisms that lead to resistance is a crucial issue for improving CRC treatment and survival.

Material and Methods: In this work we tested p38α inhibitors in combination with molecularly-targeted drugs and chemotherapeutic agents in CRC cell lines *in vitro* and in CRC-xenografted nude mice, APCmin/+ mice and in the AOM/DSS colitis-associated carcinoma preclinical model. To this aim, animals were treated with the p38α inhibitor SB202190 alone or in combination with the MEK1 inhibitor PD0325901, the multikinase inhibitor Sorafenib or cisplatin (CDDP).

Results: We previously demonstrated that p38α is required to maintain CRC metabolism and recent studies identified p38α as a mediator of resistance to irinotecan and of impaired response to FOLFIRI therapy, while its inhibition sensitized resistant CRC cells to irinotecan and 5-fluorouracil. Our data show that p38 is activated in response to cisplatin treatment and mediates chemoresistance in HT29-xenografted tumors. MEK1 inhibition has been found to reduce CRC cell proliferation *in vitro* and to decrease tumor growth in xenograft models and we recently reported that MEK-ERK1/2 inhibition is followed by over-activation of the p38 MAPK pathway.

Here we found that p38a and MEK combined inhibition specifically induces apoptosis by enabling TRAIL signaling propagation through t-Bid and caspase 3, and fosters cell death in CRC cells. Sorafenib is reported to inhibit nine protein kinases, including BRAF, VEGF and the DGF-out conformation state of p38α. Our results show that the SB202190 (type I-p38a inhibitor) and Sorafenib (type II-p38a inhibitor) synergize at the molecular and biological level enhancing tumor growth inhibition and induction of apoptosis in CRC both *in vitro* and *in vivo*. The combined use of SB202190 and PD0325901, Sorafenib or CDDP significantly reduced tumor growth by inducing a higher degree of apoptosis compared to each single treatment.
Conclusions: Our data validate *in vivo* the combined inhibition of the p38α and ERK pathways or their association with chemotherapy as a promising approach to treat CRC. Moreover, they suggest that the phosphorylation status of p38 MAPK may be a marker of resistance in CRC.
No conflict of interest.

2416 POSTER

Notch and Delta-like 4 ligand (DLL4) expression in bevacizumab-treated colorectal cancer patients

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Background: DLL4-induced Notch signalling has been found to mediate tumour-resistance to anti-vascular endothelial growth factor therapy by inducing the formation of large vessels and by activating multiple pathways in preclinical models and has recently emerged as an attractive target for angiogenesis-based cancer therapies. In order to investigate potential mechanisms of resistance to angiogenesis inhibitor bevacizumab, Notch and DLL4 expression was correlated with response and survival in a series of bevacizumab treated advanced colorectal cancer patients.
Material and Methods: Notch and DLL4 expression was evaluated by immunohistochemistry (IHC) on 67 primary colorectal cancer patients enrolled within randomized clinical trials assessing first-line bevacizumab plus chemotherapy. A control series of advanced colorectal cancer patients treated with chemotherapy alone was also examined.
Results: Notch positivity was localized to the cytoplasm or nucleus of malignant epithelial cells. In all, 12/63 (19%) evaluable primary tumours had a high Notch expression (IHC 3+). A cytoplasmic DLL4 immunoreactivity of large and small tumour vessels was observed in 21/46 (46%) and in 10/58 (17%) evaluable colorectal cancers, respectively. Seven of the 12 cases (58%) with high Notch expression experienced progressive disease compared with 5/51 (10%) Notch negative cases ($p < 0.01$). Median progression-free survival was 2.4 months for Notch positive cases compared with 12.2 months for Notch negative cases ($p < 0.01$). Median overall survival was 17.7 months for Notch positive cases compared with 30.8 months for Notch negative cases ($p < 0.01$). No correlation was found between Notch expression and clinical response in a smaller series of patients treated with chemotherapy without bevacizumab. No correlation was found between DLL4 expression and outcome.
Conclusions: Clinical trials investigating the therapeutic efficacy of bevacizumab in colorectal cancer did not explore the impact of DLL4-Notch pathway on response and clinical outcome. Our results might suggest the involvement of Notch pathway in mediating tumour resistance to bevacizumab in colorectal cancer patients.
No conflict of interest.

2417 POSTER

MET expression and prognostic effect in metastatic colorectal cancer (mCRC)

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Background: MET is a transmembrane receptor tyrosine kinase (RTK) mediating downstream signaling in human malignancies. In clinical trials, high METexpression by immunohistochemistry is predictive of response to MET targeted therapy in lung, gastric and hepatocellular carcinomas. The objective of this study is to determine MET expression and prognostic effect in mCRC and to measure association with other biomarkers.
Methods: A previously well characterized tissue microarray of 96 patients with advanced colorectal cancer was stained for MET [SP44; Ventana® CONFIRM anti-total rabbit monoclonal antibody]. Immunohistochemical MET expression was scored as either absent (<10% stain), low (>10% to <50% of tumor cells with >1+ cytoplasmic staining) or high (>50% of tumor cells with >1+ cytoplasmic staining). Phosphorylated AKT (pAKT) was scored as negative (no staining) or positive (1, weak; 2, moderate; 3, intense). Kaplan–Meier survival analysis was conducted from diagnoses of distant disease to death [Overall Survival (OS)] and from early stage disease to relapse [Disease Free Survival (DFS)]. Fishers exact and chi-square tests were used to compare MET expression between primary and distant disease and association with biomarkers.
Results: Median age among 96 patients was 60 of which 34% had rectal cancer and 51% presented with early stage disease. A KRAS mutation was documented in 35%. MET expression was high in 45% and associated with a trend for inferior OS, Hazard Ratio 1.4, 95% CI: (0.92, 2.2), $p = 0.12$. MET was not prognostic of relapse in early stage disease. Among 28 cases with paired primary and metastatic tumors, MET status was concordant among 71%, $p = 0.051$. pAKT was positive in 65% and was associated with high MET expression, $p = 0.035$.
Conclusion: High MET expression is documented in a significant proportion of patients with colorectal cancer and is associated with a trend to inferior outcome in the advanced setting. High concordance of MET expression between primary and metastatic tumors was seen and high MET status was associated with activation of PI3KCA-AKT signaling. Results suggest that MET may be a relevant therapeutic target in mCRC. FISH analysis will be presented.
No conflict of interest.

2418 POSTER

Ex-vivo activation of natural killer (NK) cell effector by cetuximab (CTX) is effective in patients (pts) with colorectal cancer (CRC)

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Background: Antibody-dependent cellular cytotoxicity (ADCC) may play a role in antitumor activity of CTX. The efficacy of this is determined by the interaction of the Fc portion of the target cell-bound antibody and Fc receptors (FcγR) present on the immune effectors cells. This study aimed to evaluate the *ex vivo* immune response of NK cells from pts with CRC to CTX and panitumumab (PANI).
Material and Methods: Activation of NK cell from CRC pts and healthy donors (HD) was measured with a flow cytometry (FC)-based assays. FC was used to measure CD16 modulation and CD107a expression on NK cells incubated in microplates (10^5cells/well) sensitized with a saturating concentration (5 μg/mL) of 3G8 (mouse anti-FcγRIIIA), human myeloma (hm) IgG1, IgG2, CTX or PANI. The % and absolute number of peripheral blood CD3+ (T cells), CD19+ (B cells), CD4+, CD8+ and CD3−CD56+ cells (NK cells) were evaluated by FC after staining with fluorescent mAbs in 15 CRC pts before and after chemotherapy (CT) and in 5 HD.
Results: No difference was found between CRC pts and HD in terms of % of T, B, CD4+, CD8+ and NK cells. The number of each population was slightly decreased in CRC pts (compared to HD) and further after CT (in CRC pts), whereas the therapy did not modify the % of each sub-population. We observed CD16 modulation on 59% and 62% of NK cells from HD and CRC pts after hm IgG1 stimulation and on 60% and 50% of NK cells from HD and CRC pts after CTX stimulation, respectively. Whatever the group, CD16 modulation was significantly reduced after stimulation with hm IgG2 (30% and 17% of NK cells from HD and CRC pts, respectively. $p < 0.001$ compared to IgG1) and with PANI (8% and 7% of NK cells from HD and CRC pts, respectively. $p < 0.001$ compared to PANI). We observed CD107a expression on 14% and 11.5% of NK cells from HD and CRC pts after hm IgG1 stimulation and on 10% and 9% of NK cells form HD and CRC pts after CTX stimulation, respectively. In accordance with the CD16 modulation, CD107a expression was significantly reduced after stimulation with hm IgG2 (5% and 2.5% of NK cells from HD and CRC pts, respectively. $p < 0.001$ compared to IgG1) and with PANI (3% and 1% of NK cells from HD and CRC pts, respectively. $p < 0.001$ compared to PANI). The % of CD16 modulation and of CD107a expression on NK cells from CRC pts observed before and after 2 months of CT were very similar. The difference between CTX and PANI remained significative after CT.
Conclusion: These results suggest that this novel cell-based assay is able to predict ADCC effect of CTX.
No conflict of interest.

2419 POSTER

Comparison between different scoring systems for pathological response in relation with clinical assessment in the EORTC liver metastases intergroup randomized phase III study 40983

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Background: The EORTC study 40983 demonstrated that perioperative chemotherapy with FOLFOX increases progression free survival compared to surgery alone for patients with resectable liver only metastases from colorectal cancer (ASCO 2007). The secondary endpoint overall survival results were reported (ASCO 2012). A retrospective central collection of tumor tissue was organized to assess pathological response and compare different scoring systems for the first time in a randomized study.
Methods: Pathological response (PR) was evaluated by one senior pathologist blinded from clinical data, according to Blazer's score (percentage of residual viable cancer cells), tumor regression grade according to Rubbia-Brandt (TRG), and tumor thickness at the tumor-normal interface (TTTNI). The results are presented by treatment arm and the correlation with radiological responses was assessed. Radiological response to preoperative chemotherapy was locally assessed using RECIST (version1.0) in the CT arm. No type I error adjustment was made for multiple testing.
Results: Tumor tissue (liver metastasis) was available for 89 patients with a R0-R1 resection achieved after surgery, 42 in the perioperative chemotherapy arm (CT arm) and 47 in the surgery alone arm (S arm). Patients' demographics and baseline disease characteristics were balanced between the two arms of this subset. As expected, there were more PR in the CT arm than in the S arm (Blazer 45.2% vs 25.5% $p = 0.07$, TRG 47.6% vs 19.1% $p < 0.01$, TTTNI<0.5 mm 41% vs 21.7% $p = 0.06$). In the S arm, while Blazer and TTTNI classified more than 21% of the patients as major response, TRG classified no patient as major response. In the table, correlation between RECIST and PR is provided for the CT arm. Spearman's rank correlation was significant for TRG only (0.4716, $p < 0.01$).

CT arm	RECIST response (N = 23)	RECIST no response (N = 19)
TRG		
partial response	11 (47.8%)	3 (15.8%)
major response	5 (21.7%)	1 (5.3%)
Blazer major response	12 (52.2%)	7 (36.8%)
TTTNI <0.5 mm	10 (43.5%)	6 (31.6%)

Conclusions: The TRG, which takes into account the extent of fibrosis, was the more accurate pathological score for evaluating tumor response, and the only one to correlate significantly with radiological response in our series. The new ongoing EORTC trial on resectable liver metastasis (BOS2) shall provide us with larger tissue sample sizes enabling us to correlate pathological response to DFS after targeted therapies.
No conflict of interest.

2420 POSTER

Non-invasive detection and monitoring of plasma KRAS mutation status in advanced colorectal cancer using Therascreen® KRAS RGQ PCR

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Background: Presence of *KRAS* mutations in tumor negatively predicts patients' response to cetuximab and panitumumab in advanced colorectal cancer (CRC). The FDA approved therascreen® KRAS RGQ PCR Kit (Qiagen) can detect six codon 12 and one codon 13 *KRAS* mutations. Limited data is available as to whether plasma *KRAS* mutation status can be assessed and longitudinally monitored in CRC using therascreen® KRAS RGQ PCR Kit.
Materials and Methods: Patients with advanced CRC undergoing palliative chemotherapy were prospectively recruited from the Christie Hospital, Manchester, UK between February 2011 and April 2012. The study was approved by a local research ethics committee. Plasma samples were collected before (TP1) and 6 weeks after (TP2) chemotherapy for each patient. *KRAS* mutation status in plasma was assessed using KRAS RGQ PCR. Tumor mutation status was examined by pyrosequencing and/or KRAS RGQ PCR.
Results: Matched tumor/plasma (taken at both TP1 & TP2) *KRAS* mutation data was available in 30 patients. Ten patients (33%) had *KRAS* mutations in tumor. Of those, 8 (80%) had the same mutation in TP1 plasma. Of 20 patients with *KRAS* wild type tumor, a *KRAS* mutation was found in TP1 plasma of one patient. Sensitivity of plasma *KRAS* mutation detection was 80% and specificity 95%. Concordance between TP1 plasma and tumour *KRAS* mutation status was 90%. Of 11 patients who achieved partial response to chemotherapy (by CT scan after 6 cycles of 2 weekly chemotherapy), 5 patients had detectable plasma *KRAS* mutation in TP1 but only 1 (20%) had persistent mutation at TP2. In contrast, of 9 patients who had progressive disease, 4 patients had mutation in TP1 plasma which remained detectable in 3 (75%) at TP2. In 22 patients whose tumor *KRAS* mutation was examined by both KRAS RGQ PCR and pyrosequencing, tumor mutation status was 100% concordant between the two methods.
Conclusions: *KRAS* mutation can be detected in plasma of advanced CRC patients with high sensitivity and specificity using therascreen® KRAS RGQ PCR Kit in this exploratory study. Longitudinal monitoring of *KRAS* mutation status in plasma may help identify patients who are unlikely to respond to anticancer treatments early in the course of their treatments.
Conflict of interest: *Ownership: AstraZeneca Pharmaceuticals,Qiagen Ltd. Other substantive relationships: Employees*

2421 POSTER

The prognostic value of total cell free DNA measurement in patients with heavily pre-treated metastatic colorectal cancer treated with gemcitabine and capecitabine

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Background: Translational research is important regarding all clinical investigations, and our previous data have shown promising results for cell-free DNA (cfDNA) measurements in mCRC. Patients with chemotherapy refractory metastatic colorectal cancer (mCRC) have no established treatment options when standard chemotherapy with 5-FU, oxaliplatin and irinotecan or new biological agents fails. Gemcitabine acts synergistically with fluoropyrimidines and the combination is known to be clinically active in patients with mCRC and has an acceptable toxicity profile. Capecitabine is orally administered and convenient for treatment in this setting. The present study aimed to investigate the efficacy and safety of the combination of capecitabine and gemcitabin (GemCap) in heavily pre-treated, therapy-resistant mCRC patients and to validate previous observations of the clinical importance of cell-free DNA measurement.
Methods: Inclusion criteria comprised: histopathologically verified mCRC refractory to standard chemotherapy, adequate organ function and performance status. Patients received capecitabine (2000 mg/m^2 day 1−7 q2w) and gemcitabine (1000 mg/m^2 day 1) until progression or unacceptable toxicity. Plasma was obtained from a pre-treatment EDTA blood-sample, and the number of DNA alleles was assessed using an in-house qPCR as previously described.
Results: Forty-nine patients were included and GemCap was well tolerated. The rate of disease control was 30% at three months, and the median PFS and OS by intention to treat analysis were 2.7 (95% CI 2.6−2.8) and 6.8 (95% CI 5.0−7.7) months, respectively. Data showed impaired survival with increasing levels of cfDNA at baseline, and the median OS in patients with cfDNA concentrations above the median of 13200 alleles/ml was 4.7 months (3.7−9.6 mo) compared to 7.8 months in the remaining patients (HR 2.22 (1.07−3.9), $p = 0.0186$). The prognostic value was confirmed in a multivariate analysis.
Conclusions: GemCap was well tolerated with moderate but encouraging efficacy, and data revealed shorter OS with increasing levels of pre-treatment cfDNA, which could serve as a new prognostic marker in mCRC. Further investigations of both aspects are justified.
No conflict of interest.

2422 POSTER

Prediction of mitomycin C sensitivity in peritoneal metastases of colorectal carcinoma

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Background: Patients with peritoneal metastases (PM) originating from colorectal carcinoma (CRC) are curatively treated by cytoreductive surgery (CRS) and hyperthermic intra-peritoneal chemotherapy (HIPEC) with Mitomycin C (MMC). We aim to improve patient selection and personalize treatment for patients treated with HIPEC by predicting MMC sensitivity.
Methods: MMC sensitivity was determined *in-vitro* for 12 CRC cell lines using two separate assays. This was correlated to mRNA expression levels of 36 known genes related to the Fanconi Anaemia-BRCA pathway, ATM-ATR pathway and enzymatic activation of MMC. We also determined Fanconi Anaemia-BRCA pathway functionality in cell lines using chromosomal breakage assay and Western Blot for key protein FANCD2. Genes showing significant up- or downregulation on mRNA level were subsequently validated by staining for the corresponding protein with immunohistochemistry (IHC) on both CRC cell lines and patient material.
Results: In 12 CRC cell lines two out of 36 analyzed genes showed significant correlation between MMC sensitivity and mRNA expression. Sensitivity to MMC correlated with a decrease in BLM ($p = 0.01$) and BRCA2 ($p = 0.02$) mRNA expression levels. Chromosomal breakage assay showed no correlation to MMC sensitivity nor did FANCD2 protein expression, indicating no effect by BRCA2. BLM IHC staining in cell lines, showed that weak intensity correlated with high sensitivity to MMC ($p = 0.04$). This effect was also found in patient material: High BLM protein expression was significantly correlated to a decrease in overall survival in patients with minimal residual disease after CRS and HIPEC ($p = 0.04$).
Conclusion: Analysis of 36 known genes related to the Fanconi Anaemia-BRCA pathway and enzymatic activation of MMC correlated to MMC sensitivity, revealed that BLM expression, not FA-BRCA functionality, corresponds with MMC sensitivity. Moreover, high BLM protein expression was negatively correlated to survival in patients with minimal residual disease after CRS and HIPEC. BLM could be a potential clinical predictive biomarker for PM with CRC.
No conflict of interest.

2423 POSTER

Predictive value of plasma angiopoietin-2 level in metastatic colorectal cancer patients treated with anti-VEGF containing chemotherapy

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Background: Angiogenesis is a complex process implicated in carcinogenesis and associated with tumor progression. Nevertheless, specific prognostic biomarkers related to angiogenesis are still lacking in metastatic colorectal cancer (mCRC) patients. Angiopoietin-2 (Ang-2) is a ligand of Tie-2 receptor involved in the regulation of vascular remodeling. Then, we decided to monitor the prognostic value of baseline level of plasmatic Ang-2 in prospective studies of mCRC patients treated with bevacizumab.
Material and Method: Plasmatic Ang-2 was measured in healthy volunteers, and in patients with first-line mCRC treated with bevacizumab containing chemotherapy in a prospective phase 2 clinical trial (training cohort). Plasma samples of the patients were taken at baseline. Enzyme-linked immunosorbent assays (ELISA) were used to measure Ang-2 in plasma samples (sensitivity: 21.3 pg/ml). We determined cut-off value of Ang-2 levels using ROC curve for treatment response. A second set of 132 mCRC patients prospectively included in multicentric clinical trial (STIC-Avastin study) was used as a confirmatory cohort.
Results: In our training cohort, Ang-2 levels remained below 5ng/mL in all normal volunteers ($n = 20$) and all stage II−III CRCs ($n = 20$). Ang-2 level was significantly higher in patients with mCRC ($n = 51$) compared to healthy controls and stage II−III CRCs ($p = 0.03$). There was no significant difference between high Ang-2 level (Ang-2 high, >= 5ng/ml) and low baseline plasma Ang-2 level (Ang-2 low, <5ng/ml) regarding age, sex, *KRAS* status and metastatic sites. Median progression-free survival (PFS) and overall survival (OS) were significantly prolonged in patients with low Ang-2 levels (13.7 vs. 7.7 months, $p < 0.01$; and 36.6 vs. 7.7 months, $p < 0.001$; respectively). Response rate was also higher in patients with low Ang-2 levels (71.4 vs. 28.6%; $p = 0.06$).
These results were validated in an independent confirmatory cohort. In this cohort, median PFS and OS were significantly prolonged in patients with low Ang-2 levels compared to patients with Ang-2 levels higher than 5ng/mL (11.8 vs. 8.6 months, $p < 0.001$; and 28.2 vs 15.7 months, $p < 0.001$; respectively). In multivariate analysis, Ang2 levels and metastatic surgery were the only independent factor for PFS and OS.
Conclusion: These results underscore the negative impact in terms of response rate, PFS and OS of high baseline plasma levels of Ang-2 in mCRC treated with bevacizumab containing therapy.
No conflict of interest.

2424 POSTER

RAC1b and activated Insulin-like growth factor receptor as markers of resistance to cetuximab and panitumumab in metastatic colorectal cancer

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Introduction: Rac1b (a splicing activated form of Rac1) constitute an alternative survival pathway to oncogenic KRAS in mCRC (Matos et al, 2009). IGF-1R activation may result in resistance to anti-EGFR targeted treatment. We examined potential correlations between markers related to activation and location of p-IGF-1R and Rac1b expression pathways and clinical benefit from the anti-EGFR monoclonal antibodies plus irinotecan in pre-treated mCRC patients (pts).
Methods: A cohort of 54 pre-treated mCRC pts, who were treated with cetuximab (C) or panitumumab (P) plus irinotecan as second or third-line, was tested for anti-pY1316 antibody (provided by M. Rubini) IGF-1R and Rac1b immunoreactivity (ie, immunohistochemistry [IHC]) and KRAS and BRAF mutations. The association among IHC (p-IGF-1R, Rac1b), KRAS and BRAF mutational status on both, primary tumor and paired metastases, and treatment outcomes were investigated.
Results: Forty-five (14 KRAS mutant, 3 BRAF mutant and 28 WT/WT for KRAS/BRAF) of 54 pts were evaluable for concordance analysis. Phospho-IGF-1R show a similar pattern of IHC expression in primary and paired metastases (76−67% peri-nuclear, 12−10% apical-membrane and 12−22% peri-nuclear associated with apical-membrane) respectively. 14% of pts also show concomitant nuclear p-IGF-1R (np-IGF-1R) staining. The percentage of np-IGF-1R expression increases in metastatic samples compared with primary tumors in 67% of pts. Levels of concordance between primary tumors and paired metastases were 45%, 62% and 83% for Rac1b, p-IGF-1R and np-IGF-1R respectively. Phospho-IGF-1R and np-IGF-1R status on primary tumors or metastases, did not predict response or progression free survival (PFS). 6/23 (26%) metastatic samples with KRAS wt and low Rac1b expression were responders, compared with 0/11 (0%) that showed high Rac1b immunoexpression ($p = 0.022$). The median PFS of patients with Rac1b-positive metastases was 3.1 months compared with 4.7 months for those with Rac1b-negative metastases ($p = 0.29$).
Conclusion: Percentage of np-IGF-1R expression increases in metastatic samples compared with primary tumors. Rac1b positive expression in metastases may be predictive of resistance to anti-EGFR antibodies in WT KRAS pts.
No conflict of interest.

2425 POSTER

Drug-disease model of tumor size and overall survival in metastatic colorectal cancer patients treated with cetuximab administered weekly or every second week

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Background: Cetuximab, administered in a standard weekly regimen (q1w) with first-line chemotherapy (CT) can improve tumor response and overall survival (OS) in metastatic colorectal cancer (mCRC) pts. Cetuximab (400 or 500 mg/m^2) every second week (q2w) was safely administered with reported activity in mCRC pts. Tumor size (response) and OS were further studied in a drug-disease model.
Material and Methods: A pharmacokinetic (PK)-disease model of tumor size was constructed (using NONMEM7.2) in a pooled analysis of mCRC pts from the 502 (EVEREST, second-line CT + cetuximab q1w) study, and 045 and CECOG/CORE.1.2.002 (CORE) studies (both first-line CT with either cetuximab q1w or q2w). The model estimated changes in tumor size from baseline for early tumor shrinkage (ETS, % change in tumor size at wk 8) and time to tumor (re)growth (TTG, time to smallest tumor size). Covariates were examined including the effects of cetuximab q1w and q2w regimens. ETS and TTG were tested as predictors of OS using Cox models.
Results: 369 pts from the 3 studies provided 3821 PK, 2053 tumor size and 233 death observations. Tumor size model fit was very good. Excluding study 502 (irinotecan-refractory pts), covariate analysis identified study (baseline tumor size was 32% lower in the CORE study; $p < 0.01$) and *KRAS* status (treatment was 43% less effective in *KRAS* mutated tumors; $p < 0.01$) as significant. TTG ($p = 0.12$) and ETS ($p = 0.28$) were not markedly different between the q2w and q1w regimens, were positively correlated (Spearman's rho=0.64), and were identified as individual predictors of OS. For ETS and TTG, pts were grouped by low (L), intermediate (I), and high (H) terciles. In pts with *KRAS* wild-type tumors, OS was longer in the H-TTG (27 to 118 wk, median OS 31.4 mth) vs L-TTG group (0 to 11 wk, median OS 15.1 mth), or H-ETS (−66 to −22%, median OS 25.9 mth) vs L-ETS group (−9 to +2%, median OS 12.8 mth). In a Cox model excluding study 502 ($n = 215$, death=93), ECOG PS grouped as fully active or restrictive activity (RA, $p = 0.038$), TTG ($p < 0.001$) and baseline tumor size ($p < 0.001$) were independent predictors of OS. In a model including ETS, ECOG PS RA ($p = 0.0044$), ETS ($p = 0.013$) and baseline tumor size ($p = 0.0055$) were independent predictors of OS. Treatment regimen was not significant.
Conclusions: In this analysis changes in tumor size from baseline and OS were not significantly modified by the cetuximab dosing regimen in mCRC pts. The model identified TTG and ETS as predictors of OS.
Conflict of interest: *Ownership: Merck Serono S.A. (PG, employment AM, employment)Merck KGaA (AK, employment BB, employment MZ, employment MS, employment RE, employment and stock ownership). Advisory board: Amgen, Boehringer, Bristol-Myers Squibb, Genentech, Imclone, Lilly, Merck KGaA, Millennium, Novartis, Onyx, Pfizer, Roche, Sanofi, Celgene (JT). Corporate-sponsored research: Merck Serono (EVC). Other substantive relationships: Merck KGaA (TB, honoraria)Amgen, Merck KGaA, Novartis, Roche, Sanofi (JT, honoraria)*

2426 POSTER

Death Associated Protein-1 (DAP-1) is associated with the clinical outcome of the patients with colorectal cancer and its role in the regulation of cell death

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Background: Death Associated Protein-1 (DAP-1), is a member of the DAP family and has been indicated in the regulation of cell growth and death including that of cancer cells. Its clinical value in patients with cancers has been reported in recent years. However, the role of DAP-1 in clinical cancer and the regulation of colorectal cancer cells is largely unknown. The present study investigated the expression profile of DAP-1 in human colorectal cancer and the impact of DAP-1 on the apoptosis and cellular response to 5-FU.
Materials and Methods: Human colorectal cancer fresh frozen specimens ($n = 94$) were used for gene transcript analysis and immunohistochemical analysis of DAP1. Expression of DAP1 was analyse against patients clinical, pathological and outcome features. Human colorectal cancer cell lines HRT18 and HT115 cells were used in *in vitro* studies. DAP-1 knockdown cells were generated using anti-DAP-1 transgenes. The cellular functions including cellular growth, migration and apoptosis were evaluated on these cells, together with the cells response to chemotherapeutic drugs.
Results: Human colorectal cancer tissues had lower levels of DAP-1 compared with normal tissues. The reduced levels were associated with higher Dukes staging and lymph node metastasis. Patients with low DAP-1 expression had a markedly reduced overall survival ($p < 0.01$). Together with grade, TNM staging, DAP1 were independent prognostic factor in the patients. Loss of DAP-1 in colorectal cancer cells resulted in a gain in cellular migration and loss of their sensitivity of apoptosis to chemotherapeutic agent, 5-FU.
Conclusions: DAP-1 is correlated with the disease progression and long term survival of the patients. It is also a pivotal regulator of the growth and apoptosis and cellular response to chemotherapy agents.
No conflict of interest.

2427 POSTER

Ultra-deep sequencing of plasma, matched primary tumor and matched liver metastasis in 16 patients with metastatic colorectal cancer reveals significant differences in the mutation pattern of these three tissue types

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Background: Sequencing of circulating, cell-free DNA (cf-DNA) from plasma of cancer patients (pts) is a promising new field in cancer diagnostics and personalized oncology. This technology would allow to determine the mutation status of important driver genes in the plasma of patients rather than in the primary tumor or in the metastatic (mets) tissue. As it is often difficult or unethical to obtain mets tissue from pts by biopsies plasma samples which are readily available represent an attractive alternative. Here we report on a feasibility study in metastatic colorectal cancer and show ultra-deep sequencing of plasma samples side-by-side with matched primary tumor and metastatic tissues.
Material and Methods: For this proof-of-principle study 16 pts with metastatic CRC (mCRC) were selected from a total of 1400 mCRC patients that are part of our prospective multicenter MSKK study with 40 hospitals in Germany. These 16 pts were selected on the ground that matched plasma, primary tumor and liver metastasis tissues were available in our MSKK biobank. All 16 pts had undergone surgical resection of the liver mets and the primary tumor. Blood was drawn from these 16 pts prior to surgery: 7 male, 9 female; 50−79 years of age (median: 66); 12 colon, 4 rectum tumors; no neo-adjuvant therapy. Cf-DNA was isolated from 2 ml of EDTA plasma using QIAamp kit (Qiagen). In parallel DNA was isolated from 16 matched pairs primary tumor and liver metastasis tissue and showed a minimum tumor cell content of 15%. For ultra-deep sequencing of the plasma samples and matched primery tumors a panel of 49 highly multiplexed amplicons (IonAmplicon, LifeTechnologies) representing 10 important driver genes was designed. For sequencing the liver mets and matched primary tumors a different custom panel of 37 driver genes (120 amplicons) was designed and used.
Results: In 6/18 pts (33%) no differences in mutations pattern were observed between plasma, primary tumor and mets tissue. In 12/18 pts significant differences in the mutations pattern were found. In two pts the primary tumor and the mets tissue had the same additional mutation (case 1: SMAD4 S138*, case 2: KRAS G12A) that was not present in the plasma. In six pts the plasma showed additional APC or TP53 mutations not present in the primary and mets tissue. In one case the primary tumor only showed two additional mutations (APC Q1406* and FBXW7 R465H) that were not present in plasma or mets tissue. In pts 68177 both the plasma and the liver mets had an additional TP53 A276T mutation which was not present in the primary tumor. The plasma though did not show the KRAS Q61K mutation that was identified in the primary and mets tissue. In addition, the mets tissue had a PTEN R173C mutation that was not present in the plasma and primary. In pts 6816 the plasma and mets tissue displayed an additional PIK3CA E545K mutation in addition to a KRAS G12V and APC R1450X mutation that was present in all three tissue types. The primary tumor had on top a TP53 C275F mutation.
Conclusions: Ultra-deep plasma sequencing side-by-side with matched liver mets and primary tumor tissue can be used to identify de-novo actionable mutations in the plasma not present in the primary tumor. This

technology holds promise to change the diagnostic practise in mCRC patients.
Conflict of interest: *Ownership: Signature Diagnostics AG. Other substantive relationships: Employment, stock ownership*

2428 POSTER

Increased TGFa as a mechanism of acquired resistance to the anti-EGFR inhibitor cetuximab through EGFR–MET interaction and activation of MET signaling in colon cancer cells

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Background: Although cetuximab, an anti-EGF receptor (EGFR) monoclonal antibody, is an effective treatment for KRAS wild type metastatic colorectal cancer (mCRC) patients, its clinical use is limited by onset of resistance.
Material and Methods: We characterized a CRC model to study the mechanisms of acquired resistance to cetuximab.
Results: Following chronic treatment of nude mice bearing cetuximab-sensitive human GEO colon xenografts, cetuximab-resistant GEO cells (GEO-CR) were obtained. In GEO-CR cells proliferation and survival signals were constitutively active despite of EGFR inhibition by cetuximab treatment. Whole gene expression profiling identified a series of genes involved in the hepatocyte growth factor HGF-MET-dependent pathways, that were up-regulated in cetuximab-resistant GEO-CR cells. Further, activated, phosphorylated MET was detected in GEO-CR cells. Inhibition of MET expression by siRNA restored cetuximab sensitivity in GEO-CR cells, whereas exogenous activation of MET by HGF stimulation in cetuximab-sensitive GEO cells induced resistance to cetuximab. Treatment of GEO-CR cells with PHA665752, a selective MET inhibitor, inhibited cell growth, proliferation and survival signals and impaired cancer cell migration. Overexpression of transforming growth factor α (TGFa), a specific EGFR ligand, was involved in the acquisition of cetuximab resistance in GEO-CR cells. In fact, TGFα overexpression induced the formation of EGFR–MET *heterodimers*, with subsequent MET phosphorylation and activation of MET down-stream effectors in GEO-CR cells.
Conclusions: These results suggest that overexpression of TGFα through induction of EGFR–MET interaction contributes to cetuximab resistance in CRC cells. The combined inhibition of EGFR and MET receptor could represent a strategy for preventing and/or overcoming cetuximab resistance in CRC patients.
No conflict of interest.

2429 POSTER

Exposure to nintedanib, a triple angiokinase inhibitor, is accompanied by activation of EGFR and other ErbB/HER-family members in colorectal cancer (CRC) models, providing a rationale for combinations of nintedanib with the ErbB family blocker afatinib

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Background: Combinations of EGFR and VEGF(R)-targeted agents have consistently shown at least additive activity in preclinical CRC models when the targeted agents were administered alone. We have recently shown that combinations of afatinib, a pan-HER/ErbB family blocker and nintedanib, a triple angiokinase (VEGFR, FGFR, PDGFR) inhibitor show synergistic activity in CRC models (*Poindessous et al., Clin Cancer Res 17:6522, 2011*). However, the mechanistic basis for the synergistic effects of the combination is incompletely understood. EGFR is activated following exposure to a wide range of therapeutic modalities including ionizing irradiation and irinotecan. We speculated that nintedanib exposure could also activate EGFR signaling which might explain the synergistic activity of the combination.
Material and Methods: Mice with human CRC xenografts were treated with nintedanib and afatinib alone or in combination and the influence on tumor growth, viability and the presence of phosphorylated HER family members was determined. Different scheduling regimens were explored to identify an administration schedule which combined optimal antitumor activity with minimal toxic side effects. Finally, the combination was tested in three CRC xenograft models with mutant *KRAS* status.
Results: We here show that nintedanib treatment results in activation of EGFR and HER2 in multiple CRC xenograft models in a dose-dependent manner. Among the different regimens tested, continuous nintedanib with administration of afatinib every second week proved almost as efficient as continuous administration of the two agents together and was less toxic. Furthermore, the proportion of apoptotic cells, as measured by the TUNEL assay, was compatible between the two regimens. Finally, nintedanib plus afatinib was superior to nintedanib alone in three different tumor xenografts with mutant *KRAS*.
Conclusions: We here report that prolonged exposure to nintedanib, a small molecule angiogenesis inhibitor, is accompanied by activation of EGFR and HER2. Accordingly, afatinib, an ErbB family blocker, was synergistic with nintedanib. We subsequently identified a novel regimen for optimizing the antitumor effects of the combination with limited toxic side effects and showed that this regimen is active in four different CRC tumor models including three with mutant *KRAS*. These findings provide a rationale for clinical trials of the two small molecules.
Conflict of interest: *Advisory board: AdG. Corporate-sponsored research: AKL, AdG*

2430 POSTER

The detection of low frequency KRAS mutant alleles by pyrosequencing predicts the response to EGFR therapy in metastatic colorectal cancer

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Background: KRAS mutational status is the only biomarker routinely used to select EGFR therapy in metastatic colorectal cancer (mCRC), with direct sequencing (DS) being the gold standard for the detection of KRAS mutations. However, other high sensitive technologies have been proposed, and, among others, pyrosequencing (PS), but, at present, the level of test sensitivity which is required to provide predictive information in clinical practice is still in question.
Patients and Methods: A retrospective analysis of KRAS codons 12 and 13 mutations by PS and DS was performed in 192 mCRCs to evaluate whether PS may improve the predictive value of KRAS mutational status.
Results: DS failed to detect KRAS mutations in 4/31 mCRCs with low frequency of mutated alleles, whereas PS allowed the detection of an additional 12 low frequency KRAS mutations in 141 mCRCs KRAS-wild type at DS. After analyzing the cohort of 97 KRAS-wild type tumors treated with anti-EGFR antibodies, 9 additional mutations were revealed in the non-responders, whereas none of the responders exhibited a KRAS-mutated genotype upon PS re-evaluation. Of note, KRAS-mutated tumors upon PS re-evaluation showed a worst progression free survival after EGFR therapy. Finally, KRAS-wild type mCRCs with both technologies, but primarily resistant to EGFR therapy, exhibited 3 BRAF and 5 exon 20 PIK3CA mutations which were absent in the responder subgroup.
Conclusions: The capacity of PS to detect low frequency of mutant alleles suggests that it may improve the KRAS predictive value for the selection of anti-EGFR agents.
No conflict of interest.

2431 POSTER

Prognostic value of incidental betablockers use in metastatic colorectal cancer patients receiving first-line treatment: An update

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Background: Preclinical and retrospective studies suggested an antitumor activity for the incidental use of anti-hypertensive betablockers in various tumour types, reducing metastasis, tumor recurrence and increasing survival. Data regarding colorectal cancer are lacking. We tried to assessed the correlation between the incidental use of betablockers and clinical outcome in colorectal cancer patients receiving first-line therapy.
Material and Methods: 250 colorectal cancer patients, treated with first-line chemotherapy alone (135 patients) and with chemotherapy plus Bevacizumab (115 patients), were analysed for progression free survival and overall survival, using the Kaplan–Meier method. A p value <0.05 was considered for statistical significance. Patients were stratified for betablockers use, age, sex, site of metastases, previous adjuvant chemotherapy and ECOG performance status.
Results: 31 patients (12%) were on treatment with betablockers at the time of first-line therapy: 22 (16%) in the chemotherapy alone group and

9 in the bevacizumab group (8%). In both groups patients receiving or not betablockers were similar for all main clinical characteristics. In the chemotherapy alone group, patients receiving betablockers showed an improved RR (60% vs. 33%, p = 0.044) and overall survival (mOS 41.3 vs 25.7 months, p = 0.03, HR:2.26, 95% CI: 1.05–3.24). Only a trend for improved progression free survival was noticed.
In the 115 patients receiving chemotherapy with bevacizumab a trend towards a worse overall survival was seen for patients receiving betablockers, although this was not statistically significant (mOS 16 vs 23.7 months, p = 0.26, HR:0.64, 95% CI: 0.22–1.49). No significant differences were seen in regards of progression free survival or different response rate patterns between the two groups.
Conclusions: Our analysis confirms a potential prognostic role for the use of betablockers in colorectal cancer patients treated with chemotherapy. Our findings are in line with preclinical studies suggesting that beta-adrenergic signalling may regulate cancerogenesis and tumor invasiveness. Our analysis suggests a potential worse outcome for patients on betablockers receiving Bevacizumab-based treatment, although the small number of patients precludes any definitive conclusion. We suggest that in future prospective trials the incidental use of betablockers will be considered a stratification factor for clinical outcome.
No conflict of interest.

2432 POSTER

Thymidine phosphorylase induction with chemotherapy in metastatic site as predictive marker for response to chemotherapy and survival: Analysis of six biomarkers in primary site and liver metastatic site of colorectal cancer

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Background: Some groups have evaluated the predicative relevance of several biomarkers on the response to chemotherapy and the survival of patients with metastatic colorectal cancer (mCRC). But the association of expression of such biomarkers between primary tumor site and chemotherapy-treated metastatic site, is not known. In this study, we assessed the difference of expression of molecular biomarkers between primary site and liver metastatic site treated with chemotherapy in mCRC.
Materials and Methods: We analysed 43 mCRC patients with liver-limited disease from January 2007 to November 2011. They all received resection of primary tumors followed by oxaliplatin-based chemotherapy. After chemotherapy, they all received secondary hepatic resection. Total 86 RNA was derived from paraffin-embedded primary and metastatic tumor specimens to measure mRNA expression of six biomarkers (thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), excision repair cross complementing gene 1 (ERCC1), thymidine phosphorylase (TP), folylpolyglutamate synthase (FPGS), and regenerating islet-derived family, member 4 (REG4)), using Danenberg Tumor Profile (DTP) method.
Results: 36 good quality tumor mRNA were identified. High TP expression in liver metastatic site, and ratio of TP expression in liver metastatic site to primary site (L/P ratio) were significantly associated with response to chemotherapy (P = 0.046 and 0.038, respectively). And L/P ratio of TP, TP expression in primary site, DPD in primary and metastatic sites, REG4 in primary site were significantly associated with overall survival (OS). (P = 0.039, 0.045, 0.016, 0.032, 0.022, respectively) In multivariate analysis, high DPD expression in primary site was significant poor prognostic factor of OS (HR: 9.66 (95% CI: 1.04–89.52), P = 0.046).
Conclusions: High L/P ratio of TP was significantly associated with response to oxaliplatin-based chemotherapy and survival. It may be useful predictive biomarker of survival, and potential indicator for the individualization of postoperative chemotherapy for mCRC patients.
No conflict of interest.

2433 POSTER

Peripheral CD45RO, PD1, and TLR4 expression in metastatic colorectal cancer patients treated with bevacizumab/5FU/irinotecan (B-FOLFIRI)

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Background: CD45RO, PD1 and TLR4 immune pathways have proven pivotal in regulating antitumour response and correlate with survival for localised colorectal cancer (CRC). We evaluated if their peripheral expression was associated with outcome in metastatic (m) CRC.
Material and Methods: 31 mCRC patients (Male:Female=13:18, colon:rectum=26:5, median age=69 years) were eligible for this prospective study (clinicaltrial.gov registration NCT01533740) and treated between april 2010 and may 2011 with standard firstline B-FOLFIRI (n. of administered cycles: median 12, range 3−24). Blood was drawn before the first and third cycle, and analysed by flow cytometry for frequency(%) of CD4+,CD8+,CD45RO+and PD1+mononuclear cells and for TLR4 expression on neutrophils.
Results: A trend towards increased CD45RO expression was seen after two cycles (median CD45RO+cell% from 55% to 57%, Wilcoxon test p-value: 0.09). At survival analysis, pre-third-cycle (ptc) CD45RO+CD8+cell% displayed a significant association with progression-free Survival (PFS) (median PFS 22.4 vs 9.4 months and 1 year PFS rate 80% vs 33% for patients with CD45RO+CD8+cell% > vs < the median value of 12%, respectively, HR 0.30, p 0.02). Patients with high ptc-CD45RO+CD8+cell% had also prolonged overall survival (OS) (2 year OS rate 70% vs 44% for CD45RO+CD8+cell% > vs <12%, respectively). Surprisingly, ptc-PD1 overexpression was also associated with improved PFS (HR 0.31, p 0.02). A Cox-regression multivariate analysis for PFS including ptc-CD45RO+CD8+, ptc-PD1+cell%, CEA, CA19.9, LDH and Köhne risk class demonstrated low ptc-CD45RO+CD8+cells to be the strongest independent prognostic factor (HR 6.95, p 0.02). Moreover, the trend of CD45RO+CD8+cell% after two cycles (increase vs decrease) significantly correlated with RECIST response rate (83% v 14%, p 0.01). TLR4 was not associated with outcome.
Conclusions: CD8+CD45RO+ cells were confirmed to be of independent prognostic value in mCRC patients. Overexpression of the PD1 immunosuppressor after two cycles may be an indirect sign of a triggered antitumour response (negative feedback) and thus be associated with better outcome. Enhancement of CD8+CD45RO+immune response may be a fascinating therapeutic target to improve efficacy of standard chemotherapy.
No conflict of interest.

2434 POSTER

Gastric differentiation markers expression in ulcerative colitis-associated dysplasias

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Background: It is predictable that we can easily calculate the increase in colorectal cancer (CRC) patients complicating ulcerative colitis (UC) with the increasing prevalence of UC. The development of carcinoma in patients with UC has been thought to be involving precursor stages of low- and high-grade epithelial dysplasias against inflamed colonic mucosa. No definite strategies for detection of dysplasias which are potentially progressive to carcinoma in longstanding UC patients have established yet. For practical purposes, the useful markers to detect potentially progressive lesions of dysplasia in longstanding UC patients are required. Gastric-type mucin secretion has been reported to be affected in inflammatory bowel disease. Recent identification of several mucin genes could contribute to the differential diagnosis between UC-associated neoplasms and sporadic CRC. We have herein described the obviously frequent expression of gastric differentiation markers, such as human gastric mucin (HGM), MUC5AC and pS2 in lesions of dysplasia and the surrounding mucosa around tumours with 4 patients(case1−4) of UC accompanying advanced colorectal cancer already.
Materials and Methods: Immunohistochemical examination for gastric phenotypic markers was carried out using an ENVISION/HRP kit (DakoCytomation, Glostrup, Denmark) after antigen retrieval by autoclaving was performed with the following monoclonal antibodies, (clones, dilution): HGM (45M1, 1:50), MUC5AC (CLH2, 1:100), and pS2 (NCL-pS2, 1:200). Immunopositivity was designed as sporadically positive (1+) when <5% of cells were positive, focally positive (2+) when 5−50% cells were positive, and diffusely positive (3+) when >50% cells were positive.
Results: All patients underwent surgical treatment because of having advanced cancer (case2, 3: Total colectomy and case1, 4: partial colectomy). Case 3 and 4 were almost diffusely positive for all gastric-type markers, and case 1 and 2 were partly diffusely positive. HGM expression was also detected diffusely or partly in goblet cells in surrounding mucosa around dysplasias in all cases, which was not showed in the epithelium away from disease.
Conclusions: Our results suggested that gastric differentiation markers expression is potentially useful for the easy detection of UC-associated dysplasias potentially progressive to carcinoma, which contributes to clarify the characteristics of UC-associated colorectal carcinogenesis as well as the good prognosis of UC-associated neoplasms.
No conflict of interest.

2435 POSTER

Interim results of observational study to determine K-ras mutation rates in patients with metastatic colorectal cancer in Turkey (TURKRAS study)

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Background: K-ras mutation in metastatic colorectal cancer (mCRC) patients is an important bio marker in determining the response to targeted therapies. In our study, primarily we aimed to investigate the frequency of K-ras mutation in colorectal cancer patients in Turkey, and secondly to determine the frequency of sub-types of the K-ras mutation and the regional distribution of this distinction, and the relationship between demographic characteristics.
Material and Methods: Prospective, single-arm, multi-center, non-comparative, case-based, epidemiologic observational study of one year duration. All samples for K-ras examination were evaluated by an accredited, independent central laboratory in Turkey and data were recorded in a collective data base to provide reliability. Written informed consent was obtained from all patients. The laboratory procedures to be performed for pathologic specimens obtained from the patients are sample preparation, DNA isolation, amplification by polymerase chain reaction method and identification of the mutations in codons 12 and 13 of the K-ras gene using minisequencing method. For statistical analysis chi-square test were used to perform comparisons of independent bilateral and multilateral categorical variables.
Results: We have planned to enroll 2500 metastatic colorectal cancer patients to the study from 52 centers in Turkey. This is the first interim analysis with the data obtained from 1106 patients. 40% of patients were female. Half of the patients (50.1%) were from Marmara region. Patients from other regions were distributed as the Aegean, the Middle and East Anatolia, the Mediterranean and Southeastern Anatolia, the Black Sea regions; and the percentage of patients included from these regions were 17.3%, 14.1%, 11%, and 7.5% respectively. The frequency of K-ras mutation in all patients was 45%. G12D mutation is the most common mutation (28.9%). There is no significant difference between the frequency of G12 and G13 mutations when compared according to gender and regional distribution. ($p>0.05$).
Distribution of mutations frequency according to gender and geography is shown in the table.
Conclusion: K-ras mutation frequency for Turkish population is compatible with other studies reported in the literature. In our study, G12D mutation the most common mutation seen in Turkish population and gender and regional distribution of mutations did not differ significantly. In addition to comparison of gender and geographical distribution of mutations, comparison of histopathological features and other demographic characteristics will be useful for appropriate treatment approach.
No conflict of interest.

(n, %)		Mutant (N = 498, % 45)	Wild Type (N = 608, % 55)	p
Gender	Female	208 (47.1)	234 (52.9)	0.268
	Male	290 (43.7)	374 (56.3)	
Region	Mediterranean and South East Regions	44 (36.1)	78 (63.9)	0.084
	Aegean Region	90 (47.1)	101 (52.9)	
	Middle and East Anatolia Regions	80 (51.3)	76 (48.7)	
	Black Sea Region	32 (38.6)	51 (61.4)	
	Marmara Region	252 (45.5)	302 (54.5)	

2436 POSTER

K-ras status in colorectal cancer tumors from 292 Saudi patients: Frequency, clinco-pathological association and clinical outcome

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Background: K-ras oncogene mutations are confirmed factor for lack of clinical benefit from antibodies targeting EGFR in patients with colorectal cancer (CRC). Mutations are reported in 40% of CRC tumors in western patients. There is scarcity of data on population from Asia and the Middle East. The primary endpoint of this study is to determine the frequency of K-ras mutation in Saudi patients with CRC. Secondary endpoint is association between clinico-pathological features and K-ras. Outcome of primary endpoint is presented in this report.
Patients and Methods: 292 consecutive patients diagnosed with CRC between September 2001 and April 2012 in 5 hospitals in western province of Saudi Arabia. K-ras status was determined at some stage of their disease as requested by treating oncologist. Clinical information was extracted retrospectively from paper and electronic records.
Results: Median age at primary diagnosis was 56 (20−87) years. Site of primary disease was available in 233 patients (rectum: 34%, left colon: 41% and right colon: 26%). AJCC staging at primary diagnosis was available in 264 patients (stage I: 1%, II: 26%, III: 20% and IV: 53%). K-ras was wild type in 173/293 patients (59.2%) and mutant type in 119/293 patients (40.8%). Site of codon mutation was reported in 105 out of the 109 mutant genes. Mutations were at codon 12 in 95/105 patients (90.5%) and at codon 13 in 10/105 patients (9.5%). Results of secondary endpoint will be presented at the meeting.
Conclusion: This is the largest study investigating K-ras status in Middle Eastern CRC patients. This series shows that rate of K-ras mutation and codon site of mutation in Middle Eastern Saudi patients with CRC is similar to what is reported in western Caucasian population.
No conflict of interest.

2437 POSTER

Tolerance and antigenic flare in chemoimmunotherapy of advanced colorectal cancer

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Background: In blood of cancer patients (Pts), autologous tumor antigens with immunotherapeutic activity have been described, but the development of procedures to translate such activity to medical practice has been difficult. In the past years, two phenomena that could improve the feasibility of autologous hemoderivative cancer vaccination have been reported.
First, the role of chemotherapy as releaser and presenter of autologous tumor antigens was monitored in Pts with colorectal cancer (CRC) treated with oxaliplatin (OX) through a flare of blood CEA levels. Second, the immunity tolerance, which is induced by carcinogenesis and it conditions the immunization failure to tumor antigens, was monitored through level of circulating T-regulatory cells (T-Reg).
In this study, we explored the correlation among OX effects on survival and antitumor immunity versus flare of CEA release and level of circulating T-Reg.
Methods: Data of 204 Pts from several reported clinical trials were analyzed. Characteristics: metastatic CRC, recurrent after surgery and adjuvant 5FU-chemotherapy, treated with OX and available CEA and T-Reg assessment in peripheral blood. Four groups were configured according to T-Reg high or normal, with or without CEA flare after OX. Statistical differences (ANOVA test) among the 4 groups were calculated: response, 1 year survival, and IFN-γ ELISPOT test challenged with an antigenic blood fraction that was previously described.
Results: See the table.
Conclusions: In this series, although small and retrospective, the prevalence of CEA flare and increased T-Reg has reproduced values previously reported. These parameters did not modify the response rate to OX, but 1-year survival was significantly higher in the group that associates CEA flare phenomena and not-High T-Reg level. The study suggests that the primary cytotoxic effects of chemotherapy could be prolonged by endogenous hemoderivative immunotherapy. This protective antitumor

immunity of chemotherapy would require an Immunomodulatory procedure which will be the target of future studies.
No conflict of interest.

Table: Colorectal cancer recurrence post surgery + adjuvant FU

Groups	Not CEA flare		CEA flare	
	T-Reg High (n = 98)	T-Reg Not-High (n = 16)	T-Reg High (n = 10)	T-Reg Not-High (n = 12)
IFN-γ ELISPOT + (%)	7.7	12.5	10.0	83.3
Response rate (%)	35.2	31.3	30.0	33.3
1 Year Survival (%)	50.0	56.3	50.0	91.7

CEA flare ⩾15% baseline after oxaliplatin. High/Not-High: ⩾/<2SD + mean normal control. IFN-γ ELISPOT +>10/10^5 PBMC. Response rate according to RECIST.

2438 POSTER

A randomised clinical trial of chemotherapy compared to chemotherapy in combination with cetuximab in k-RAS wild type patients with operable metastases from colorectal cancer: The new EPOC study

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Resection of liver metastases from colorectal cancer with or without neoadjuvant chemotherapy is the standard of care. The EPOC study (Nordlinger *et al.*, Lancet 2008) randomised patients between surgery and surgery with chemotherapy and demonstrated an improvement in 3 year progression free survival (PFS) of 7.3% (from 28.1% to 35.4%). As a rational extension to the EPOC study data, the New EPOC study evaluates the benefit of cetuximab, an EGF receptor antibody, in addition to standard chemotherapy in patients with operable liver metastases.
272 patients were randomised between February 2007 and November 2012 into the New EPOC study. Eligible patients were required to be k-RAS wild type, have operable liver metastases and to be sufficiently fit for chemotherapy and surgery. Patients with the primary tumour in situ, and those who required short course rectal radiation were eligible. Patients were randomised to receive a fluoropyrimidine and oxaliplatin plus or minus cetuximab. Patients who had been treated with adjuvant oxaliplatin could receive irinotecan and 5 − fluorouracil.
Following a recommendation from the Independent Data Monitoring Committee on 19/11/2012, the New EPOC study was stopped when the study met a protocol pre-defined futility analysis. With 45.3% (96/212) of the expected events observed, progression free survival was significantly worse in the cetuximab arm (14.8 vs 24.2 months, HR (95% CI) 1.50037 (1.000707 to 2.249517) p < 0.048).
It can be concluded that the addition of cetuximab to chemotherapy as neoadjuvant therapy for operable liver metastasis from colorectal cancer is unhelpful. Although the data are too immature to conclude that this approach is harmful, more events are unlikely to change this result, indeed the data are likely to become more significant over time. The addition of cetuximab to chemotherapy for k-RAS wild type tumours in this context is currently accepted clinical practice, but these data suggests that this approach is not beneficial. Updated data will be presented.
Conflict of interest: *Advisory board: Merck*

Proffered Papers Session (Tue, 1 Oct)
Gastrointestinal Malignancies − Noncolorectal Cancer

2450 ORAL

WISP2 is an independent prognosis indicator of gastric cancer patients and regulates the biological function of gastric cancer cells via the JNK pathway

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Background: WISP proteins (Wnt-inducted secreted proteins) are a subfamily of the CCN [Cyr61 (cysteine rich as a protein), connective tissue growth factor, and Nov (nephroblastoma overexpressed gene)] family of growth factors. The CCN family proteins share conserved multimodular domains with diverse biological functions, including angiogenesis, stem cell differentiation, and carcinogenesis. However, the role of WISP proteins in cancer cells and in clinical cancers remains controversial. The present project aimed to investigate the clinical relevance and the role of WISP played in human gastric cancer.
Materials and Methods: The expression of the three WISP molecules at the mRNA and protein levels in a cohort of 316 cases of human gastric cancers and normal gastric tissues were analysed using Q-RT-PCR and immunohistochemistry (IHC) assays respectively and correlated with the clinicolpathological features and clinical outcome of the patients. We also carried out genetic manipulation and created sublines from human gastric cancer cell lines, HGC27 and AGS, that differentially expressed the WISP molecules. The biological impact of differentially expressed WISP(s) on the biological functions, namely, cell growth, adhesion, migration and invasion, on the cells and potential mechanisms by which cells were influenced.
Results: WISP-2 and WISP-3, but not WISP-1 showed significant difference between normal tissues and tumours (P = 0.0009, P = 0.027 and P = 0.46, respectively). Expression of WISP2 was more interesting in that it was correlated with several clinicopathological parameters. Levels of the WISP2 transcript were found significantly lower in TNM1 and 2 stage tumours (P =0.012) compared with TNM3 and 4 stages, lower in T1 than in T4 tumours (P = 0.007), and significantly lower in node negative tumours than node positive tumours (P = 0.0029). IHC assay of WISP2 in corresponding gastric cancer pathological slides showed significant correlation with poor differentiation (P = 0.024). Using Cox Regression analysis, WISP2 protein was a significant independent prognosis indicator of gastric cancer patients (P = 0.018). In in-vitro studies, WISP2 gene was successfully knocked down in HGC27 and AGS cells. WISP2 knockdown resulted in significant change in the growth rate and in vitro invasiveness, with little effect on the adhesive capability, compared with its transfection controls This was found to be linked to the MMP activities, mediated by the JNK pathway.
Conclusion: WISP family proteins, in particular WISP-2, have different expression profile in gastric cancers and affects the biological functions of gastric cancer cells. The WISP family is therefore an important prognostic regulator in gastric cancer.
No conflict of interest.

2451 ORAL

Pilot study for a European upper GI cancer audit (EURECCA Upper GI)

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Background: In Europe, several countries have implemented audit programs to improve national care for oesophageal and gastric cancer patients. So far, no international comparisons have been made. Purposes of the present study were to compare patterns of care and outcomes in several European countries and to assess the possibility for a European Upper GI Cancer audit.

Methods: National data were obtained from cancer registries or clinical audits in the Netherlands, Sweden, Denmark, and England. Differences in 30-day postoperative mortality and two-year survival were analyzed between countries and between hospital volume categories, adjusting for available case-mix factors.
Results: Between 2004 and 2009, 10,854 oesophagectomies and 9,010 gastrectomies were registered. Resection rates varied widely between countries (18−30% for oesophageal, 22−42% for gastric cancer). Adjusted 30-day mortality after oesophagectomy was lowest in Sweden (1.9%, Table). After gastrectomy, adjusted 30-day mortality was significantly higher in the Netherlands (6.9%) compared with Sweden (3.5%) and Denmark (4.3%). Oesophagectomies and gastrectomies were performed in highest hospital volumes in Denmark, and in lowest hospital volumes in Sweden. Increasing hospital volume was associated with lower 30-day mortality after oesophagectomy and gastrectomy.
Conclusions: The present results confirm a volume-outcome relationship in oesophagogastric cancer surgery. However, differences in outcomes between several European countries could not be explained by existing differences in hospital volumes. To understand these differences in outcomes across Europe, a European Upper GI Cancer Audit (EURECCA Upper GI) with uniform data registration is currently developed.
No conflict of interest.

Table. Outcomes of oesophagogastric cancer surgery per country and per hospital volume category.

	Oesophagectomy				Gastrectomy			
	30-day mortality		2-year survival		30-day mortality		2-year survival	
		95% CI		95% CI		95% CI		95% CI
Absolute	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**
Country								
Netherlands	4.6	3.3–5.9	56.8	54.5–59.3	6.9	5.1–8.8	59.0	56.8–61.3
Sweden	1.9	0.0–3.8	61.0	54.6–68.0	3.5	1.5–5.6	59.0	54.2–64.3
Denmark	4.6	2.4–6.8	58.2	54.8–61.9	4.3	2.4–6.2	62.8	58.5–67.5
England	5.8	4.7–6.9			5.9	4.3–7.4		
Odds/hazard ratio	**OR**	**95% CI**	**HR**	**95% CI**	**OR**	**95% CI**	**HR**	**95% CI**
Annual hospital volume								
1−10 (ref.)	1.00	0.61–1.11	1.00	0.78–1.08	1.00	0.67–1.05	1.00	0.93–1.15
11−20	0.82	**0.50–0.93**	0.92	0.63–1.11	0.84	**0.41–0.99**	1.04	0.84–1.22
21−30/⩾21	**0.68**	**0.39–0.85**	0.84	**0.63–0.94**	**0.64**		1.01	
31−40	**0.58**	**0.42–0.72**	**0.77**	**0.66–0.96**				
⩾41	**0.55**		**0.79**					

Boldface indicates $P < 0.05$.

2452 ORAL

Clinical validation on the role of FDG-PET/CT in radiation treatment planning for patients with esophageal cancer

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Background: The aim of this prospective study was to determine the additional value of PET/CT for (chemo)radiotherapy treatment planning in esophageal cancer by assessing the proportion of patients in which locoregional recurrences (LRR) could have been prevented if PET/CT-based treatment planning was used instead of CT-based treatment planning.
Materials and Methods: Sixty-five esophageal cancer patients who were planned for high dose (chemo)radiotherapy, as primary treatment or in neo-adjuvant setting followed by surgical resection, were included in this prospective cohort trial (RESPECT). All patients underwent a planning FDG-PET/CT-scan. Radiotherapy target volumes were delineated on planning CT only and patients were treated according to the CT-based treatment plans. The PET images remained blinded. After treatment, the PET/CT was used to adjust the target volumes when appropriate. Follow up included routine CT-thorax/abdomen every half year. If LRR was suspected, an additional PET/CT was conducted in the original treatment position and the site of recurrence was compared to the original target volumes. If the recurrence was located outside or at the border of the CT-based clinical target volume (CTV) and inside the PET/CT-based CTV, we considered this as an event and as a possibly preventable.
Results: Based on the additional PET information, the gross tumour volume (GTV) was enlarged in 23% and reduced in 27% of the cases. The proportion of the PET/CT-based GTV which would be missed if the treatment planning was based on CT, was >5% in 28 patients (43%). The median follow up time was 27 months (95% CI 24.1–30.0). LRR were seen in 6 patients (9%), with synchronic distant metastases in 3 patients. All LRR were considered not preventable by the use of PET/CT, since 3 were located within the radiation-field, while in 3 the recurrences were located regionally, far from both the CT- and PET/CT-based CTV. Distant metastases were the most frequently reported first site of recurrence (35%).
Conclusion: In this prospective study, no preventable LRRs were found by the addition of FDG-PET/CT. Therefore, the additional value of PET/CT for the radiotherapy treatment planning for esophageal cancer remains limited in terms of prevention of LRRs.
No conflict of interest.

2453 ORAL

Evaluation of HER2 status in advanced or metastatic gastric, esophageal, or gastro-esophageal adenocarcinoma for entry to the TRIO-013/LOGiC trial of lapatinib in combination with capecitabine plus oxaliplatin

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Background: The human epidermal growth factor receptor (EGFR) type 2 (HER2) is commonly amplified and overexpressed in adenocarcinomas of the stomach, gastroesophageal junction (GEJ) and esophagus and is a potential target for therapeutic intervention. We report on the HER2 screening in a trial of lapatinib, a dual tyrosine kinase inhibitor of HER2 and EGFR, in combination with chemotherapy in advanced HER2-positive upper gastrointestinal (UGI) adenocarcinomas.
Material and Methods: Patients enrolled in this randomized, phase III trial had advanced, HER2-positive UGI adenocarcinomas as evaluated in local laboratories (Immunohistochemistry [IHC] 2+ and fluorescence in situ hybridization [FISH]-amplified, or IHC3+, or FISH-amplified) or a central laboratory (FISH-amplified). Patients were required to have tumor tissue submitted to a central laboratory for assessment of HER2 gene amplification by FISH (PathVysion) and expression by IHC (HercepTest) either for eligibility screening or confirmation of local result. The primary efficacy population (PEP) of the trial was composed of all patients whose tumors were centrally determined as HER2-amplified. The primary endpoint was overall survival in the PEP.
Results: Overall, 4674 patients underwent screening for eligibility; central HER2 testing was performed in 1995 patients for eligibility and 339 for confirmation of local result. Of the carcinomas screened by the central laboratory, 324 (16.2%) had *HER2* amplified disease. *HER2* genomic heterogeneity was evident in 2.1% of cases. In the patient cases centrally assessed, HER2 status by FISH and IHC is known for 1250 with 83.4% of amplified cases IHC3+/2+; 96.7% of non-amplified cases IHC1+/0. There were no cases that were IHC3+/FISH-negative. In total, 545 patients were accrued to the trial: 87.3% with gastric, 8.3% GEJ and 4.4% esophageal cancer. 487 patients were centrally confirmed as having HER2 amplified disease; 51 had HER2 non-amplified disease and HER2 amplification status was unknown in 7 patients. The concordance with central and local HER2 testing was 83%. In the 487 patients who comprise the PEP, 297 had cancers that were HER2 IHC3+ (61%), 108 were IHC2+ (22%), 54 were IHC1+ (11%), 27 were IHC 0 (6%), 1 was IHC unknown.
Conclusions: *HER2* is commonly amplified in adenocarcinomas of stomach, GEJ and esophagus and gene amplification is highly correlated with overexpression. While *HER2* genomic heterogeneity does occur, the prevalence rate is low.
Conflict of interest: *Ownership: T Grob and G Sauter have performed contract work for Abbot Molecular. C Ellis and S Santillana are employed by and hold stock in GlaxoSmithKline.D Slamon holds stock in Amgen and Pfizer. Advisory board: YJ Bang has performed consultancy/advisory work for GlaxoSmithKline. MF Press has performed consultancy/advisory work for GlaxoSmithKline, Roche, NanoString, Halozyme, Ventana and Genentech. DJ Slamon has performed consultancy/advisory work for Novartis and Sanofi-Aventis. Corporate-sponsored research: JR Hecht has received research funding from GlaxoSmithKline. MF Press has received research funding from Roche, Genentech and Ventana. Other substantive*

relationships: MF Press has received honoraria from GlaxoSmithKline, Roche, NanoString, Halozyme, Ventana and Genentech.

2454 ORAL

Influence of time interval from histologic diagnosis to chemotherapy (CTx) on benefit of chemotherapy for advanced pancreatic adenocarcinoma

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Introduction: In our previous study, we found that variation in time interval between diagnosis and CTx did not significantly affect survival (OS) in these patients (pts) (Teo et al, ASCO GI 2013, abstr 306), which might be due to less effective CTx or inherent aggressiveness of pancreatic adenocarcinoma. This follow-up study aimed to investigate if the time interval impacts on the benefit of CTx, based on landmark analysis of Irish population-based registry data.
Methods: Anonymised individual level data were obtained from National Cancer Registry of Ireland. Pts who underwent curative surgery were excluded. OS was calculated from diagnosis to death or last follow-up. Pts who started CTx within 28 days were compared to untreated pts surviving at least 28 days; Pts who started CTx between days 29 and 56 were compared to untreated pts surviving at least 56 days; and pts who started CTx between 57 and 84 days were compared to untreated pts surviving at least 84 days; Pts were analysed as per disease stage (M0 − non-metastatic vs M1 − metastatic vs Mx − unknown stage) and age (⩾70 vs <70 years old). Benefit of CTx was presented as Cox estimated hazard ratio (HR), controlling for age and M status, respectively.
Results: Between 1998 and 2010, a total of 4509 pts were identified. Median age group was 70−74 and 49.5% were males. 942pts (21.0%) received CTx. 28.1% of treated pts and 73.3% of untreated pts were ⩾70 ($p < 0.001$). Amongst treated pts, 21.3% were M0 and 53.9% were M1, compared to 15.0% M0 and 38.6% M1 in untreated pts ($p < 0.001$). 417 received CTx within 28 days of diagnosis, 317 between 29 and 56 days and 108 pts between 57 and 84 days. Time intervals between diagnosis and CTx and their influence on CTx benefit were tabulated below.

	CTx within 28 Days			CTx within 29−56 Days			CTx within 57−84 Days		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
M0	0.63	0.44–0.88	0.005	0.76	0.56–1.02	0.068	0.67	0.42–1.03	0.070
M1	0.70	0.60–0.82	<0.001	0.77	0.62–0.93	0.008	0.93	0.65–1.29	0.669
Mx	0.83	0.65–1.05	0.128	0.80	0.59–1.06	0.124	0.86	0.58–1.22	0.412
⩾70	0.80	0.65–0.97	0.026	0.83	0.64–1.05	0.117	0.95	0.65–1.33	0.769
<70	0.71	0.62–0.82	<0.001	0.74	0.62–0.87	<0.001	0.85	0.64–1.11	0.240

Conclusion: Our population-based data suggests a uniform diminish of CTx benefit with increasing time interval between diagnosis and treatment. This effect appears most pronounced in elderly or M1 pts.
No conflict of interest.

2455 ORAL

Comprehensive arrays for expression profiling identify key microRNA to distinguish short and long survivors among resected pancreatic cancers patients

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Background: Extensive studies have characterized the complex genetic networks and transcriptomics alterations underlying the progression of pancreatic ductal adenocarcinoma (PDAC). The recent discovery of microRNAs (miRNAs) provided additional insights potentially explaining the gap that exists between tumor genotype and phenotype. However, high-throughput technologies detecting hundreds of miRNAs provide new effective ways to unravel key miRNAs that might explain why patients with similar clinicopathological characteristics can have different clinical outcomes. Therefore, in this study we evaluated whether comprehensive miRNA profiling, using a chip detecting more than 1200 types of human miRNA, can distinguish between PDAC patients with very short OS compared to long-term survivors.
Material and Methods: High-resolution miRNA profiles were obtained with the Toray's 3D Gene-miRNA-chip. RNA was isolated from paraffin-embedded tumors of 26 radically-resected stage-pT3N1 homogeneously treated patients (gemcitabine 1000 mg/m^2/day, days 1/8/15, every 28 days), selected according to their outcome (OS<12 vs. OS>30 months, i.e. short/long OS). Highly stringent statistics included t-test, distance matrix with Spearman-ranked correlation, and iterative approaches.
Results: Unsupervised hierarchical analysis revealed that PDACs clustered according to their short-/long-OS classification, while the feature selection algorithm RELIEF identified the top 4 discriminating miRNAs. Validation of these miRNAs was performed by PCR in a second cohort of patients (N = 60), showing a strong correlation of miR-211 expression and outcome (i.e., low miR-211 expression was an independent factor of poor prognosis, hazard ratio 2.3, P = 0.03, at multivariate analysis). Conversely, patients with miR-4231 expression below median had only a trend towards a significant longer OS (25.8 vs. 16.7 months, P = 0.194).
Among predicted targets of miR-211, we performed functional analyses on ribonucleotide reductase subunit 2 (RRM2), an important target of gemcitabine, showing its significant reduction in the pancreatic cells MIA PaCa-2 and LPC028 after transfection with pre-miR-211. These findings support the hypothesis that modulation of gemcitabine sensitivity by miR-211 might be caused at least in part by inhibition of RRM2. Finally, pre-miR-211 significantly decreased cell migration and invasion, as demonstrated in 2 clones of the SUIT02 cells characterized by differential metastatic capability (SUIT02–028 and −007), using wound-healing and invasion assays.
Conclusions: Through comprehensive microarray analysis we identified miRNA with prognostic potential resected PDAC. Functional analyses suggested the role of RRM2 as target of miR-211 in the modulation of gemcitabine activity. These results prompt further prospective studies as well as research on the biological role of selected miRNAs in PDAC.
No conflict of interest.

Poster Discussion Session and Poster Session (Mon, 30 Sep)
Gastrointestinal Malignancies − Noncolorectal Cancer

2456 POSTER DISCUSSION

Intraperitoneal chemotherapy in advanced gastric cancer − meta-analysis of randomised trials

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Background: Gastric cancer (GC) is the second leading cause of cancer death and the fourth most common cancer in the world. GC disseminates principally through the haematic torrent or through the peritoneal cavity fluids. An important component of treatment failure is cancer dissemination within the peritoneal cavity and nodal metastasis. Intraperitoneal chemotherapy (IPC) gave a fundamental contribute in treating advanced GC. The purpose of the study is to investigate the effects of IPC in patients with advanced GC.
Material and Methods: A meta-analysis of randomised trials was performed.
Results: Twenty prospective randomized trials have been included for a total of 2145 patients. 1152 into surgery + IPC arm and 993 into control arm. 1, 2 and 3-years mortality rate were favourable to the surgery plus IPC arm (OR = 0.31, 0.27, 0.29 respectively). 2 and 3 years mortality in patients with loco-regional nodal metastasis were favourable to the surgery plus IPC arm (OR= 0.28, 0.16 respectively). 1 and 2-years mortality rate in patients with serosal infiltration was favourable to the surgery plus IPC arm (OR = 0.33, 0.27 respectively). The overall recurrence rate was favourable to the surgery plus IPC arm (OR = 0.46). The peritoneal recurrence rate was favourable to the surgery plus IPC arm (OR = 0.47). There were no statistically significant differences in lymph-nodal recurrence rate. The rate of haematogenous metastasis was favourable to the surgery plus IPC arm (OR = 0.63).
Conclusions: 2 and 3 years mortality rates in patients with nodal invasion are improved by the use of IPC. Loco-regional nodal invasion in patients affected by advanced GC is not a contraindication to IPC. 1, 2 and 3 years survival is incremented by IPC. No differences have been found at 5 years in survival rate. A positive effect of IPC has been found on distant metastasis.
No conflict of interest.

2457 POSTER DISCUSSION

Adjuvant chemoradiotherapy improves survival after a microscopically irradical (R1) gastric cancer resection

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Background: A microscopically irradical (R1) resection is a known unfavourable prognostic factor after gastric cancer surgery. Currently, there are no clear guidelines how to manage patients who underwent an R1 gastric cancer resection. Adjuvant chemoradiotherapy (CRT) has been proposed, but evidence for any substantial benefit is very limited. In this study, overall survival of patients with non-metastatic gastric cancer who had undergone an R1 resection with and without adjuvant CRT was evaluated.
Material and Methods: Patients who had undergone an R1 resection for non-metastatic gastric cancer between 2002 and 2011 were included. We compared a cohort of patients from the population-based Netherlands Cancer Registry who did not receive adjuvant CRT (no-CRT group) with a group of patients who had been treated with adjuvant chemoradiotherapy (CRT group) at our institute. CRT consisted of radiotherapy (45 Gy/25 fractions) combined with concurrent cisplatin and/or 5FU based chemotherapy. Independent prognostic factors for overall survival were identified using multivariable Cox regression analyses.
Results: A series of 409 gastric cancer patients who had undergone an R1 resection was studied, including 369 patients who did not receive adjuvant CRT and 40 patients who were treated with adjuvant CRT. Median follow-up was 11 months in the no-CRT group and 18 months in the CRT group, respectively. In the no-CRT group, median age was higher (70 versus 57 years, $p < 0.001$) and the percentage of patients with diffuse type tumours according to Laurén was lower (43% versus 80%, $p < 0.001$). Tumour location was also significantly different between the two groups ($p = 0.005$). There were no significant differences in pathological T- and N-stage. Three-year overall survival was 19% in the no-CRT group, compared to 40% in the CRT group. There was a significant difference in median overall survival between the no-CRT and CRT group (13 versus 24 months, respectively, $p = 0.003$). In a multivariate analysis, adjuvant CRT was an independent prognostic factor for improved overall survival (HR 0.556, $p = 0.004$). Other factors that affected prognosis significantly were tumour location ($p = 0.047$), pathological T-stage ($p < 0.001$) and pathological N-stage ($p < 0.001$).
Conclusions: In this study, adjuvant chemoradiotherapy after a microscopically irradical (R1) resection for non-metastatic gastric cancer was associated with a significant survival benefit.
No conflict of interest.

2458 POSTER DISCUSSION

KIAA1199 knockdown attenuates cell growth of gastric cancer cells and its over-expression is associated with disease progression in patients with gastric cancer

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Background: KIAA1199, also named CCSP1 (colon cancer secreted protein 1) and TMEM2L, was originally described as an inner ear specific protein but emerging evidence has demonstrated that over-expression of KIAA1199 in human cancer is linked to poor survival. The clinical implications of this molecule in human gastric cancer and the biological impact on gastric cancer cells remain unknown. In this study, we aimed to investigate the influence of KIAA1199 on cell functions in gastric cancer cells and the potential clinicolpathological value in patients with gastric cancer.
Materials and Methods: Human gastric cancer cell lines HGC27 and AGS were used for screening the levels of KIAA1199 gene transcripts using q-RT-PCR analysis. Anti-KIAA1199 transgene ribozymes were constructed and transfected into HGC27 and AGS to stably down-regulate the expression of KIAA1199. Cell growth, adhesion, migration and invasion assays were carried out using conventional or ECIS (Electrical Cellular Impedance Sensing) methods. Wnt-pathway small inhibitors FH535 and IWP2 were used to elucidate the potential pathways involved in migration potentially regulated by KIAA1199. The levels of KIAA1199 gene transcripts were determined using high throughput cDNA microarrays analysis and q-RT-PCR analysis in a cohort of human gastric tissues ($n = 313$). Patients' clinicolpathological parameters and outcome results were analysed against the levels of KIAA1199.
Results: KIAA1199 gene was successfully knocked down in HGC27 and AGS cells. The KIAA1199-knockdown cells displayed significantly influence on the growth rate, cell mobility, invasiveness and apoptosis. There was no difference in adhesive capability compared with the transfection controls. β-Catenin/Tcf Inhibitor FH535 and Wnt Inhibitor IWP-2 had no effects on cell migration. In clinical cohort, the KIAA1199 transcript was over-expressed in gastric cancers compared with adjacent normal tissues ($P<0.001$). High levels of KIAA1199 were associated with tumour infiltration, advanced TNM staging and poor cell differentiation ($P<0.001$, $P<0.001$ and $P = 0.0002$, respectively).
Conclusion: KIAA1199 is a potential oncogene over-expressed in gastric cancer cells and tissues. It is closely related with cell growth, apoptosis, cell cycle, migration and invasive ability of HGC27 and AGS cells. High levels of KIAA1199 expression in gastric cancer patients are seen in advanced stages and poorer prognosis, thus indicating a potential prognostic value.
No conflict of interest.

2459 POSTER DISCUSSION

The prediction using artificial neural network of the outcome of radiotherapy for esophageal cancer

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Background: Esophageal cancer continues to have a poor prognosis despite recent improvements in diagnosis and treatment. It is widely considered chemoradiation for esophageal cancer may achieve the same survival benefit as radical surgery especially for responders. In light of these findings, it may be desirable to choose an appropriate treatment option on an individual-patient basis and to identify responders for CRT, who can avoid surgery and its risk. An artificial neural network (ANN) is one of machine learning classifiers and a computational model simulating neural networks in the human brain. The ANN can learn the relationship between input data and teaching data. The purpose of this study was to construct of an ANN for the prediction of the tumor response of the patients treated with radiation therapy for esophageal cancer and its varidation.
Methods and Materials: The study group consisted of 167 patients with esophageal cancer of T1−4 and Stage I−III for the construction of an ANN for prediction of tumor response. We investigated the correlation between the tumor response of primary tumor after radiation therapy and each of the clinical factors in regard to patients or tumors with 167 patients. We constructed and trained an ANN to predict the tumor response using these correlative factors. The relationship between the predictive value using this ANN model and actual response was examined in 167 patients. In addition, the ANN constructed by the 167 patients was applied to a different group of 23 patients for variation analysis, and the correlation between the predictive response and actual response was also tested. We estimated the correlation between the predictive value by these ANN model and the actual value in tumor response by ROC analysis.
Results: We selected the predictive factors; T stage, tumor finding type, tumor length and SUVmax of primary tumor in 56 patients who performed FDG-PET before radiation (arm A) or wall thickness of tumor region in 111 patients which were not performed (arm B), which were significantly correrated with tumor response. We constructed two ANN models in arm A and B, and trained in each four predictive factors, respectively. In ROC analysis for the comparison between the predictive values by these ANN models and the actual value in tumor response, area under the curve (AUC) were 78% and 91% in arm A and B when the ANN constructed by the 111 patients was applied to the 111 patients. When the ANN was applied to the different set of 23 patients, AUC were 88% and 90% in arm A and B, respectively.
Conclusion: We constructed the ANN model to be able to predict the tumor response after radiation therapy. This ANN model could be used for determination of an optimal treatment strategy for esophageal cancer.
No conflict of interest.

Table (abstract 2460).

	3DCRT	PBT	p value (t-test)	Dose difference	p value (paired t-test)
MLD	9.32 Gy (±42.1 Gy)	5.73 Gy (±25.3 Gy)	5.76×10^{-8}	4.17 Gy (±0.789 Gy)	2.22×10^{-10}
Lung V5	34.3% (±4.89%)	19.6% (±1.88%)	5.87×10^{-7}	17.6% (±3.39%)	3.07×10^{-10}
Lung V10	26.8% (±3.36%)	16.8% (±1.49%)	5.98×10^{-5}	12.7% (±2.71%)	1.89×10^{-9}
Lung V20	19.6% (±9.27%)	12.5% (±1.11%)	7.87×10^{-6}	7.63% (±1.97%)	5.50×10^{-8}
Heart V30	63.3% (±29.7%)	21.5% (±5.24%)	1.53×10^{-2}	37.3% (±7.85%)	1.60×10^{-9}
Heart V40	51.8% (±26.8%)	15.3% (±3.17%)	4.34×10^{-6}	31.0% (±8.06%)	6.11×10^{-8}
Heart V50	29.0% (±13.8%)	5.51% (±2.08%)	6.21×10^{-6}	15.6% (±6.15%)	2.89×10^{-5}

Brackets enclose 95% CI.

2460 POSTER DISCUSSION

Comparison of adverse effects of proton and X-ray chemoradiotherapy for oesophageal cancer using an adaptive dose-volume histogram analysis

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Background: Concurrent Chemo-radiotherapy (CCRT) is playing an important role in treating patients with oesophageal cancer, but late toxicities of the heart and lung are an issue. The anatomical arrangement of the oesophagus, and the characteristics of oesophageal cancer make it difficult to decrease the toxicities after CCRT. Proton beam therapy (PBT) can deliver high doses to deep tissues reducing doses of organs at risk (OAR), and could be an answer to this. We conducted a dose volume histogram (DVH) study to compare dose distributions of PBT with those of conventional 3D conformal radiation therapy (3DCRT) in oesophageal cancer and to evaluate dose differences of the heart and lung when target volumes in PBT and 3DCRT were identical.
Materials and Methods: CCRT using PBT was performed in 25 oesophageal cancer patients (stage I, II, III, and IV in 11, 5, 8, and 1, respectively) from 2009 to 2011 at our department. We recalculated all treatment plans using 3DCRT, and compared DVHs of the heart and lung as OARs. Dose of planning target volumes treated by PBT were same as those by 3DCRT. Dose constraints were set only for the spinal cord at a maximum (Dmax) of 40 Gy (2 Gy/Fr equivalent dose), and doses of other OARs were minimized as possible observing these constraints. Planning CTs were generally obtained multiple times during treatment, and all of them were used to calculate accumulated plans. In order to accumulate doses more accurately, we fused the structures and doses of these plans utilizing deformation techniques provided by MIM Software (Cleveland, USA).
Results: After CCRT using PBT, we have experienced no Grade 2 or severe late toxicity at the heart and lung and only one Grade 1 pericardial effusion. Lung V5, V10, V20 and MLD, heart V30, V40 and V50 for each patient were significantly lower in PBT plans compared to those in 3DCRT plans ($p < 0.01$ paired t-test). Similarly, median of these doses of all 25 patients were significantly lower in PBT plans ($p < 0.01$ t-test).
Conclusion: There were no severe toxicity in this series, and this volumetric study for patients with oesophageal cancer showed that the irradiated doses to the heart and the lung in PBT were significantly lower than those in 3DCRT. Hence, superiority of PBT in the DVH analysis possibly affected these favorable results. As a next step, making PBT plans for patients who actually received 3DCRT will inform us whether this hypothesis is true or not.
No conflict of interest.

2461 POSTER DISCUSSION

Centralization of esophagectomy for cancer: How far should we go?

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Background: Increasing hospital volume is associated with improved outcomes after esophagectomy, but reported definitions of 'high hospital volume' in literature vary (>7 to >80). Therefore, guidelines for minimal annual hospital volume standards in different countries around the world show considerable variation. Most studies aiming to define the optimal annual hospital volume for esophagectomy use predefined volume categories which are based on the available data. Non-linear statistical modeling techniques allow the use of annual hospital volume as a continuous variable, thereby providing the ability to define a meaningful cutoff point regardless of predefined categories.
The purpose of the current study is to define a statistically sound and clinically meaningful cutoff point for optimal annual hospital volume in esophagectomy for cancer.
Methods: Data were derived from the Netherlands Cancer Registry. Annual hospital volumes were analyzed as a continuous variable, and not as a categorical variable. Restricted cubic splines were used to investigate the non-linear effects of annual hospital volume on 6-month and 2-year (conditional on surviving 6 month) overall mortality rates. Outcomes were adjusted for year of diagnosis, case-mix and (neo)adjuvant treatment.
Results: Between 1989 and 2009, 10,025 patients underwent esophagectomy for stage I−III esophageal carcinoma in the Netherlands. Annual hospital volumes varied between 1/year to 83/year and increased over time. Increasing annual hospital volume showed a continuous, non linear decrease in HR (Hazard Ratio) for mortality along the curve. Increasing hospital volume from 20/year (baseline, HR = 1.00) to 40/year and 60/year was associated with a decrease in 6-month mortality with a HR of 0.73 (95% Confidence Interval (0.60–0.90) and 0.67 (0.58–0.77) respectively. Beyond 60/year, no further decrease in HR was detected. Higher hospital volume was also associated with a decrease in 2-year mortality until 50 esophagectomies/year with a HR of 0.84 (0.79–0.90).
Conclusions: Centralization of esophagectomy to a minimal annual hospital volume of 20/year has been effectively introduced in the Netherlands. Increasing annual hospital volume was associated with a non-linear decrease in mortality up to 40−60 esophagectomies/year, after which a plateau was reached. This finding may guide quality improvement efforts worldwide.
No conflict of interest.

2462 POSTER DISCUSSION

CT-based predictive model for circumferential resection margin in oesophageal cancer

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Background: Circumferential resection margin (CRM) is an important prognostic factor in oesophageal cancer (OC) but there are no established assessment criteria to predict CRM status preoperatively. We aimed to define and validate a CRM predictive model based on computed tomography (CT) findings in OC.
Material and Methods: Following IRB approval, we retrospectively identified 234 consecutive patients who underwent oesophagectomy between 2000–2007 from our institutional database. A total of 68 patients were included in the development of the model. Exclusion criteria were failure to retrieve CT images for review (n = 162), poor image quality (n = 3) and absence of postoperative pathology (n = 1). All patients underwent contrast enhanced CT prior to surgery which were reviewed by radiologists blinded to the pathological results. CT parameters analysed included invasion/contact of adjacent structures (ICA), circumferential aortic contact >90º, largest primary tumour axial dimension (LAD), maximum wall thickness, tumour length, presence and number of lymph nodes >1 cm and presence of intact fat plane around tumour. Aortic contact >90º and ICA were combined and considered as a separate variable (ICAA). Univariate (UVA) and multivariate analyses (MVA) were performed and significant variables with $p \leqslant 0.21$ in the MVA were included in the predictive model (CRM3); continuous variables were dichotomised using median values. The performance of this model was assessed using receiver operating characteristic (ROC) curve analysis − area under the curve (AUC). This

model was validated in a separate validation cohort of 67 patients identified from our database who were treated between 2007–2010.
Results: Prevalence of positive CRM were 40% and 36% in the development and validation cohort respectively. The following parameters were significant predictors of CRM in UVA and were independent predictive factors in MVA: ICAA (UVA: p= 0.040, MVA: p=0.210), LAD (UVA: p = 0.004, MVA: p = 0.020) and nodal status (UVA: p = 0.050, MVA: p=0.180). In the CRM3 model, a score of 1 was given for presence of either ICAA, enlarged node or LAD greater than median value of 2.6 cm. The AUC for this model was 0.73 (95% CI 0.61–0.85) with 33% sensitivity and 95% specificity for a score of 3 in the development cohort. The AUC was 0.64 (95% CI 0.50–0.77) with 36% sensitivity and 86% specificity for a score of 3 when the model was applied in the validation cohort.
Conclusions: The CRM3 model has good discriminatory ability to identify patients at risk of positive CRM and could be useful in stratifying patients for more intensive neoadjuvant therapy.
No conflict of interest.

2463 POSTER DISCUSSION

Everolimus plus octreotide long-acting release (LAR) for the treatment of advanced neuroendocrine tumors (NET) associated with carcinoid syndrome (RADIANT-2): Updated overall survival results

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Background: RADIANT-2 (NCT00412061) showed that everolimus (EVE) + octreotide (OCT) LAR improved median adjudicated central review-assessed progression-free survival (PFS) by 5.1 months versus placebo + OCT LAR in patients with advanced NET and carcinoid syndrome (HR 0.77, 95% CI. 59−1.0; one-sided P=.026; prespecified $P \leqslant .0246$). Here we report the secondary endpoint of overall survival (OS).
Methods: Patients were randomized to EVE (10 mg/d, n = 216) or placebo (n = 213), both + OCT LAR (30 mg q28d). Survival endpoints were calculated using the intent-to-treat patient population (N = 429; all randomized patients). Patients in the placebo arm who switched to open-label everolimus after disease progression (n = 143) were retained in the placebo arm for OS analysis. Final OS analysis was planned after 252 events.
Results: Data cut-off date was April 23, 2012. Median EVE exposure was 37.0 wks (range 1–270) in pts randomized to EVE and 34.1 wks (range 1–200) in pts randomized to placebo who switched to open-label EVE; 36 patients had $\geqslant$144 wks of EVE exposure, including 8 randomized to placebo and switched to open-label EVE. Kaplan–Meier estimates (95% CI): 1 year, 80.5% (74.5–85.3) and 81.8% (75.8–86.4); 2 years, 57.0% (49.9–63.4) and 63.6% (56.6–69.8); 3 years, 42.9% (36.0–49.6) and 48.5% (41.4–55.3) in the EVE + OCT LAR and placebo + OCT LAR arms, respectively. Median OS (95% CI) after 253 events was 29.2 (23.8–35.9) months for EVE + OCT LAR and 35.2 (30.0–44.7) months for placebo + OCT LAR (HR 1.16, 95% CI. 91–1.49). When adjusted for baseline covariates (age, gender, race, WHO PS, and prior SSA usage), HR was 1.06, 95% CI. 82–1.36. Adverse events (AEs) reported during the open-label phase (n = 170) were consistent with those observed during blinded treatment; the most common included diarrhea (47.1%), stomatitis (37.6%), nausea (35.3%), edema (35.3%), fatigue (34.7%), and rash (34.1%).
Conclusions: There was no significant difference in OS between the EVE + OCT LAR and placebo + OCT LAR arms of RADIANT-2, even after adjusting for imbalances in baseline covariates. The likelihood of detecting OS differences may have been compromised by the crossover of many patients from the placebo arm to open-label EVE. Other factors that may have confounded the OS comparisons include imbalanced informative censoring, unknown therapy after study end, and imbalance in other baseline characteristics between treatment arms which could not be adjusted.
Sponsor: Novartis Pharmaceuticals Corp
Conflict of interest: *Ownership: Stocks: Novartis. Advisory board: Novartis, Ipsen, Pfizer, Camurus Lund, Medison (Israel). Corporate-sponsored research: Novartis. Other substantive relationships: Honoraria: Novartis, Ipsen, Pfizer. Employee: Novartis. Research Grant: Novartis. Organizer: Advanced Course in Neuroendocrine Tumors (15 courses).*

2464 POSTER DISCUSSION

Clinical characteristics in 127 patients with advanced G3 gastrointestinal neuroendocrine carcinoma: The FFCD-GTE national cohort study

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Background: Data on grade 3 gastrointestinal neuroendocrine carcinoma (GI-NEC) are limited or retrospective. We designed a French national cohort study to describe the clinical characteristics of GI-NEC at diagnosis and evaluated prognostic factors for overall survival (not presented).
Patients and Methods: All patients with a G3 GI-NEC (WHO 2010) and a diagnosis done after 01/01/2010 could be included in this national prospective cohort study using an e-crf available online (www.cepd.fr). The cut-off for data was March 7, 2013.
Results: 127 patients were included in 33 centers: 62% were male, median age was 66 (23−90) years. No GI-NEC was associated with a familial syndrome. Main primary locations were duodenum-pancreas (24%), unknown (18%), rectum (16%), stomach (13%), oesophagus (11%) and colon (11%). None was located in the appendix and only two in the small bowel. The initial symptom was pain (58%). At diagnosis, the performance status was 0−1 in 78% of the patients. Most of the patients were metastatic (79%), with a median of 2 (0−5) metastatic sites (liver (76%), distant lymph nodes (54%), lung (15%), bone (16%), peritoneal (12%), cerebral (5%), other (11%)). Median (range) chromogranine A, NSE (Neuronal-Specific Enolase) and lactate dehydrogenase (LDH) levels were 151 μg/L (27–23500), 61 μg/L (2–3460), and 427 U/L (145–5115), respectively. 18F-FDG TEP scan and Octreoscan® were positive in 46/52 (89%) and 12/20 (60%), respectively. Pathological data showed: small/large cell NEC in 40%/60%, with necrosis in 76%, and a Ki67 index of 70% (15%-100%). 74 (58%) tumors are currently reviewed by the French national referent network (TENpath). The primary tumor was resected in only 18 (14%) patients. At least one (cisplatin/etoposide in 53/79 (67%) or carboplatin/etoposide in 16/79 (20%) of cases), two (Folfiri in 18/39 (46%) of cases) or >2 palliative systemic chemotherapies were given in 79 (62%), 39 (31%) and 19 (15%) patients, respectively.
Conclusions: GI-NEC are mainly diagnosed at advanced stage. Several parameters should be considered to evaluate the prognosis and adjust the treatment, which will be presented at the meeting.
No conflict of interest.

2465 POSTER DISCUSSION

Circulating tumor cells and circulating endothelial cells as predictors of efficacy of pazopanib in patients with progressive neuroendocrine tumors

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Background: The objective of this study is to evaluate the predictive and prognostic role of circulating tumor cells (CTC) and circulating endothelial cells (CEC) in patients with progressive neuroendocrine tumors (NETs) treated with Pazopanib (PAZONET trial − ESMO 2012).
Methods: Patients with advanced NETs progressing with prior treatment, including antiangiogenic drugs were treated with Pazopanib 800 mg/day until progression or unacceptable toxicity. Blood samples were retrieved at baseline and after 12 weeks of treatment. CTC and CEC were detected by immunomagnetic isolation. Disease was evaluated bimonthly via CT scans (RECIST1.0).
Results: 44 patients were included and baseline CTC were determined in 21 patients, 11 of which had detectable CTC (range 1 to 108 cells/ml).

One patient (9.1%) with a baseline presence of CTC presented a partial response (PR) compared with 4 patients (44.4%) without (p = 0.13). Duration of pazopanib-adjusted OR for PR is 6.2 (95% CI 0.45–86.5, p = 0.17) for patients without CTC compared with patients with CTC at baseline. Patients without and with baseline CTC had a median progression-free survival (PFS) of 9.1 versus 5.8 months, respectively (p = 0.12). There were no changes in CTC in the second determination. CEC were determined at baseline and after 12 weeks of therapy in 18 and 9 patients respectively. Median decrease in CEC was −12.5% (p = 0.077). Patients with a lower baseline CEC count (⩽median) had a trend towards a higher response rate (44.4% vs. 12.5%, p = 0.29) and longer PFS (duration of pazopanib-adjusted OR 0.58, 95% CI 0.17–1.98, p = 0.22).
Conclusions: Baseline CTC were detected in 52% of patients tested, and did not change during pazopanib therapy. A trend for an association between the presence of CTC and higher CEC counts at baseline and worse clinical outcome was observed. CEC seemed to decrease during pazopanib treatment, although the association with clinical outcome is unclear.
Conflict of interest: *Other substantive relationships: GlaxoSmithKline*

2466 POSTER DISCUSSION

NADEGE prospective cohort: Demographic data of 335 small bowel adenocarcinomas

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Background: Small bowel adenocarcinoma (SBA) is a rare tumour poorly studied. Data are coming from register study or monocentric retrospective studies. The purpose of the NADEGE cohort (*Cohorte Nationale d' ADEnocarcinomes du GrêlE*) is to describe characteristics, prognosis and chemotherapy regimens of SBA in unselected patient at a nationwide level.
Material and Methods: All the patients with a SBA diagnosed from January 2009 to December 2012 were enrolled in the NADEGE cohort. The study involved 72 centres in France that enrolled 335 patients. This work presents the first demographic data.
Results: Patients were predominantly male (58) and median age was 63 years [23−90]. The median number of patient enrolled by center was 2 (1−33). The primary locations were duodenum (51%), duodeno-jejunum (8.7%), jejunum (20.6%), ileum (16.1%) and not determined (ND) (3.6%). The tumour was poorly differentiated (12%), moderately (33%), and well differentiated (32%). A predisposing disease was reported in 63 (18.8%) of cases: Crohn disease 29 (46%), Lynch syndrome 19 (30%), familial adenomatous polyposis (FAP) 7 (11%), celiac disease 6 (9.5%) and Peutz-Jeghers syndrome 2 (3%). The disease was localized and resected in 55% of patients, locally advanced and not resected in 5.7%, metastatic and resected in 10.1%, metastatic and not resected in 23% and ND in 6.2%. The 184 tumours resected without metastases were 6 stage 0, 55 stage I−II, 77 stage III, and 48 ND. Adjuvant chemotherapy, mainly by FOLFOX regimen (88%), was performed in 16% of stage I−II, 56% of stage III and 26% of resected stage IV. A palliative chemotherapy was performed in 74% of cases in metastatic disease, by FOLFOX regimen in 60% of cases. According to the location of primary tumours duodenum/jejunum/ileon, the tumours were T4 in respectively 27%, 41% and 33% of cases, metastatic in 33%, 29% and 35% of cases and poorly differentiated in 11%, 13% and 19% of cases. Primary tumours were mainly ileal in 76% of patient with Crohn disease and duodenal in 42% of patient with a Lynch syndrome and 57% of patients with FAP.
Conclusions: NADEGE cohort is the largest prospective SBA study. A high rate of predisposing disease is observed with a difference in tumor site according to the predisposing disease. FOLFOX chemotherapy is the main regimen used in adjuvant and metastatic setting. Follow-up is ongoing until 2015.
Acknowledgments: Grant from ARCAD, sponsor GERCOR, intergroupe collaboration GERCOR, FFCD, FRENCH, AGEO, UNICANCER-GI, SNFGE.
No conflict of interest.

2467 POSTER DISCUSSION

Sorafenib alone versus Sorafenib combined with Gemcitabine and Oxaliplatin (GEMOX) in the first-line treatment of advanced hepatocellular carcinoma: final analysis of the randomized phase II GoNext trial (a UNICANCER/FFCD/PRODIGE 10 study)

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Background: Hepatocellular carcinoma (HCC) is a vascular tumor with poor prognosis. Even though Sorafenib has been shown to improve survival, its ability to induce tumor shrinkage is very low. Given the reported activity of Gemcitabine and Oxaliplatin (GEMOX) in HCC, a randomized phase II study testing Sorafenib combined to GEMOX was undertaken to define efficacy and safety profile in HCC patients.
Methods: Patients with inoperable advanced and/or metastatic HCC (BCLCC B or C), with or without prior palliative chemoembolization, Child pugh score A, WHO performance status (PS) 0−1, were eligible for this open-label, two-stage, randomized phase II trial. Patients received Sorafenib (S) (400 mg BID) alone (ARM A) or in combination with GEMOX every 2 weeks (gemcitabine, 1000 mg/m^2 [10 mg/m^2/min] at day 1; oxaliplatin, 100 mg/m^2 at day 2) (arm B). Randomization was stratified according to CLIP score (0−1 vs 2−3) and center. Tumor assessments were performed every 8 weeks according to RECIST 1.0. The primary endpoint was crude 4-month Progression-Free Survival (PFS) rate (H0, <50%; H1, ⩾70%; α = 10%; 1- β= 90%). Secondary endpoints were Objective Response Rate (ORR), Disease Control Rate (DCR), PFS, Overall Survival (OS), and toxicity (NCI-CTC v3.0); translational studies consisted of pharmacokinetic, pharmacogenetic, mRECIST assessment and blood/tumor VEGFR signalling pathway analysis.
Results: From 12.2008 to 10.2011, we enrolled 94 pts: median age, 64 yrs; male, 88%; PS 0 (69%) 1(31%), CLIP 0−1 (48%) 2−3 (52%), cirrhosis (63%), portal vein thrombosis (29%), extra hepatic metastasis (69%). These characteristics were well balanced in both arms. Median duration and dose intensity of Sorafenib were respectively 4 months (1−27) and 81% in both arms. Median number of GEMOX cycles was 7 (1−12) in arm B. Main severe (grade 3−4) toxicity (arm A/B) consisted of neutropenia (grade 3−4: 0%/7%), fatigue (18%/24%), thrombocytopenia (0%/9%), diarrhea (grade 2−4: 10%/21%), peripheral neuropathy (grade 2−3: 0%/10%), and hand foot syndrome (grade 2−3: 13%/7%). For evaluable pts (n = 83), the ORR was 9%/16% and the DCR was 70%/77%, in arm A/B respectively. For all pts (median follow-up, 17.6 months), 4-month PFS rate was 54%/61%, median PFS was 4.6 (3.9−6.2)/6.2 (3.8−6.8) months, and median OS was 13.0 (10.4–22.2)/13.5 (7.5–19.1) months, in arm A/B respectively.
Conclusions: Sorafenib plus GEMOX regimen is feasible in HCC and this randomized trial met its primary endpoint (4-month PFS ⩾50%). Moreover, ORR, median PFS and OS are encouraging compared to the literature data. Exploratory analyses are underway to try to identify subgroups of patients most willing to derive benefit from this combination.
Conflict of interest: *Advisory board: Bayer. Corporate-sponsored research: Bayer*

Poster Session (Mon, 30 Sep)
Gastrointestinal Malignancies − Noncolorectal Cancer

2468 POSTER

Chemotherapy induced DNA repair enhancement is a potential resistant mechanism in hepatocellular carcinoma

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Background: Hepatocellular carcinoma (HCC) has long been recognized as a chemotherapy refractory cancer. Antitumor activity of most chemotherapeutic drugs depends on the induction of DNA damage. In eukaryote, DNA end-joining (EJ) is the predominant repair mechanism of the most toxic DNA double strand breaks (DSBs). In this study, we tried to investigate the role of EJ repair in HCC chemo-resistance.

Methods: Drugs induced HCC cells characters changes were assessed using flow cytometry, immunofluorescence staining, MTT assay, quantitative real-time PCR, small interfering RNA and western blotting. Cancer stem cell population was separated by MACS®.
Results: We observed drugs (cisplatin, oxaliplatin, doxorubicin and 5-FU) with different antitumor mechanism can all induce γ-H2AX foci (a DSBs marker) formation and increase DNA repair gene expression in HCC cells (97L and PLC) shortly (2 h) after treatment. Significant decrease of foci number in 97L cells 48 h afterwards indicated 97L may possess a more efficient DSBs repair. Cytotoxicity assay showed that 97L was more resistant to chemotherapy than PLC cells. Furthermore, 97L presented a significantly enhanced EJ activity after chemotherapy both *in vivo* and *in vitro*. XRCC4-like factor (XLF), also known as NHEJ1 or cernonnus, is an important protein involved in EJ repair. We transient knocked down XLF in the more resistant 97L cells by siRNA. EJ repair activity was significantly suppressed and subsequently restore chemo-sensitivity in XLF-deficient 97L compared with wild type 97L, indicated inhibit XLF may be a potential chemo-sensitizer for HCC. Recently, cancer stem cells attract great interest as the origin of recurrence following chemotherapy. CD133 is the most widely used cell surface marker to distinguish CSCs subpopulation from HCC cells. We first segregated CD133+ from CD133− HCC cells by magnetic cell separation technology. Compared with CD133− HCC cells, CD133+ cells were more resistance to chemotherapy and possessed a significant increment of chemotherapy induced EJ genes expression and EJ repair capacities. ERCC1 is an important protein involved in nucleotide excision repair (NER), the major repair mechanism of DNA crosslink damage. Also ERCC1 expression is closely associated with platinum based chemotherapy outcomes in NSCLC. Interestingly, we found a significantly suppression of ERCC1 expression in XLF-deficient HCC cells which implied a cross-regulation between ERCC1 and XLF.
Conclusions: Chemotherapy can induce DSBs and activate relative repair in HCC. Suppression of XLF can significantly inhibit EJ repair and restore chemo-sensitivity in HCC cells. HCC CSCs subpopulation may contribute to chemotherapy activated EJ repair and consequent chemo resistant. Our results suggested that HCC cells may develop an enhanced DNA EJ repair to eliminate induced DSBs during chemotherapy and targeting XLF could be a potential supplement to HCC treatment as a chemo-sensitizer.
No conflict of interest.

2469 POSTER

Clinical relevance and functional role of nuclear Met in hepatocellular carcinoma

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Background: Met is a receptor tyrosine kinase which triggers a wide range of normal physiological signalling cascades. However, a perturbation of the Met pathway is commonly found in human cancers. Emerging evidence has shown the presence of nuclear Met (nMet) in some cancerous tissues and cell lines, suggesting that nMet could have unexplored functions in the nucleus. The present study aimed to assess the expression and functions of nMet in hepatocellular carcinoma (HCC).
Material and Methods: nMet expression of 103 clinicopathologically characterised HCC paired samples was examined by immunohistochemistry using an antibody against the carboxyl terminus of Met. Statistical analyses were applied to evaluate the association of nMet with different clinical parameters. Nuclear localisation of Met was determined by western blot analysis and immunofluorescence microscopy. Met cytoplasmic fragments were characterised by *in vitro* functional assay such as migration, invasion and proliferation in HCC cells.
Results: nMet is overexpressed in 89.3% samples and its expression is progressively increased along HCC development from non-tumorous liver tissue to advanced HCC. Nonetheless, nMet overexpression is significantly associated with venous invasion and poorer overall survival. We found that nMet, which has a lower molecular weight than Met, could only be detected using an antibody against the carboxyl terminus of Met (C28) in tumorous tissues. This finding strongly suggests that nMet only comprises of the carboxyl cytoplasmic region of full length Met. Moreover, both western blot analysis of nuclear fraction of HCC cells and immunofluorescence confirmed the nuclear localization of Met. We designed construct J1, J3 and T2 that encode Met fragment truncated after tyrosine residues D972 and P1027 in the juxtamembrane region and after tyrosine kinase domain beginning at L1157, respectively. Immunofluorescence microscopy showed both J1 and J3 constructs are dominantly expressed in the nucleus whereas T2 construct is expressed in the cytoplasm. These observations indicated the region in between J1 and T2 as the important region that facilitates the nuclear localisation of Met. *In vitro* functional study showed that overexpression of nMet augments the invasiveness of HCC cells suggesting the unexplored functional effect of nMet exerted within nucleus in promoting HCC invasiveness.
Conclusions: nMet is overexpressed and associated with venous invasion and poorer overall survival in HCC. We found that nMet is actually the carboxyl terminal fragment of Met and translocates into nucleus to promote invasiveness in HCC cells.
No conflict of interest.

2470 POSTER

MAGIs, membrane-associated guanylate kinase with inverted structure protein, involved in the metastatic properties of gastric cancer cells, the clinical implications

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Background: Tumor metastasis is a multistage process in which a network of related molecules and signal pathways are intimately involved. Tumor invasion and metastasis are directly related to the prognosis of patients with gastric cancer. Membrane-Associated Guanylate Kinase With Inverted Structure, MAGIs are a relatively new gene family that has been postulated to have a role in invasion and metastasis based on the predicted protein structure and functions. The MAGI proteins are a group of scaffolding proteins located in cell-cell junctions and play important roles in the process of tissue development, the stabilization/maintenance of tight junctions and cell signaling. However, there has been very limited clinical and scientific evidence on this suggestion. The present project aimed to investigate the clinical relevance and the biological impact of differentially expressed MAGI(s) on the biological functions as cell growth, adhesion, migration and invasion, on the cells and potential mechanisms by which cells are influenced.
Materials and Methods: The levels of MAGI1, 2 and 3 transcripts were determined using quantitative transcript analysis in a cohort of human gastric tissues (n = 317). Patients' clinicolpathological parameters and more than 5 year's outcome results were analysed against the levels of MAGI 1, 2 and 3. For the potentially interested gene(s), we would either knockdown or over-express the gene(s) in human gastric cancer cell lines HGC27 and AGS and use the newly created sublines to investigate cell functions including growth, adhesion, migration and invasion using conventional and ECIS (Electrical cellular impedance sensing) methods.
Results: The gene expression of MAGI1, and to a lesser degree MAGI2 and MAGI3, was linked to infiltration depth of the stomach wall and distant metastasis of the patients. Levels of the MAGI1 transcript were negatively correlated with distant metastasis (disease free VS. distant metastasis, P = 0.0015). Human gastric cancer cell lines HGC27 and AGS highly expressed MAGI-1. We successfully knocked down MAGI1 from both cells and produced stable MAGI-1 knockdown sublines. MAGI1-knockdown rendered cells with significantly decreased growth rate and adhesive capability but increased cell mobility, invasive ability compared with control cells.
Conclusion: MAGI1, rather than MAGI2 and MAGI3, has a metastasis suppressive role in gastric cancer, by influencing the invasiveness and growth of the cells. Its prognostic and therapeutic value warrant further exploration.
No conflict of interest.

2471 POSTER

Clinical significance and cell functions of Tubedown-100 (TBDN100) in gastric cancer

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Background: Protein acetylation is an important posttranslational modification regulating oncogenesis, apoptosis and cell cycle. Tubedown-100 (TBDN100), also known as NAA15 (N(alpha)-acetyltransferase 15), is a gene encoding a protein of unknown function. It was expressed at a low level in most human adult tissues, including the normal thyroid gland. Increased TBDN100 expression has been seen in a Burkitt lymphoma cell line and in adult human testis. Knockdown of TBDN100 may trigger apoptosis in human cancer cell line Hela. Although TBDN100 has been indicated in the regulation of apoptosis, its biological function and involvement in cancers remained to be elucidated. Here, we report the expression of TBDN100 in gastric cancer and the effect of TBDN100 on human gastric cancer cells.

Materials and Methods: The levels of TBDN100 gene transcripts were tested using q-RT-PCR analysis in human gastric cancer cell lines HGC27 and AGS, and a gastric cancer cohort. TBDN100 over-expression plasmid were constructed using a mammalian expression vector and was used to transfect into gastric cancer cells to generate TBDN100-overexpresion sublines. Cell growth, apoptosis, cell cycle, adhesion and migration were evaluated. TBDN100 expression levels in the clinical cohort were analysed against patient's clinicolpathological parameters and prognosis results.
Results: HGC27 and AGS cells were negative for TBDN100 expression. Overexpression of TBDN100 in HGC27 and AGS cells by way of transfection resulted in significant changes in the growth rate, cell cycle distribution, adhesive capability and *in vitro* invasiveness. However, levels of TBDN100 transcript were significantly higher in gastric tumours compared with adjacent normal gastric tissues ($p < 0.001$). More interestingly, level of the TBDN100 transcript was significantly higher in tumours of who remained alive than from those who died of gastric cancer 5 years after surgery ($P = 0.0484$). It was also higher in cardiac tumours than on corpus tumours ($P = 0.0079$) and higher in those without lymph node metastasis.
Conclusions: TBDN100 has different expression profile in gastric cancer tissues and cells, with high levels seen in gastric tumours from patients with longer survival and negative lymph node metastasis, thus indicating a potential prognostic value.
No conflict of interest.

2472 POSTER

The "cavitary" type of vessels formation in gastric cancer: Morphological characteristics and clinical significance

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Background: For the first time, a 'cavitary' type of vessels (CTVs) formation was described in patients with gastric cancer (GC). The morphological features and clinical significance of the CTVs were the objects of this study.
Material and Methods: The samples of tumor and adjacent gastric mucosa (GM) in 69 radically operated patients with GC were studied. The sections were stained with hematoxylin and eosin and by IGH using antibodies to CD34. The number of CTVs was assessed the visual analog way (no, single, multiple). The obtained data were compared with clinical features, 2-year overall (OS) and relapse-free survival (RFS).
Results: The following steps of the CTVs formation were identified: 1) a formation of the cavitary structures in the tumor and adjacent GM; 2) then they are being lined by endothelial cells (ECs); 3) and merged with the blood vessels of the organ. Two main mechanisms of the CTVs formation were marked:

1. The 'cavities' can be formed at the expense of desquamation layers of epithelial cells (both normal and tumor) in the lumen of the gastric glands (GG) having no connection with gastric lumen. By IHC it was revealed that the internal surface of the described 'cavities' can be fully or partially lined by ECs. The newly formed vessels (type I) had different shapes and often have been spaced according to the virtual topographic projection of GG on the section plane. Both the columnar epithelium and ECs lining the blood vessel wall can sometimes be seen in the area of vessel and GG 'merger'. The epithelial and tumoral emboli were often found in the lumen of such vessels.
2. The 'cavities' can also be formed by dilatation of the GG with a gradual reduction of the epithelial cells height, their flattening, thinning and then merging with vessels adjacent to theirs wall. The vessels of type II, as well as adjacent GG were dilated and often had irregular shape. By IGH it sometimes seemed that the endothelial lining was over the epithelial layer.

The vessels of type I significantly correlated with the presence of metastases in regional lymph nodes (RLN) ($R = 0.494$, $p < 0.0002$); OS ($R = -0.709$, $p < 0.0001$) and RFS ($R = -0.701$, $p < 0.001$). Multiple vessels of this type are found significantly more often in patients with metastases in RLN (50% and 14.3% respectively in stage N1−2 and N0, $p < 0.006$). RFS was 89.6% and 41.2% ($p < 0.0003$) and OS was 95.8 and 70.6% ($p < 0.004$) in patients with the absence or the single vessels in GM and in patients with multiple vessels, respectively. A presence in anamnesis of antibacterial therapy (AT) in connection with the preliminary diagnosis of a gastritis or a stomach ulcer considerably improved the 2-year survival of patients with metastasis in RLN (RFS was 80% and 43.5%, $p = 0.03$ and OS was 100% and 66.7%, $p < 0.04$ respectively with and without AT) and decreased the number of patients with multiple vessels of type I (18.2% and 58.3% respectively with and without AT, $p < 0.04$). The vessels of type II significantly correlated only with the degree of GM metaplasia ($r = 0.590$, $p < 0.0002$).
Conclusions: The described CTVs formation has a large clinical importance.
No conflict of interest.

2473 POSTER

Mutant GNAS found in IPMN can alter global gene expressions with mucin upregulation

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Background: *GNAS*, a gene encoding G-protein stimulating alpha subunit, is frequently mutated in intraductal papillary mucinous neoplasms (IPMNs), which is an indolent and slow-growing pancreatic neoplasm that secretes abundant mucin. *GNAS* mutation is not observed in conventional ductal adenocarcinomas of the pancreas or pancreatic cystic neoplasms except IPMN. Mutated *GNAS* has been reported to induce the high intracellular cAMP concentration and to activate GPCR pathway. However, the phenotypes in pancreatic ductal cells with mutated *GNAS* are still unknown.
Materials and Methods: To determine the functional significance of *GNAS* mutation, we examined the *in vitro* phenotypes and gene expression profiles of pancreatic cancer cells with exogenous expression of either wild-type or mutant (R201H) *GNAS*, using PK-8, PCI-35, and MIA PaCa-2 cells. Measurement of cAMP, real time PCR for mucin gene expressions, colony formation assay for survival, MTT assay for proliferation, flow cytometry for cell cycle and serial analysis of gene expression were performed. The experiments using a MAPK inhibitor were also carried out to clarify the crosstalk between GPCR and MAPK signaling pathway, and to determine the contribution of MAPK activity to mucin gene expression.
Results: The exogenous expression of *GNAS* increased intracellular cAMP, however, the degree of this upregulation appeared to be cell-type specific. The exogenous expression of *GNAS* induced no obvious cell-growth promotion; rather, it suppressed the proliferation and survival of cells. Cell cycle was not affected by exogenous *GNAS*. The exogenous expression of *GNAS* induced varying degrees of alterations in global gene expression profiles. PK-8 was most sensitive to the mutated *GNAS*, as it exhibited drastic alterations in the gene expression profile and upregulation of *MUC2* and *MUC5AC*. PCI-35 and MIA PaCa-2 cells were less sensitive and exhibited a lower number of genes with altered expression, with downregulation of mucin genes. Pathway analysis revealed that genes on PI3K-AKT and MAPK signaling pathway were primarily altered by mutated *GNAS*. Moreover, MAPK activity partially contributed to mucin gene expression under active *GNAS*.
Conclusion: PK-8 cells expressing mutated *GNAS* exogenously can be used as an ideal model of IPMN for its GPCR-dependent character. The *GNAS* mutation can play an important role in altering gene expression profiles, with promotion of mucin gene expression.
No conflict of interest.

2474 POSTER

Id1-induced IGF2 promotes bidirectional interaction between esophageal cancer cells and fibroblasts in the tumor microenvironment

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Background: Esophageal squamous cell carcinoma (ESCC) is highly prevalent in Asia. Over 90% of ESCC overexpress Id1 protein. This study aims to investigate the interaction between Id1-overexpressing ESCC cells and stromal fibroblasts, and the mechanism and role of this crosstalk in ESCC progression.
Material and Methods: Human ESCC cell lines with ectopic expression of Id1, co-expression of Id1 and shRNA against insulin-like growth factor-2 (shIGF2), or empty vector were established. MTT assay was used to compare the proliferation of cells. Western blotting and ELISA were used to analyze the protein expressions in cell lysates or conditioned medium. Boyden chamber assays were performed to investigate the migration and invasive potential of cells. Tumor xenografts were established by subcutaneous injection of cancer cells into the flank of nude mice.
Results: Our data showed that the conditioned medium harvested from ESCC cells with overexpression of Id1 could induce esophageal fibroblasts to produce vascular endothelial growth factor (VEGF) *in vitro,* and co-expression of shIGF2 greatly abrogated this effect. The conditioned medium collected from Id1-overexpressing ESCC cells also significantly increased the migration potential, but not the proliferation, of fibroblasts. Similar results were obtained by treating fibroblasts with synthetic recombinant human IGF2, in the presence or absence of neutralizing antibody against IGF2, which confirmed that Id1-induced IGF2 secreted by ESCC cells could induce esophageal fibroblasts to produce VEGF and actively migrate. Interestingly, the invasive potential of ESCC cells was enhanced by the conditioned medium from the IGF2-treated

fibroblasts, and addition of IGF2-neutralizing antibody partially attenuated these effects. To mimic the condition of tumor microenvironment, 3D co-culture system of fibroblasts with ESCC cell lines expressing Id1, Id1-shIGF2 or empty vector was performed, and the same effects were observed. Furthermore, our *in vivo* data indicated that mice bearing Id1-overexpressing ESCC xenografts had significantly higher microvessel density and host-derived VEGF in serum than the Id1-shIGF2 and control vector groups.
Conclusions: IGF2 secreted by Id1-overexpressing ESCC cells can promote bidirectional interaction between ESCC cells and stromal fibroblasts in a paracrine manner.
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No conflict of interest.

2475 POSTER

Effects of carbon ion beam alone or in combination with sorafenib on putative liver cancer stem cells

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Purpose: To investigate whether carbon ion beam alone or in combination with sorafenib has beneficial effects compared to X-ray by targeting putative cancer stem cells.
Methods: Human liver cancer stem-like cells sorted from HepG2 and Huh7 cells were treated with carbon ion or X-ray irradiation alone or in combination with sorafenib, and then colony and spheroid formation assay, apoptosis assay, ϒH2AX foci formation assays were performed. Histopathological changes of xenograft tumours after carbon ion beam or X-ray irradiation was also examined.
Results: CD133+/CD90+ cells significantly have higher number of colony and spheroid compared to CD133−/CD90− cells. CD133+/CD90+ cells have shown more potential to form tumours in SCID mice than CD133−/CD90− cells. Colony assay showed that CD133+/CD90+ cells appeared to be radioresistant to both X-ray and carbon ion beam, but carbon beam, especially carbon ion combined with sorafenib remarkably destroyed those of cancer stem-like cells. The percentage of apoptotic cells as well as the number of ϒH2AX foci in the CD133+/CD90+ cells was significantly lager after carbon ion beam compared to X-ray irradiation, and it was more increased when combined with sorafenib. Carbon ion irradiation with 15 Gy induced more severe xenograft tumour cell cavitation and fibrosis compared with 30 Gy X-rays, and tumours were significantly regressed following 30 Gy carbon ion irradiation.
Conclusion: Taken together, carbon ion beam combined with sorafenib has more potential to kill CD133+/CD90+ cancer stem-like cells at relatively lower doses via unrepairable DNA damage *in vitro* as well as tumour regression *in vivo* compared to X-ray.
No conflict of interest.

2476 POSTER

JAK2 inhibitor blocks the inflammation and development of esophageal squamous carcinoma in vitro through JAK/STAT3 signaling pathway

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Background: It has been found that the abnormal activation of JAK/STAT3 (Janus kinase/signal transducer and activator of transcription3) signaling pathway in a variety of human tumors. This study aimed to investigate the role of JAK2 inhibitor AG490 in the development of esophageal squamous carcinoma cells and the cross talk between JAK/STAT3 signaling pathway and nuclear factor-kappa B (NF-KB) and cyclooxygenase-2 (COX-2) which are important inflammatory factors associated with tumorigenesis.
Material and Methods: Three esophageal squamous carcinoma cell lines were selected to detect the basal expression of STAT3. The Jak2 inhibitor AG490 and interleukin-6 (IL-6) were added to the culture media of human esophageal squamous carcinoma cell TE-1 and EC-1, respectively. Cell growth was measured by CCK8 assays. Cell cycle and apoptosis was detected by flowcytometry. The expression of STAT3-phosphorylated STAT3 (p-STAT3), vascular endothelial growth factor (VEGF), NF-KB p65, phosphorylated NF-KB p65 (p-NF-KB p65) and COX-2 proteins after treated with AG490 or IL-6 were detected by western blotting.
Results: STAT3 was abnormally activated in three esophageal squamous carcinoma cell lines in varying degrees. The Jak2 inhibitor AG490 remarkably decreased the expression of p-STAT3 and VEGF in TE-1 cells. And AG490 also inhibited the cell growth and affected the cell cycle and apoptosis ($p < 0.05$). Protein expression of p-STAT3 and VEGF was increased significantly in EC-1 cells after IL-6 stimulation. In addition, the expression of inflammatory factors NF-KB p65 and COX-2 was also elevated in three cell lines. P-NF-KB p65 and COX-2 proteins were elevated in EC-1 cells treated with IL-6 and decreased in TE-1 cells treated with AG490.
Conclusions: The Jak2 inhibitor AG490 inhibits the growth and metastasis in esophageal cancer cell lines through ablation of the JAK/STAT3 signaling pathway. Additionally, our results demonstrate AG490 decreases the expression of inflammatory factors NF-KB p65 and COX2, indicating a cross talk between JAK/STAT3 signaling pathway and NF-KB pathway. The JAK/STAT3 signaling pathway may also play a critical role in tumor inflammation through interaction with NF-KB and COX-2 to promote tumorigenesis.
No conflict of interest.

2477 POSTER

***Antrodia camphorata* exhibits antitumor activity via down-regulation of IL-6 signaling in hepatocellular carcinoma**

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Background: *Antrodia camphorata* (*AC*), a medicinal mushroom indigenous to Taiwan, is well known for its anticancer, antioxidant, hepatoprotective, immunomodulatory, and anti-inflammatory properties. *AC* has been widely used as a dietary supplement for cancer prevention in several Asian and European countries. However, mechanisms responsible for its antitumor effects are not fully understood. Cancer-related inflammation is thought to promote tumor progression in many ways, such as cell proliferation, survival, and migration. Given that IL-6, a major cancer-related inflammatory cytokine, mediates STAT3 activation and is upregulated in hepatocellular carcinoma (HCC), we aimed to investigate the IL-6-regulated mechanisms underlying the antitumor effects of *AC* on HCC.
Material and Methods: The present study evaluated antitumor activity of an ethanol and water extract of *AC* fruiting body. Human HCC cell lines, Huh7 and PLC/PRF/5, were treated with *AC* alone or in combination with antitumor agents, and the antiproliferative effect of *AC* was determined by MTT assay. IL-6 levels were measured by ELISA. Protein levels of STAT3 and phosphor-STAT3 (Y705) were determined by immunoblotting and mRNA levels of STAT3 target genes were measured by qRT-PCR. The effect of *AC* on *in vivo* tumor growth was evaluated by xenograft and allograft tumor models, and combination effect of *AC* and doxorubicin was assessed in the former model.
Results: *AC* enhanced growth inhibition by antitumor agents in HCC cells, and significantly reduced IL-6 in cell culture supernatants and mouse tumor allografts. Additionally, *AC* treatment led to the reduction of IL-6-induced STAT3 activation, as well as the inhibition of downstream target genes, including cyclin D1, survivin, and c-Myc. Oral administration of *AC* attenuated tumor growth in allograft mouse models without significant toxicity to normal tissues. The growth of subcutaneous tumor xenografts was delayed by a combination of *AC* and doxorubicin treatment. Collectively, these findings suggest that *AC* exhibits anti-HCC potency through inhibition of IL-6 signaling.
Conclusions: The current study sheds new light on the role of *AC* as an antitumor agent through inhibiting the IL-6 signaling pathway. Moreover, *AC* enhances the efficacy of doxorubicin in minimizing the tumor size. Thus, *AC* offers new prospects for overcoming antitumor drug resistance, with great potential as an adjuvant in the treatment of HCC.
No conflict of interest.

2478 POSTER

Prognostic assessment of cofilin in patients with gastric cancer

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The estimated new cancer cases worldwide in 2008 were 12.6 million, with 5.4 million cases diagnosed in developed and 6.7 millions in developing countries. The number of cancer-related deaths was 7.6 million, 2.9 million in developed and 4.7 million in developing countries. Malignant neoplasm ranks second (12.5%) as causes of death worldwide, surpassed by cardiovascular causes (19.6%). Gastric Cancer (GC) ranks fourth as the most frequent cause of cancer worldwide, with one million new cases in 2007, behind lung, breast and colon and rectum. 70% of new cases occur in developing countries. Currently, GC is the second most common cause of cancer deaths, accounting for 800,000 deaths annually. In Brazil, estimates for 2013 point to the occurrence of 518,510 new cases of cancer, and the GC occupying fifth place in attendance with 20,000 new cases. The acquisition of the migratory behaviour of cancer cells is a prerequisite to

break up organized tissue structures, invade and metastasize. Recently, the expression of proteins that block actin has been associated with the invasive behaviour of tumours. The cofilin is an actin-blocking protein, which regulates the actin cytoskeleton to maintain and depolymerize actin filaments. The interest for cofilin and its cascade have increased because of its relationship with tumour invasion, metastasis and be a potential prognostic factor in cancer. We conducted a retrospective study, observational, descriptive and analytical. We used all the pathological reports of patients undergoing gastrectomy for adenocarcinoma between June 2002 and June 2012, totalling 380 cases. The average age of patients was 68 years, with 63.6% of male sex. In assessing the depth of invasion, advanced lesions with involvement beyond the submucosa corresponded with 72.7% of cases. The diffuse type in Lauren's classification was the most prevalent with 68.1%. The bacterium *H. pylori* was positive in 72.7% of carcinomas. Lymph nodes involvement accounted for 70.4% of cases. At the end of the study 56.8% of patients were alive. When applied statistical tests to assess the relationship of cofilin with the other independent variables, the depth of tumour invasion and the presence of positive lymph node were statistically significant. In conclusion, despite the cofilin is not statistically significant in overall survival, high cofilin is correlated positively with advanced and lymph node metastatic tumours. Cofilin can be regarded as valuable tool for predicting metastasis to lymph nodes in patients with gastric cancer.
No conflict of interest.

2479 POSTER

Metalloproteinases gene polymorphism and prognosis of HCV related hepatocellular carcinoma in Alsharkia governorate, Egypt

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Background: Liver cancer is the sixth most common form of cancer and the third most common cause of cancer death worldwide. Hepatocellular carcinoma (HCC) accounts for a vast majority − 84% − of all liver cancers, and a large proportion of HCC cases are attributable to hepatitis C virus (HCV) infectionthe. Matrix metalloproteinases (MMPs) are a prerequisite for cancer invasion, metastasis, and angiogenesis. In this study, we examined the relationship between the gene polymorphisms of MMP-1, MMP-3, and MMP-9 and the prognosis of hepatitis C virus HCV-related HCC.
Subjects and Methods: 60 HCV and 60 HCV-related HCC patients were enrolled in the study, and gene polymorphisms of MMP-1 −1,607 1G/2G, MMP-3 −1,171 5A/6A, and MMP-9 −1,562 C/T were analyzed using PCR RFLP technique.
Results: In HCC, MMP-3 5A carriers had significantly larger tumor size than MMP-3 6A homozygotes. In HCC prognosis, MMP-3 5A carriers had a significantly poorer prognosis than MMP-3 6A homozygotes.
Conclusion: MMP-3 5A allele is cooperative risk factors for poor prognosis in HCC patients, suggesting that this gene polymorphism might be potential markers for predicting the prognosis of HCC patients.
No conflict of interest.

2480 POSTER

Expression and prognostic significance of livin in gastric cancer

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Background: Livin is one of the most important members of the inhibitors of apoptosis protein family. It is overexpressed in various tumours and may have prognostic significance. The study investigated the biologic roles of livin on oncogenic behaviours of gastric cancer cells, the expression of livin in gastric cancer tissue and the relationship of its expression with various clinicopathological parameters and patient survival.
Materials and Methods: Small interfering RNA blocked livin gene expression in AGS and SNU638 human gastric cancer cell lines. The expression of livin by RT-PCR, Western blotting and immunohistochemistry was investigated in gastric cancer tissues. Associations with various clinicopathological parameters and survival were analysed.
Results: Livin knockdown inhibited tumour cell migration, invasion and proliferation in AGS and SNU638 cells. Livin knockdown induced apoptosis by activating caspase-3, −7 and PARP. Livin knockdown induced cell cycle arrest by decrease of cyclin D1, cyclin-dependent kinase 4 and 6 and increased expression of p21 and p27. The ERK1/2 and JNK signalling pathways were inhibited by livin knockdown. Livin expression was up-regulated in gastric cancer tissues at mRNA and protein levels. However, no significant correlation was found between livin expression and various clinicopathological parameters including survival.
Conclusions: Livin expression may be important in the alteration of invasive and oncogenic phenotypes of gastric cancer cells. The prognostic relevance of livin remains unclear.
No conflict of interest.

2481 POSTER

Induction chemotherapy followed by surgery for primarily incurable oesophageal carcinoma

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Introduction: In patients with advanced oesophageal carcinoma that are not eligible for a curative multimodal treatment, induction chemotherapy can be applied with the aim to downstage the tumour. After response evaluation, an oesophagectomy can be performed in selected cases. The aim of this study was to evaluate the clinical outcome of these patients.
Methods: All patients with primarily incurable loco regional oesophageal or gastroesophageal junction cancers who are treated with induction chemotherapy between January 2005 and December 2012 were identified from a prospectively collected database. The indication, assessment of radiological response with CT scanning and plan of treatment were determined at multidisciplinary team meetings. Clinical outcome was analysed for all patients who received induction chemotherapy. Survival was calculated from the date of diagnosis until last date of follow up or death using Kaplan Meier method. Univariate and multivariate analyses were performed to identify prognostic factors for survival.
Results: A total of 134 patients received induction chemotherapy mainly for loco regional advanced disease (n = 85) determined by T- and/or N-staging and involvement of lymph nodes outside the planned radiation field (n = 34). Carboplatin-paclitaxel (78.4%) and epirubicin-oxaliplatin-capecitibine (11.9%) were the commonly used regimes. After response evaluation, surgery was withheld in 45 patients because of progressive disease (n = 21), stable disease or partial response but still irresectable (n = 13), severe co morbidity (n = 2) or other reasons (n = 9). Median overall survival of this group was 14 months (95% CI: 12.3–15.7).
Thirteen patients had an irresectable tumour or distant metastatic disease at explorative surgery. Seventy-six patients underwent oesophagectomy, with a median survival of 20 months (95% CI: 9.9–30.1) and a 5-year survival of 27%. Tumour free resection margins (R0) were achieved in 50 (66%) patients and the median survival in this group was 39 months (95% CI: 11.4–66.6), with a 5-year survival of 37%. In uni- and multivariate analyses resection margins and pathological N-stage influence survival in this selected group of patients.
Conclusion: After induction chemotherapy for primarily incurable oesophageal cancer, oesophagectomy was feasible in the majority of patients (57%). Patients who had tumour free resection margins without positive lymph nodes had the most favourable prognosis, with a 5-year survival of 37%.
No conflict of interest.

2482 POSTER

Residual esophageal cancer after neoadjuvant chemoradiotherapy frequently involves the mucosa and submucosa

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Objective: To gain insight into the exact location of residual esophageal cancer in the esophageal wall and regional lymph nodes after neoadjuvant chemoradiotherapy (nCRT) and to determine the pattern of regression.
Background data: Data from the recently published CROSS trial showed that 49% of squamous cell carcinomas and 23% of adenocarcinomas had a pathologically complete response (pCR) in the resection specimen after nCRT. These results impose the ethical imperative to reconsider the necessity of esophagectomy with its substantial morbidity and mortality in patients with pCR. However, it remains challenging to accurately identify these patients before resection.
Methods: Between January 2003 and July 2011, all patients with esophageal cancer in a tertiary referral center, who underwent nCRT (5 weekly courses of carboplatin and paclitaxel plus 41.4 Gy concurrent radiotherapy) and surgical resection, were analyzed. The resection specimens were carefully re-evaluated by an experienced gastrointestinal

pathologist. Tumor regression grade (TRG) was meticulously scored for each specific layer of the esophageal wall and for all removed lymph nodes.
Results: One-hundred and two consecutive patients were included. Seventy-one (70%) of 102 patients were non-complete responders (⩾TRG2) and in 63 of these patients (89%) residual tumor cells were seen in the mucosa and/or submucosa. Five of eight patients without involvement of the mucosa and submucosa had isolated remnants in the muscle layer (5/102=5%); the other three patients had tumor cells only in a single lymph node (3/102=3%). The surrounding stroma showed the highest percentage of TRG1 (=pCR: 47%). In patients with pretreatment lymph node positivity, the percentage of TRG1 in all lymph nodes was also favorable (52%). Overall regression showed a non-random mixed pattern of both concentric regression and regression towards the lumen.
Conclusions: After neoadjuvant chemoradiotherapy for esophageal cancer both the mucosa and submucosa show frequent residual malignant involvement. The surrounding stroma and the regional lymph nodes show the highest percentage of pathologically complete response and the overall regression pattern is most frequently a mixed pattern of both concentric regression and regression towards the lumen. This overall regression pattern lends support to careful testing of a wait-and-see approach in a subgroup of esophageal cancer patients after nCRT.
No conflict of interest.

2483 POSTER

Primary tumour resection impact on survival in patient with carcinoid syndrome (CS). Analysis of 139 patients (pts) with well differentiated neuroendocrine tumors (WDNETs) from database of Istituto Nazionale Tumori Milano

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Background: The tumors causing CS arise from enterochromaffin (EC) or enterochromaffin-like cells (ECL) and can originate throughout the digestive system. About 10% of NET pts develope CS clinically evident. Serotonin which normally regulates intestinal movements is most often hyper-secreted by the EC/ECL cells in the gut and in such condition an increase in urinary5-hydroxyindoleacetic acid (5-HIAA) levels is observed. The overproduction of serotonin determines the typical CS: skin flushing, chronic diarrhea, bronchoconstriction, and right heart disease (CHD), which accounts for 95% of cases. Atypical CS is rare, associated with foregut NETs and histamine hyperproduction. It is characterized by flushing, salivation, bronchoconstriction, lachrymation and hypotension.
Aim: To assess the clinical features and survival of WDNETs pts with CS.
Materials and Methods: We analyzed 1100 NET pts, followed between 1979 to 2012 at our Institution, identifying a cohort of 139 consecutive pts with Typical (98%) or Atypical (2%) CS.
Results: Median age was 53 years, male/female = 67/72. All histological types were classified as WDNET and the majority were Gastro-entero-pancreatic tumors (77%), distinct by sites: Midgut/Foregut/Hindgut/Primary unknown: 60/53/6/20. Liver involvement was found in 115 pts: synchronous (89%); metacronous (11%). Primary tumor resection was performed in 95% of midgut (57) in 55% of foregut (29) and 100% of hindgut (6) pts. The most common symptoms were flushing/diarrhea/CHD in 43.5%/37%/7% of cases respectively. Cromogranin-A/5-HIAA pathological levels, were reported in 59.5% − 47.5% of pts. Significant difference in median overall survival (mOS) was found for age (cut off = median age 56 years), $p < 0.05$, but not for gender. Median OS was 93 months (mos) (95% CI 74–135 range), 5 and 10 years survival rates were 66% and 43%, respectively. Significant difference in mOS was evident considering carcinoid/ pancreatic NET/primary unknown, 130/62/46 mos, respectively ($p < 0.05$). Primary tumor resection improves survival independently of histology: 141/37 mos in resected/ not resected pts, respectively ($p < 0.05$).
Conclusions: Liver involvement was the main feature related to CS appearance. The resection of primary tumour was an independent and favourable prognostic factor related to survival in syndromic WDNETs. Impact evaluation of surgery and loco-regional treatment in pts with only liver metastases is ongoing.
No conflict of interest.

2484 POSTER

Phase I open label multicenter trial SAKK 77/09/SASL 30 investigating the combination of everolimus and transarterial chemoembolisation (TACE) with doxorubicin in patients with hepatocellular carcinoma

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Background: Everolimus is an inhibitor of mTOR, a central kinase linking cell metabolism to cell proliferation. The combination of sorafenib 400 mg bid with everolimus 5 mg qd was investigated in a recently closed randomised phase II SAKK/SASL trial. There is a strong rationale to combine also everolimus with TACE. TACE stimulates the release of growth factors, whose carcinogenic effects can be prevented by everolimus. The goal of this phase I trial was to determine the recommended dose (RD) of everolimus in patients (pts) with HCC treated with TACE.
Methods: Using a 3+3 design with dose de-escalation, pts with BCLC B HCC were enrolled to receive continuous everolimus starting 1 week before the first TACE with doxorubicin eluting beads. Dose limiting toxicity (DLT) was defined mainly as ⩾G3 febrile neutropenia or any ⩾G3 haematological toxicities requiring dose interruption or any >G3 non-haematological toxicities or any toxicities requiring >2 weeks dose interruption, which occurred during the first TACE period (5 weeks after first everolimus treatment). Pts enrolment at a given dose level (DL) had to be discontinued as soon as 2 DLTs were observed.

DL	Dosage by therapy	
	TACE (mg)	Everolimus (mg qd)
1	150	7.5
−1	150	5.0

Results: Between June 2009 and May 2011, 10 pts were accrued, 4 of which were in DL 1. Two DLTs (1 neutropenia with fever and 1 thrombocytopenia which persisted for more than 6 days) occurred 35 and 30 days after registration in DL 1 while no DLT was found in DL −1. Further G3 toxicities were dyspnea (G3, 1 pt in DL 1), mood alteration (G3, 2 pts in DL −1), platelets (G3, 1 pt in DL −1) and pulmonary (G3, 1 pt in DL 1) during the first TACE period, in which no G4 toxicity was seen. Three pts in DL1 as well as in DL −1 had stable disease and three pts in DL −1 had complete response.
Conclusion: The results of this phase I study establish 5 mg qd as the RD for everolimus in combination with TACE and support the decision to proceed to a randomized phase II trial (NCT01009801).
Conflict of interest: *Advisory board: Bayer, BMS, Gilead, MSD, Novartis, Roche.*

2485 POSTER

Clinical outcomes in patients with resectable esophageal squamous cell carcinoma with supraclavicular lymph node metastasis: Surgery versus definitive chemoradiotherapy

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Background: In the 7th edition UICC-TNM classification, supraclavicular lymph node (SCLN) metastasis in thoracic esophageal cancer is regarded as distant metastasis and is not considered to warrant surgery. In contrast, in Japan, three-field lymphadenectomy is a standard procedure for thoracic esophageal squamous cell carcinoma (ESCC), and in the 10th-edition Japanese classification of esophageal cancer the SCLNs are regarded as regional lymph nodes. A recent report showed the clinical benefits of SCLN dissection and suggested that resectable ESCC with SCLN metastasis (rSCLN+) has no worse a prognosis than TNM-N3 [J Surg Oncol. 2012; 106: 742–747]. Therefore, in Japan, surgery with curative intent is considered to be indicated in rSCLN+. However, there are no data on clinical outcomes and promising treatments for rSCLN+.

Our primary objective was to explore the most promising treatment for rSCLN+ after adjusting for background factors by multivariate analysis. The secondary objective was to clarify prognostic factors in rSCLN+.
Materials and Methods: We retrospectively analyzed 97 patients with rSCLN+ initially treated by surgery (S group) or with definitive chemoradiotherapy (CRT group) at our institution (January 2001 through April 2012). Preoperative resectability was reviewed by surgical specialists. Overall survival (OS) and relapse-free survival (RFS) in the S group and progression-free survival (PFS) in the CRT group were calculated by the Kaplan–Meier method. Groups were compared by log-rank test. Univariate and multivariate analysis were calculated with Cox's proportional hazards model.
Results: There were 66 patients in the S group and 31 in the CRT group. There was no significant difference in patient demographics across groups. Median follow-up period was 21.8 months. Median RFS was 11.7 months in the S group. In the CRT group the clinical complete response rate was 58% and the median PFS was 9.3 months. Median OS was 26.5 months in the S group and 24.4 months in the CRT group. There was no significant difference between groups (log-rank: $P = 0.275$). The 3-year OS was 46.2% in the S group and 34.5% in the CRT group; the 5-year OS was 40.8% in the S group and 24.1% in the CRT group. The S group therefore seemed to have an advantage. In the multivariate analysis, age ($\geqslant$65 vs. <65 years old; HR 1.803, 95% CI 1.067–2.993, $P = 0.05$) and primary lesion depth (T1−T2 vs. T3; HR 0.326, 95% CI 0.129–0.826, $P = 0.018$) were strongly associated with poor survival. With background factor adjustment by multivariate analysis, treatment procedure (S vs. CRT) was not significantly associated with survival (HR 0.859, 95% CI 0.493–1.497, $P = 0.592$).
Conclusion: There was no significant survival difference between the S and CRT groups. There was a trend for the S group to have better long-term survival than the CRT group.
There seems to be a subgroup with curative potential in the rSCLN+ population. For these patients, surgery might be an important option for eradicating esophageal cancer.
No conflict of interest.

2486 POSTER

Phase I trial of chemoradiation with capecitabine and vorinostat in pancreatic cancer

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Background: Histone deacetylase inhibitors (HDACi) and fluoropyrimidines are synergistic and are radiation (R) sensitizers. NCT00983268 evaluated the fluoropyrimidine capecitabine (C) and the HDACi vorinostat (V) with R in the treatment (tx) of non-metastatic pancreatic cancer(NMPC).
Methods: Patients (Pts) with NMPC received C + V + R. C dose was 1000 mg q12 Monday (M) − Friday (F) on the days of R. R was given via 3D conformal therapy to a total dose of 3000 cGy in 10 fractions over 2 weeks (wk). V was given daily M-F x 4 wk. Primary endpoint was maximum tolerated dose (MTD) of V when given with C + R. Planned V doses for evaluation were: 100, 200, 300, and 400 mg. Resectability assessment occurred within 6 wk after R completion. Unresectable pts could opt for continuation of C + V (CCV) at systemic doses (C 1000 mg q12 x 14 days and V 300 mg QD x 14 days q21 day cycle) or come off study. DW-MRIs were obtained pre tx and one wk after tx initiation to assess tumor cellularity. Peripheral blood mononuclear cells (PBMCs) were collected to assess tx effects on histone acetylation (HA).
Results: 21 pts were accrued from Nov 2009-Dec 2012. Tumor statuses pre-tx were: resectable (n = 1), borderline resectable (n = 12), and unresectable (n = 8). One DLT each occurred at dose levels 1, 3, and 4: 2 GI toxicities and one thrombocytopenia. Most common related grade $\geqslant$3 adverse events were lymphopenia (76%), nausea (14%), and fatigue (9%). On DW-MRI, the apparent diffusion coefficient (ADC) increased in most tumors but did not correlate to clinical outcome. PBMC HA increased in some pts. 19 (90%) pts had stable disease (SD), and 2 (10%) pts had progressive disease at tumor re-evaluation. 11 pts underwent exploration with 4 R0 resections and one R1 resection. 25% of the initially borderline resectable pts ultimately underwent an R0 resection. No unresectable pt converted to resectable. 4 unresectable pts opted for CCV, 2 with SD for 6 cycles.
Conclusions: C + V + R is feasible with no unexpected toxicity. The MTD was dose level 4: C 1000 mg q12 on days of radiation, V 400 mg daily M-F x 4 wk. CCV after chemoradiation was tolerated. PBMC HA and ADC increase on DWI-MRI were seen.
This study was approved and funded by the National Comprehensive Cancer Network (NCCN) from general research support provided by Merck & Co., Inc. Study was also supported by the Vanderbilt-Ingram Center Support Grant P30CA68485.
Conflict of interest: *Advisory board: Emily Chan serves on the Colon/Rectal/Anal Panel of the National Comprehensive Cancer Network (NCCN), which is the non-profit organization that funded this trial. Jordan Berlin serves on the Neuroendocrine Panel of the NCCN. Corporate-sponsored research: All industry sponsored trial funding goes to the institution rather than individual investigators.*

2487 POSTER

Outcomes and prognostic factors following R1 and R2 resection of non-metastatic pancreas cancer

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Background: We previously reported outcomes and prognostic factors in patients with complete resection of pancreas cancer at our institution. The purpose of this study was to review outcomes and examine potential prognostic factors in patients with incomplete resection.
Materials and Methods: A retrospective chart review was performed on 172 consecutive patients with non-metastatic exocrine pancreas carcinoma who underwent curative intent, but margin positive resection at Mayo Clinic between 1985 and 2009. Extent of resection was R1 (microscopic residual) or R2 (macroscopic residual). Tumor (T) and nodal (N) staging was performed as per AJCC 7th edition. Post-operatively 30 (17.5%) patients were observed (Ob), 114 (66.3%) received immediate chemoradiation (ICR), 21 (12.2%) received 2 cycles of gemcitabine, chemoradiation (CR) and 2 additional cycles of gemcitabine (GCR), and 7 (4%) patients received gemcitabine alone (GA).
Results: Median patient age and follow-up time was 68.2 years (range, 32−86) and 15 months (range, 2–139), respectively. Tumor location was pancreas head (85.5%), body (4%), tail (4.5%), or unspecified (6%). Tumor grade was I (1%), II (12%), III (77%), or IV (10%). T stage was 1 (2.3%), 2 (14%), 3 (68.2%), or 4 (15.5%). N stage was 0 (35%) or 1 (65%). Extent of resection was R1 (77%) or R2 (23%). Three- and 5-year overall survival (OS) for the entire group was 17.9% and 9.53%, respectively. Prognostic factors of improved OS include tumor grade <4 ($p = 0.0006$), R1 resection ($p = 0.003$), use of adjuvant RT ($p = 0.0002$), and use of up front chemotherapy followed by chemoradiation ($p = 0.0039$). Three and 5 year OS in the R1 group for Ob, ICR, GCR and GA was 9% and 4.5%, 20% and 10.7%, 47.6% and 26.5%, 28.6% and 14.3%, respectively ($p = 0.0005$). To account for improvements in recent radiation delivery systems, we excluded patients treated prior to 2000, and similarly statistically significant results were observed. In R2 patients median survival (MS) for Ob and ICR was 8 months and 15.3 months, respectively. R2 patient numbers were insufficient to analyze GCR and GA.
Conclusions: In patients with R1 and R2 resection of pancreas cancer, MS is improved with CR. GA also improved survival above Ob, yet the magnitude of benefit improved further with the addition of CR after 2 cycles of gemcitabine. Further studies are warranted to evaluate the benefit of adjuvant therapy.
No conflict of interest.

2488 POSTER

Toxicity of definitive chemoradiation in patients with inoperable or irresectable esophageal carcinoma

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Background: Definitive chemoradiation (dCRT) is considered curative intent treatment for patients with inoperable or irresectable esophageal cancer. In the Netherlands the preferred radiochemotherapy regimen consists of carboplatin plus paclitaxel concurrent with radiation, which is based on the results of the Dutch CROSS study. Toxicity data are lacking.
Methods: A retrospective analysis of all patients treated with definitive chemoradiation consisting of 6 cycles of paclitaxel 50 mg/m^2 and

carboplatin AUC2 concomitant with radiotherapy (50.4 Gy\1.8 Gy) from 2006 through 2011 at a single tertiary referral center was performed. Patients were divided into two groups based on the reason for treatment with dCRT.
Inoperable patients were defined as patients with surgical contraindications because of comorbidity. Irresectable patients were technically irresectable patients. Toxicity, hospital admissions, recurrence and survival were analysed.
Results: 127 patients were treated with definitive chemoradiation. 33 patients were medically inoperable, 94 patients were irresectable, Grade $\geqslant$3 toxicity was significantly recorded more often in the inoperable patients (44%) than in irresectable patients (20%) ($p < 0.05$). The patients with inoperable esophageal carcinoma had a significantly shorter tumor length (5.1 cm vs 6.6 cm, $p < 0.05$) and consequently a smaller radiation field. Furthermore in the inoperable group 40% of the patients had low stage disease with stadium I−II disease. In spite of a smaller radiation field and lower tumor stage the observed toxicity was significantly higher. Hospital admission occurred more often in the inoperable patients (39%) than in the irresectable patients (22%) ($p < 0.05$). Reasons for hospital admission were dehydration as a result of mucositis or esophagitis and neutropenic fever. Median number of cycles of chemotherapy was five for inoperable patients ($p = 0.01$), while six cycles could be administered to patients with irresectable disease. Recurrence and survival were not significantly different. The odds ratio for developing toxicity $\geqslant$ grade 3 was 2.8 (95% CI 1.1−7.5 $p = 0.04$) for being an inoperable patient and 1.3 (95% CI 1.1−1.5 $p = 0.01$) per 10 extra micromol/l creatinine.
Conclusion: Our data show that toxicity of definitive chemoradiation is worse in patients with medically inoperable esophageal carcinoma compared to patients with irresectable esophageal cancer, mainly occurs in the 5th cycle of treatment and requires hospital admission. Improvement of supportive care should be undertaken in this more fragile group.
No conflict of interest.

2489 POSTER

Recent trends in multidisciplinary treatment of oesophageal and gastric cancer in The Netherlands

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Objectives: In recent years, evidence for multidisciplinary treatment of oesophageal, oesophagogastric junction (OGJ) and gastric cancer has grown. The objective of this population-based study was to investigate changes in treatment strategies for oesophageal, OGJ and gastric cancer in The Netherlands during the last decade.
Methods: Data on treatment of M0 oesophageal, OGJ and gastric cancer patients were obtained from the Netherlands Cancer Registry. Factors associated with the administration of (neo-)adjuvant therapy were adjusted for age, year of diagnosis, clinical tumour stage, geographic region and hospital type.
Results: Between 2000 and 2011, a total of 13,041 patients underwent surgical resection for M0 oesophageal ($n = 5,039$), OGJ ($n = 1,959$) or gastric ($n = 6,043$) cancer. The percentage of patients who received neo-adjuvant and/or adjuvant therapy increased in oesophageal cancer patients from 23% in 2000 to 91% in 2011, in OGJ cancer patients from 6% to 87%, and in gastric cancer patients from 1% to 50%. In oesophageal cancer patients, neo-adjuvant chemoradiotherapy (CRT) was most frequently administered (83% of patients in 2011). In OGJ cancer patients, neo-adjuvant CRT was administered to 8% of patients in 2008 increasing to 46% of patients in 2011. In gastric cancer patients, the use of neo-adjuvant chemotherapy (CT) with or without adjuvant CT increased from 3% in 2005 to 41% in 2011. Adjuvant CRT was administered to 4% of gastric cancer patients in 2005, slightly increasing to 7% in 2011. Oesophageal cancer patients who were treated in academic hospitals were more likely to receive (neo-)adjuvant therapy than those treated in non-academic hospitals ($p = 0.028$). In the group of gastric cancer patients, a similar trend was seen, but the effect of hospital type did not reach statistical significance ($p = 0.12$). Oesophageal, OGJ and gastric cancer patients who were treated with (neo-)adjuvant therapy had a lower risk of death than those who did not receive (neo-)adjuvant therapy ($p < 0.001$ for all groups).
Conclusions: In The Netherlands, the use of multidisciplinary treatment in oesophagogastric cancer has increased during the past decade. In oesophageal and OGJ cancer patients, neo-adjuvant therapy has become standard practice. In gastric cancer treatment, however, there is room for improvement as 50% of patients were not treated with (neo-)adjuvant therapy.
No conflict of interest.

2490 POSTER

Chemoradiotherapy for locally advanced inoperable gastric cancer: A prospective analysis of survival

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Background: The proportion of patients with initially locally advanced inoperable gastric cancer (LAIGC) is up to 30%. Currently, chemotherapy (CT) is the only and purely palliative treatment approach for patients with LAIGC. Radiation therapy (RT) alone or in combination with the CT of 5-fluorouracil, for inoperable gastric cancer is usually administered for relieving the symptoms of disease. Studies have shown the advantage of chemoradiotherapy (CRT) compared to RT, CT, but the study on the efficacy of platinum-based CT in combination with RT in LAIGC has not been published yet.
Purpose: To compare the effectiveness of CRT and CT by means of progression-free survival in patients with LAIGC in an one-center, open, prospective, randomised study.
Methods and Materials: Randomisation was carried out by the ratio 1:1. Radiation therapy was administered to a total dose of 50−68 Gy on defined target, with the first 40−44 Gy delivered within an area, encompassing lymphatic stations up to the D2+ level. Chemotherapy scheme included cisplatin 100 mg/m^2 i.v. on the D 1, 5-fluorouracil 1000 mg/m^2 by 24-hour intravenous infusion on D 1−5, totally 4−6 courses. Primary end point for comparison was progression-free survival (PFS), while secondary endpoints were response rate, toxicity of treatment, and overall survival (OS). Distributions were estimated using the chi-square test. Survival was evaluated using Kaplan–Meier method, with the differences determined by log-rank method. The influence of initial factors on was studied using Cox regression.
Results: Sixty-four patients with LAIGC were totally enrolled to CRT ($n = 32$) and CT ($n = 32$) arms. Median follow-up of all patients was 15.1 months, 28 (43.8%) patients have died. Median PFS in patients, receiving CRT, was 8.8 (95% CI 6.5–11.1) months, CT 6.5 (95% CI 3.9−9.2) months, respectively ($\chi 2 = 8.988$, $p = 0.003$). The median OS in the CRT and CT groups was 15.1 (95% CI 13.1–17.0) months and 11.1 (95% CI 8.9–13.3) months, respectively ($\chi 2 = 0.878$, $p = 0.349$). Objective response rate in the CRT group was 18.8%, in the CT group 9.4%. The multivariate Cox analysis after adjustment for other parameters showed CRT being associated with reduced progression risk, OR=0.48, (95% CI 0.23–0.96). The toxicity did not differ between the groups.
Conclusion: The progression-free survival rate was found to be higher in patients with LAIGC who received CRT compared to patients receiving CT only. Addition RT to CT in LAIGC does not lead to significant increase in toxicity compared with only CT. Phase III comparison is warranted.
No conflict of interest.

2491 POSTER

Pre-therapeutic hemoglobin level has a significant impact on tumor response and outcome in neoadjuvant chemoradiotherapy for esophageal squamous cell carcinoma

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Background: Neoadjuvant chemoradiotherapy (CRT) followed by esophagectomy confers a survival benefit upon patients with locally advanced esophageal cancer. However, neoadjuvant CRT might be less meaningful for poor responders. Therefore, the prediction of effect after neoadjuvant CRT is clinically important for the selection of optimal therapy for patients with advanced esophageal cancer.
Methods: We reviewed data from 123 patients with esophageal squamous cell carcinoma who underwent neoadjuvant CRT comprising 40 Gy of radiation with concurrent 5FU plus one of docetaxel, cisplatin or combined docetaxel/cisplatin followed by esophagectomy. We retrospectively assessed associations between clinical data obtained before starting neoadjuvant CRT and pathological responses.
Results: We compared good responders (over two-thirds of the primary tumor reduced by neoadjuvant CRT; Japan Esophageal Society response evaluation criteria Grades 3 and 2; $n = 89$, 72.4%) and poor responders (less than two-thirds of the primary tumor reduced by neoadjuvant CRT; Japan Esophageal Society Grades 1 and 0; $n = 34$, 27.6%). Primary tumor length ($p = 0.02$), hemoglobin (Hb) ($p = 0.007$) and platelet numbers ($p = 0.03$) were statistically significant parameters. Multivariable analysis

subsequently revealed Hb (OR, 1.51; 95% CI, 1.14–1.98; p = 0.004) as the sole independent covariate for a response to neoadjuvant CRT. The receiver operating characteristic curve showed that the optimal cutoff for pre-therapeutic Hb was 13 g/dL for predicting a response, and 82.9% and 51.2% of patients with Hb > and ⩽13 g/dL, respectively, were good responders (p = 0.0002). The 5-year overall survival rates of patients with Hb >13 and ⩽13 g/dL were 61.8% and 43.0%, respectively (p = 0.03).
Conclusions: Responses to neoadjuvant CRT and the survival of patients with esophageal squamous cell carcinoma can be predicted from the pre-therapeutic Hb level. Pre-therapeutic evaluation based on Hb could be easily incorporated into routine clinical practice.
No conflict of interest.

2492 POSTER

Combination of transarterial chemoembolization plus sorafenib in Chinese patients with unresectable hepatocellular carcinoma: A subgroup results of the START final analysis

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Background: START is a phase II, multicenter, open-label, single-arm study investigating the therapeutic effect of transarterial chemoembolization (TACE) plus sorafenib (sor) for intermediate stage unresectable hepatocellular carcinoma (uHCC) in Asia (NCT00990860). The preliminary final analysis was presented in the ILCA 2013. Here, we report Chinese patients subgroup results.
Methods: Intermediate stage (BCLC B) uHCC patients and candidates for TACE were enrolled. Patients received conventional TACE with lipiodol and doxorubicin (30−60 mg), followed by embolization with absorbable particles. Sor (400 mg, po, bid) was administrated 4 days after the first TACE, and then continuously with interruption of 3 days before and after TACE. Tumor response was assessed 4 weeks after every TACE, and every 3 months thereafter if no TACE was indicated. Patients continued sorafenib until disease progression or unacceptable toxicity. The primary endpoint was safety/tolerability. Secondary endpoints included progression-free survival (PFS), time to progression (TTP), overall survival (OS), and number of TACE cycles.
Results: A total of 70 Chinese patients were enrolled. The median age was 52 years (range 31−75) and 58 (83%) were male. The main etiology for HCC is hepatitis B in 63 (94%) patients. 68 (97%) patients had cirrhosis. 65 (93%) patients were BCLC B stage and all patients were in ECOG Performance Status 0−1 at baseline. 68 patients who had taken at least one dose of sor were eligible for safety and efficacy analysis.
Mean daily dose of sor was 788.24 mg, and median duration was 343.5 days (range 23 −770). Mean and median TACE cycles were 2.9 and 3.0 respectively. 88.2% of patients had ⩾1 sorafenib-related adverse events (AEs), most commonly were hand–foot skin reaction (HFSR) (52.9%), alopecia (39.7%), diarrhea (35.3%) and rash (20.6%). 11 (16.2%) patients had more than one grade 3 or 4 AEs which were predominantly hepatic function abnormal (6), HFSR (3) and diarrhea (3). 4 patients discontinued sor due to adverse events. 21 and 10 patients had complete and partial response respectively. 28 patients had stable disease. Disease control rate reached 88%. The median TTP and OS were 12.3 and 25.1 months respectively.
Conclusion: TACE and sor combination in Chinese uHCC patients is safe and tolerable. The efficacy results are consistent with preliminary final data.
Conflict of interest: *Corporate-sponsored research: Bayer Healthcare Pharmaceutical,*

2493 POSTER

Surgical (S) vs non-surgical (NS) treatment for stage I esophageal cancer (EC): Single center experience

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Background: Surgical resection (S) is a mainstay treatment for stage I esophageal cancer (EC). Although surgical outcome is favorable, patients (pts) often suffer from postoperative complications and decreased quality of life. Furthermore, medically-unfit pts cannot undergo surgery. Definitive chemoradiotherapy (CRT) or radiotherapy (RT) as an alternative treatment for stage I EC is not well delineated. We aimed to compare NS with S in stage I EC pts to verify its efficacy and feasibility.
Material and Methods: We retrospectively reviewed medical records of pts having received treatment for histologically confirmed, clinical stage I EC at Asan Medical Center from 2003 to 2012. Those pts with T1aN0M0 who received EMR were excluded. Routine clinical diagnostic work up included endoscopy, endoscopic ultrasound, computed tomography, and positron emission tomography. Baseline characteristics, treatment outcomes and complications, and survival were compared.
Results: There were 264 pts in S group, whereas 20 pts in NS group. Median age was 69.5 and 63.0, respectively. Male was predominant, and squamous cell carcinoma was main histology in both groups (97% and 100%, respectively). ECOG performance status was poorer in NS group. In NS group, 13 pts received concurrent CRT, 2 pts sequential CRT, and 5 pts RT alone. Most adverse effects were grade 1 or 2. All grade 3 or 4 toxicities were hematological, but manageable without serious complications. In S group, vocal cord palsy (13%), esophageal stricture (11%), infection (11%), wound problem (8%) were frequent. There were 5 pts (2%) with in-hospital 30 days mortaliy in S group. With a median follow up of 41.8 months, 31 pts (12%) in S group and 3 pts (15%) in NS(2 pts in RT alone, 1 pt in CRTgroup) recurred. First sites of recurrence for S and NS were locoregional (17pts vs 3pts), distant (6 vs0), and both locoregional and distant (8vs0), respectively. Median time-to-recurrence was not reached in both groups (log-rank test p = 0.583). Seven pts (35%) and 50 pts (19%) died in NS group and S group respectively.Median overall survival was 71.4 months (95% CI 30.7–112.0 months) in NS group and not reached in S group (p = 0.052).
Conclusions: For stage I EC, NS can be alternative to S, especially in medically unfit pts for surgery. The role of definitive CRT for early stage EC needs to be verified in future prospective randomized trial.
No conflict of interest.

2494 POSTER

Survival outcomes in potentially resectable T3 node positive gastroesophageal carcinomas treated with perioperative chemotherapy

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Background: Perioperative (MAGIC protocol, Cunningham et al NEJM 2006) chemotherapy has improved outcomes in resectable gastric and distal oesophageal carcinomas. However, a significant proportion of patients with localised disease present with T3 disease which is often node positive. Outcome after perioperative therapy in these patients is unclear. Furthermore, the effect of stage migration on survival is unknown.
Materials and Methods: Between December 2009 and December 2011 104 patients with T3N0/N+ potentially resectable oesophageal or gastric carcinoma were identified. Radiological pre-therapy and post resection pathological staging was recorded in accordance with TNM 7 pathological staging. Patients were treated with perioperative ECX chemotherapy (Epirubicin, cisplatin and capecitabine) at the Christie Hospital, United Kingdom. Clinical, radiological and pathological characteristics were correlated with survival (progression free (PFS) and overall survival (OS)).
Results: 104 patients (Table 1) were commenced on perioperative chemotherapy with curative intent. 34/104 patients (33%) either progressed on neoadjuvant chemotherapy or were deemed unfit and did not have surgery. 27/104 (27%) patients completed the full course of chemotherapy treatment.
The median follow up was 15.5 months. The median progression free survival (PFS) and overall survival (OS) for all patients was 18.5 months and 21 months respectively. 1 year relapse free survival was 51%.
With respect to radiological staging, the median PFS for T3N0 patients compared to T3N+ patients (was 19.3 months and 14 months respectively (HR 0.72 95% CI 0.39–1.34 p = 0.30). Moreover, overall survival (OS) for

T3N0 and T3N+ patients was not significantly different (21.8 vs. 21.0 months HR 0.38 95% CI 0.17–0.86 p = 0.78). Comparison of T3N0−1 with T3N2+ was significant for PFS alone (18.89 vs. 10.12 months HR 0.48 95% CI 0.25–0.91 p = 0.025).
When pathological nodal staging was assessed, the median PFS for ypT3N0 patients had not been reached compared to pyT3N+ patients which was 18.9 months (HR 0.37 95% CI 0.17–0.77 p = 0.001). Similarly, overall survival (OS) for pyT3No had not been reached and for pyT3N+ patients was 22.47 months (HR 0.38 95% CI 0.17 to 0.86 p = 0.02). Increase in pathological T stage and number of pathologically involved nodes were also significant for diminishing PFS and OS by univariate analysis. There was no correlation between radiological and pathological staging of either T or N status (r^2=0.007 and 0.002).
Conclusions: T3 cancers of the oesophagus/stomach have a high relapse rate. Radiological staging of T3 cancers can predict for PFS. Pathological stage predicts for PFS and OS and may be a more accurate indicator of survival in accordance with stage migration.
No conflict of interest.

Table 1

Characteristic		Number of patients (N = 104)
Age	Range	42−84 years
	median	65
Sex	Males	88
	Females	17
WHO performance status	0	21
	1	77
	2	5
	3	1
Site of tumour	Oesophagus	52
	GOJ	30
	Gastric	16
Co-morbidities	Cardiac	38
	Respiratory	11
	Diabetes	10
	Other	37
	None	31
Oesophageal stent	yes	18
	no	73

2495 POSTER

Brain metastasis in patients with esophageal squamous cell carcinoma

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Background: Patients with esophageal squamous cell carcinoma have a poor outcome. The lungs, liver, bone, pleura and adrenal gland are the most common sites of visceral metastasis, but brain metastasis is exceedingly rare. The reports about the clinical outcome of brain metastasis in esophageal squamous cell carcinoma are few. Therefore, we performed a retrospective review of esophageal squamous cell carcinoma patients with brain metastasis to assess the incidence of brain metastasis and their prognosis.
Material and Methods: Between January 1996 and December 2011, 1011 patients with esophageal squamous cell carcinoma were retrospectively reviewed, and 14 patients with brain metastases were identified. Diagnoses of brain metastasis were established using brain computer tomography (CT) scan, or magnetic resonance imaging (MRI).
Results: The incidence of brain metastasis in our series was 1.4%. The median survival from the diagnosis of brain metastasis in these 14 patients with esophageal squamous cell carcinoma was 1.9 months. The median follow-up from the diagnosis of esophageal cancer to the diagnosis of brain metastasis was 6.6 months. Systemic metastasis at the diagnosis of brain metastasis was found in 10 patients (71%). A single brain metastasis was found in 6 patients (43%), two brain lesions were found in 2 patients (14%), and multiple brain metastases were found in 6 patients (43%). Primary treatment was whole brain irradiation therapy (WBRT) alone in 5 patients (36%), surgical resection in 6 patients (43%), 5 of whom (36%) subsequently were treated with WBRT, and best supportive care in three patients (21%). Univariate analysis showed that patients with single brain metastasis (P = 0.004), treatment with surgical resection plus whole brain radiation therapy (P = 0.002), and absence of systemic metastasis (P = 0.03) were significantly associated with better clinical outcome.
Conclusions: The incidence of brain metastasis in esophageal squamous cell carcinoma is 1.4%, and the prognosis is poor. Patients without systemic metastases or with single brain metastasis have significantly superior survival, suggesting that aggressive therapy should be considered in these groups of patients.
No conflict of interest.

Table: The clinical outcome of 14 esophageal cancer patients with brain metastasis

Characteristic	Number of patients	Median overall survival (mos)	P value
Number of brain metastases			0.004
Single	6	13.4 (1.2–54.4)	
Multiple	8	1.5 (0.3−3.9)	
Treatment modality			0.002[#]
WBRT*	5	1.5 (1.2−3.9)[#]	
Resection alone	1	1.6	
Resection + WBRT	5	14.6 (6.0–54.4)[#]	
Supportive care	3	0.4 (0.3−0.7)	
Systemic metastasis			0.03
Yes	10	1.6 (0.4–12.1)	
No	4	29.3 (0.3–54.4)	

WBRT: whole brain radiation therapy.

2496 POSTER

Efficacy and safety of chemoradiotherapy using intensity-modulated radiotherapy (IMRT) for locally advanced esophageal cancer

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Background: The outcome of inoperable esophageal cancer has been reported as extremely poor. For locally advanced T4 and/or M1 (LYM) cases, chemoradiotherapy is recommended. Historically, radiation to the esophagus was delivered with 2D techniques that affected a large volume of normal tissue. This irradiation of normal tissue causes acute and late toxicity such as myelosupression, gastrointestinal symptoms, pericarditis, heart failure and radiation pneumonitis. With intensity-modulated radiotherapy (IMRT), there is not one individual beam of uniform dose but rather a series of individual beamlets each programmed to vary the dose intensity across the target/normal tissue interface. IMRT enables the intended dose to be shaped three-dimensionally to maximize the dose to the intended target and minimize the dose to the healthy tissue. We evaluated the clinical efficacy and safety of IMRT for locally advanced esophageal cancer retrospectively.
Methods: Between May 2008 and December 2012, 23 (22 male and 1 female, median age 71(56−78)) T4 and/or M1 (LYM) locally advanced esophageal cancer patients were treated with IMRT+chemotherapy. The treatment consisted of chemotherapy (5-FU and cisplatin; FP) and concurrent irradiation using IMRT of 50−60 Gy in 25−30 fractions to the esophageal primary tumor and regional lymph nodes. Histologically, 21 patients had squamous cell carcinoma, 1 patient had adenocarcinoma and 1 patient was uncertain due to undifferentiation. Clinically, 22 patients had dysphagia due to primary tumor before treatment, and when there was a need, nutritional support was provided by intravenous hyperalimentation or feeding through a percutaneous gastrostomy tube.
Results: The overall response rate of the primary lesion was 96.5%, including 13 patients (56.5%) who achieved a complete response. Dysphagea was improved in 19 patients (86.4%; p>0.01 paired t test). The median overall survival was 13.8 months, and the 1-year and 3-year survival rate were 50.0% and 36.3% respectively. The median progression-free survival was 6.5 months. Recurrences were observed in 18 patients and recurrent sites were distant metastasis, with only 1 patient having local recurrence. Three patients showed lymph node metastases within 1 year after IMRT+FP underwent secondary IMRT+FP, and have been in remission for more than 2 years. Severe (over grade 3) adverse events were observed in 9 patients. Major severe adverse events were leucocytopenia (34.8%) and neutrocytopenia (17.4%). No patient died within the treatment schedule or for 30 days after treatment.
Conclusions: IMRT+FP for inoperable locally advanced esophageal cancer showed a very high local control rate and improved dysphagea. Distant metastases were the main cause of death and adjuvant treatment will be needed to prevent them. To our knowledge, this is the first report about the use of IMRT for locally advanced esophageal cancer.
No conflict of interest.

2497 POSTER

Yttrium-90 (Y90) radioembolization for primary and metastatic liver cancer in British Columbia

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Background: Y90 is a potential therapy for both unresectable hepatocellular carcinoma (HCC) and liver metastases. Little data is available regarding differences in efficacy for different tumour primaries.
Methods: We retrospectively reviewed 41 consecutive patients (pts) with different primary cancers who were treated with Y90 between November 2009 and December 2012 at Vancouver General Hospital. Median overall survival (OS) and progression free survival (PFS) from the first Y90 treatment were examined by Kaplan–Meier. Log-rank was used to test differences in OS and PFS between groups.
Results: Forty-one pts (male: 28, female: 13) received 66 Y90 treatments and were discharged on the same day. Four pts received repeated Y90 therapy after progression on the first. Mean age was 62.2 years (range 32−83). There were 20 neuroendocrine tumours (NETs), 9 HCCs, 8 colorectal adenocarcinomas (CRCs), 1 cholangiocarcinoma, 1 urothelial carcinoma, 1 jejunum adenocarcinoma and 1 choroidal melanoma. Among pts with HCC, 77.7% had cirrhosis and 66.6% portal vein thrombosis. At the time of Y90 treatment, 34.1% of the pts had extra-hepatic disease. At the first response assessment, 25 pts (61%) achieved a partial response in the liver and 2 (4.8%) had stable liver disease. Of the 27 pts who had liver disease control, 30% had progressive extra-hepatic disease. The median PFS and OS were 5.0 months (95% CI 2.5−7.5) and 16.4 months (95% CI 10.2–22.5), respectively. Those without extrahepatic disease had a better median OS (18 vs 7.7 months), although not statistically significant ($p = 0.14$). Pts with NETs had a better median OS (not reached yet) when compared to HCC (3.03 months; $p = 0.005$) and CRC (4.37 months; $p < 0.001$). Y90 was well tolerated with no grade 4 or 5 adverse events. Only one patient died within 30 days of Y90 due to complications of small bowel obstruction. The most common side effects were abdominal pain (48.7%), nausea (29.2%) and fatigue (29.2%).
Conclusion: Our data support the safety and efficacy of palliative Y90 for both unresectable HCC and liver metastases. NETs seem to derive the greatest benefit.
No conflict of interest.

2498 POSTER

The evaluation of factors predicting recurrence and prognosis for patients with node-negative gastric cancer after curative resection

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Background: Patients with node-negative gastric cancer (GC) have better overall survival (OS) than lymph node positive GC, but some of them may develop relapse and need adjuvant therapy. In the present study, we aimed to evaluate the predictors for recurrence and prognostic factors for survival in patients with node-negative GC.
Methods: A total of 231 patients with node-negative GC who underwent curative D2 gastrectomy were retrospectively reviewed. Clinicopathological factors predicting the recurrence and survival for were evaluated.
Results: pT stage, gender, lymphatic vessel invasion, blood vessel invasion and perineural invasion were significantly associated with recurrence. Sixty-two patients developed relapse. The majority of patients had haematogenous recurrence pattern (62.7%). Patients with loco-regional recurrence had significantly better median disease-free survival (DFS) and OS intervals than those of patients with peritoneal and haematogenous recurrence (DFS, 79.3 vs. 41.8 vs. 29 months, $p = 0.04$; OS, 97.4 vs. 58.6 vs. 36.6 months, $p = 0.01$, respectively). Surgery type, advanced pT stage, clinical stage, larger tumour size and the presence of adjuvant treatment were found to be independent risk factors for recurrence by logistic regression analysis. However, multivariate analysis demonstrated that clinical stage and recurrence pattern were independent prognostic indicators for OS.
Conclusions: Patients with node-negative GC had high incidence of recurrence and some clinicopathological factors may affect the developing of relapse. Recurrent patients had worse survival except for those of loco-regional recurrence. Adjuvant treatments should be considered for node-negative GC patients with high recurrence risk.
No conflict of interest.

2499 POSTER

Prognostic significance of FDG-PET scanning in curatively resected hepatocellular carcinoma

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Background: Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) has proven to be a valuable tool in the initial diagnosis, staging, and restaging of a variety of cancers. The potential use of FDG-PET in the evaluation and management of hepatocellular carcinoma (HCC) continues to evolve.
Methods: The purpose of this study was to investigate the correlation between SUVmax, tumour to non-tumour ratio (TNR), tumour size and histologic grade in curatively resected hepatocellular carcinoma. All patients underwent PET scanning between January 2008 and December 2011. Results of the PET scan were compared with tumour size, AFP levels and histologic grade retrospectively.
Results: Of the 65 patients who underwent ^{18}F-FDG PET, the mean age was 57.5±8.9 (39−74), male and female was 46 (70.8%), and 19 (29.2%) and increased FDG uptake was noted in 44 patients (67.7%). The mean tumour size was 4.8±3.3 cm (1.0–18.0) and mean SUVmax was 3.4±3.1 (0.0–15.7). Histologic grade were as follows: Grade 1 in 1 (1.5%), 2 in 35.4% 23 (35.4%), 3 in 34 (52.3%) and 4 in 7 (10.8%). The total numbers of relapsed patients were 26 (40.0%). Progression free survival (PFS) was 30.0±3.1 (23.9–36.0) months and overall survival (OS) was 45.7±1.9 (41.9–49.4) months. We divided 2 groups according to TNR: below 2.0 ($n = 48$) and above 2 ($n = 17$). Tumour size, SUVmax, AJCC stage, TNR, and elevated AFP after operation were significant factors of PFS in univariate analysis. Tumour size, TNR and elevated AFP after operation were significant factors of PFS in multivariate analysis. OS did not relate with tumour size, SUVmax, stage, TNR and AFP level.
Conclusion: TNR over 2 is isolated significant prognostic factor of PFS in curatively resected hepatocellular carcinoma.
No conflict of interest.

2500 POSTER

Peri-operative and quality of life outcomes after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy − the Asian perspective

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Background: Although cyto-reductive surgery with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) has gained acceptance for the treatment of peritoneal carcinomatosis, the data on quality of life (QOL) after treatment remains scarce, particularly among the Asian population. This study aims to assess long term patient rated outcomes and QOL post CRS and HIPEC in an Asian cancer centre.
Methods: All patients who completed CRS+HIPEC between 6 to 18 months ago (27 patients) were enrolled in the study. QOL was measured via the administration of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaires by 2 healthcare professionals. The control group consists of QOL scores obtained from 393 disease free cancer patients, of ECOG status 0 or 1, who were not on active treatment. The one sample t-test was used to compare differences in QOL scores between the 2 groups of patients.
Results: 27 patients were analysed of which 22 (81%) were females. Median age was 51 years (15−59 years). CRS + HIPEC were performed for ovarian cancer in 15 patients (55%), appendiceal carcinoma in 5 patients (19%) and Colorectal carcinoma in 4 patients. The other primary tumours include primary peritoneal carcinoma (2 patients) and endometrial carcinoma (1 patient). The median intra-operative Peritoneal Carcinomatosis Index (PCI) score was 15 (2−31) while the Completeness of Cytoreduction (CC) Score was 0 and 1 in 25 and 2 patients respectively. The median duration post CRS+HIPEC was 10 months (6−16 months).
Peri-operative morbidities occurred in 13 patients (48%) of which 7 patients (26%) had Class III and IV morbidities. These included intra-abdominal collections requiring percutaneous drainage (4 patients), intestinal obstruction secondary to adhesions requiring repeat laparotomy (2 patients) and anastomotic leak which required operative repair (1 patient).

The QOL scores of patients post CRS+HIPEC compared to that of the control group are illustrated in Table 1. Global health status, functional and symptom scores were largely similar between our cohort of patients and the control group. Cognitive functioning scores and fatigue scores were significantly better in the group post CRS + HIPEC ($p = 0.014$ and $p = 0.04$) respectively.
Conclusion: Despite the initial morbidity associated with CRS and HIPEC, long term QOL in survivors can be comparable to that of disease free cancer patients on follow up.
No conflict of interest.

Table 1.

QOL parameter	Mean score of study population (95% confidence interval)	Control (n = 393)	p value
Function Score			
Global Health	67 (59–75)	71	0.335
Physical Functioning	85 (78–91)	85	0.908
Role Functioning	89 (83–96)	87	0.487
Emotional Functioning	83 (76–89)	81	0.567
Cognitive functioning	88 (83–94)	81	0.014*
Social Functioning	83 (74–93)	86	0.567
Symptom Score			
Fatigue	17 (10–25)	25	0.040*
Nausea and vomiting	7 (1–13)	4	0.308
Pain	13 (5–21)	18	0.204
Dyspnoea	8 (2–15)	15	0.051
Insomnia	16 (6–25)	24	0.052
Appetite Loss	7 (1–14)	11	0.230
Constipation	12 (4–20)	11	0.820
Diarrhoea	7 (1–14)	6	0.720
Financial Difficulties	21 (10–33)	23	0.776

2501 POSTER

A three-step neoadjuvant strategy for locally advanced gastric cancer: A single institutional experience

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Background: To assess the efficacy, toxicity and long term outcome of induction chemotherapy (ICT) followed by chemoradiotherapy (CRT) and surgery in patients with locally advanced gastric or gastro-esophageal adenocarcinoma (GEA).
Methods: Patients (pts) with CT-scan and endoscocopic ultrasound (EUS) T2–4 and/or N+, M0 GEA were retrospectively analyzed. ICT consisted of 3–4 cycles of Docetaxel (D) and Oxaliplatin (O) on day 1 and Capecitabine twice daily for 14 days on a 3 weekly schedule. CRT included weekly D and O administered on weeks 1, 2, 4 and 5 and daily Capecitabine concurrently with external beam radiotherapy (45 Gy). Surgery was scheduled 4 to 6 weeks after the end of CRT. Pathological response was graded according to the Becker criteria. Toxicity was scored according to NCI-CTC.
Results: From November 2004 to April 2012, 73 pts (M/F; 41/22, median age 59 were included. Pretreatment T3-T4 and/or N+ were encountered in 67 pts (92%). Grade 3–4 toxicity during ICT included anemia (3 pts), neutropenia (1 pt), diarrhea (1 pt) and vomiting (1 pt). Grade 3–4 toxicity during CRT included neutropenia (9 pts), g.i. toxicity (3 pts) and asthenia (6 pts). Admission to hospital due to toxicity was required in 22 pts (30%). Sixteen pts (21.9%) progressed while on neoadjuvant therapy. Fifty-seven pts underwent radical surgery with an R0 resection rate of 95%. Pathological response according to Becker criteria was grade1a (35%), grade1b (23%), grade 2 (26%) and grade 3(16%). pN0 was achieved in 35 pts (60.3%). Median DFS for pN0 and pN+ was NR and 17 months, respectively ($p = 0.043$). Among all operated pts, local and distant failures were reported in 21 (28.8%) and 40 pts (54.8%). After a median follow-up of 55 months (range 9–98 months) the 5-year overall and disease-free survival, were 37% and 36%, respectively.
Conclusion: Induction CT followed by CTH in locally advanced gastric and gastroesophageal adenocarcinoma is feasible and achieves a remarkable long-term outcome, with an acceptable toxicity.
No conflict of interest.

2502 POSTER

Health service research mirrors conventional and additional therapies in patients with pancreatic cancer in integrative oncology

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Background: Integrative oncology (IO) responds to patients needs by offering a variety of additional therapies like non-pharmacotherapeutic interventions (NPI) or *Viscum album* extracts (VA), which activate patients' resources, can enhance health-related quality of life and reduce adverse effects caused by standard chemo- or radiotherapy. In the present study we characterize the use of therapies in pancreatic cancer patients in IO settings.
Methods: 527 patient records diagnosed with ICD-10 C25 were collected by the Network Oncology, a conjoint clinical registry of German hospitals and out-patient practitioners active in integrative oncology. We used non-parametric Fisher exact test (F) to compare observed frequencies, Wilcoxon rank sum (W), for differences between groups. Bonferroni correction was used to adjust the level of significance in the case of multiple testing.
Results: The observed sex ratio of 0.86 (female:284, male: 243) was comparable to German incidence data of the Robert-Koch Institute. Men (66 yrs) were in median younger than women (68 yrs; $p_W = 0.02$). 58% were of UICC stage IV at first diagnosis, 6% of stage III, 37% of stage II and 1% of stage I. 16% received radiation, 76% surgery and 79% a chemo therapy. 99% received cytostatic drugs, 18% signal transduction inhibitors, other chemo-therapeutics were less than 5%. 64% had a gemcitabine mono-therapy and it was part of 74% of the recorded combinations. 7% received a combination of 5-FU/FA/oxaliplatin, 5% of erlotinib/gemcitabine, other combination occurred less than 5%. 76% received at least one additional integrative therapy. Most common were VA (f: 80%, m: 72%), nursing interventions (f: 74%, m: 59%), movement therapies (f: 58%, m: 43%), or art therapies (f: 44%, m: 29%). Except for VA, women chose additional therapies significantly more often than men in those groups (all $p_F < 0.0125$). Other types of NPI were recorded in lower frequencies. Female patients received up to 9, males up to 7 different NPI. 61% of women and 45% of men choose at least three NPI. 33% of the men and 20% of women chose none NPI at all.
Conclusions: Beside gemcitabine, VA and NPI are part of standard care and used in high frequencies by patients with pancreatic cancer in an IO setting. Although women were more likely to choose NPI there was no significant bias towards a higher proportion of women in the data base. This data reflect every day care in cancer therapy and can provide a basis for prospective studies on outcome in IO.
Conflict of interest: *Advisory board: Weleda AG, Dychweg 14, CH − 4144 Arlesheim*

2503 POSTER

Chemo-sensitization and immunological reactions to hyperacute immunotherapy, a novel approach to cancer treatment

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Introduction: Hyperacute rejection in higher primates is a well-characterized potent innate immune defense mechanism by which antibodies directed against alpha(1, 3)-Galactosyl carbohydrate epitopes leads to the rapid destruction of xenografts and zoonotic agents from lower mammals. HyperAcute™ cancer immunotherapies consist of genetically modified irradiated allogeneic tumor cells expressing αgal moieties that stimulate the development of immunity directed against antigens shared by immunotherapy cells and host tumors. Drugs of this class have been used in clinical trials with promising results in DFS, OS, tumor responses and correlative immunological data. Chemosensitizaton after immunotherapy has been anecdotally reported. We studied this effect after HyperAcute Immunotherapy.
Methods: HyperAcute immunotherapies are administered intradermally and have been tested in multiple indications; non-small cell lung (Phase, 1/2, N = 54), advanced melanoma (P, 1–2, N = 31), refractory prostate (P, 1, N = 8), and resected pancreatic cancer (P, 1–2, N = 86). Patients were followed for objective responses to follow-on chemotherapy.
Results: A potential sensitizing effect of HyperAcute immunotherapy to salvage therapy was observed with 2 different HyperAcute vaccines.

Three patients with recurrent pancreatic cancer who progressed with metastatic disease after chemo-immunotherapy subsequently had complete responses to various 2nd line regimens and all 3 are still alive (24 −48M). In the HyperAcute-Lung (tergenpumatucel-L) trial 9 of 16 patients that progressed had objective response to chemotherapy. In addition, intriguing immunological and clinical reactions have been observed with HyperAcute immunotherapies. Skin reactions ranging from immediate sensitization with wheal and flare reactions to DTH responses have regularly been observed. Most reactions are localized but some patients experience recrudescent flares at distant previously injected sites as late as one year after vaccination. In the HyperAcute melanoma trial patients developed auto antibodies (100%), Vitiligo (16%) and 2 CR's, including infiltration of tumor with CD8+ lymphocytes. Biopsy of injection sites demonstrated eosinophilic infiltrates. Interestingly, in the NLG0205-pancreas study, 70% of patients experienced some degree of peripheral eosinophilia during treatment.
Conclusions: These novel observations of greater than expected chemotherapy response after HyperAcute Immunotherapy warrants further study.
Conflict of interest: *Ownership: NewLink Genetics*

2504 POSTER

Residual nodal disease in gastroesophageal adenocarcinoma treated with perioperative chemotherapy and surgery: Its impact on disease-free survival

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Background: Perioperative chemotherapy is a standard approach to resectable locally advanced gastroesophageal adenocarcinoma. Randomized studies have shown that it improves disease-free survival and overall survival in comparison with surgery alone. Patients with pathological complete response (pCR) enjoy a long disease-free survival (DFS). However, pCR is only seen in 10−15% of cases, so other markers of prognosis would be helpful. In this study, we assessed the impact on DFS of residual nodal disease (RND) after the preoperative part of chemotherapy.
Patients and Methods: This study, which includes patients from May 2007 to December 2011, is a continuation of the McGill 0620 clinical trial, approved by the Ethics Review Board. Data have been extracted from the prospectively maintained database, built with individual patient consent. We identified 82 patients with resectable locally advanced gastroesophageal adenocarcinoma. Patients were to receive 3 cycles of chemotherapy before and after surgical resection. Postoperative chemotherapy started 6 to 12 weeks after surgery. Chemotherapy consisted of docetaxel, cisplatin and 5-flurouracil given every 3 weeks. Surgery consistently included D2 lymph node dissection. RND is defined as presence of adenocarcinoma in any lymph node retrieved at time of surgery. DFS is defined as time from surgery to time of recurrence or last follow-up. DFS was compared between 2 groups: presence of RND (RND+) or absence of RND (RND-). The log-rank test was used for analysis, with stratification for clinical staging and calculation of impact of administration or nonadministration of postoperative chemotherapy.
Results: Of 82 patients, 12 were excluded for the following reasons: no follow-up after surgery (4), no preoperative chemotherapy (3), neuroendocrine tumor or squamous cell carcinoma pathology (5). Therefore, a total of 70 patients were included in the analysis. RND was found in 50 patients. RND+ was associated with a shorter DFS in comparison with RND- (180 days vs. 720 days, *p* value <0.0001). This association was still significant after controlling for clinical lymph node disease, as diagnosed by computed tomography and/or endoscopic ultrasound (stratified log-rank test: *p* value=0.0002). Regarding possible influence of postoperative chemotherapy, 54 patients received at least one cycle of chemotherapy, 7 patients received none because of personal preference. In addition, nine cases were excluded because no postoperative chemotherapy information was available. Median DFS was respectively 358 vs. 581 days, respectively, for postoperative chemotherapy vs. no postoperative chemotherapy (stratified log-rank test: *p* value=0.6856). This was not considered statistically significant.
Conclusions: This analysis confirms that patients with residual nodal disease after preoperative chemotherapy for gastroesophageal adenocarcinoma have shorter duration of DFS, even after adjustment for clinical staging and administration of postoperative chemotherapy.
Acknowledgements: XianMing Tan, PhD, Biostatistics, McGill University Health Centre
No conflict of interest.

2505 POSTER

Hyperthermic intraperitoneal chemotherapy in combined treatment of local-advanced and peritoneal disseminated gastric cancer: Results of prospective non-randomized study

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Background: A novel strategy of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) has been shown to confer long-term survival for patients with peritoneal carcinomatosis from colorectal cancer. Patients with intraperitoneal disseminated gastric cancer (GC) have a dismal prognosis despite systemic chemotherapy or palliative surgery. Assesment of results use HIPEC in the combined treatment of such patients was purpose of the study.
Material and Methods: Between 2008 and 2012, 49 patients with advanced GC (19 patients with 'serosoinvasive' GC and high risk of metachronous peritoneal carcinomatosis, 20 patients with limited peritoneal carcinomatosis and 10 patients with diffuse peritoneal carcinomatosis and intense malignant ascitis) received treatment including HIPEC and 49 same patients received standard treatment (control group). HIPEC was performed an closed method for 90 min with mean intraperitoneal temperature 42.5ºC (range, 39.5–44.5ºC), mitomycin C 12.5 mg/m^2 and cisplatin 75 mg/m^2.
Results: The frequency of postoperative complications with the use of HIPEC was 26.5%, postoperative mortality − 4.1%. The use of HIPEC in adjuvant regime in patients with high risk of metachronous carcinomatosis permitted to obviously decrease the level of intraperitoneal relapse from 73.7% to 11.1% ($p < 0.001$), and increase 1-year and median survival from 52.6% and 12 month (group of surgical control) to 100% and 22.5 month respectively ($p = 0.001$). The use of HIPEC in combined with cytoreductive interventions and systemic chemotherapy for patients with GC with peritoneal metastasis 1-year and median survival was 68.8% and 12 months, the application of systemic palliative chemotherapy − 25% and 8 months respectively ($p = 0.004$). The use of HIPEC permitted to efficiently liquidate recurrent ascites in patients with diffuse peritoneal carcinomatosis without significant improve on survival ($p = 0.49$).
Conclusion: The HIPEC is a well-tolerated and effective method of adjuvant treatment GC with high risk of intraperitoneal progression. Cytoreduction followed by HIPEC improves survival in patients with limited peritoneal carcinomatosis of gastric origin. The HIPEC is an effective method of treating patients with recurrent intense ascites.
No conflict of interest.

2506 POSTER

Neoadjuvant chemotherapy for advanced gastric cancer; combined analysis to explore prognostic factors

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Background: Prognosis of advanced gastric cancer is still poor even after extended lymph node dissection and adjuvant chemotherapy. Neoadjuvant chemotherapy (NAC) had been energetically investigated to improve the survival of these patients. However, solid survival benefit from NAC had not yet been demonstrated. Patient selection those will obtain the benefit from NAC will be of great importance. To explore the prognostic factors in patients received NAC for advanced gastric cancer, combined analysis of two Japanese phase II study (GC-0301 and GC-0402) was performed.
Methods: 1. GC-0301: Patients with M1 disease staged by conventional CT scan and staging laparoscopy were included in this study. Patients received two courses of cisplatin and S-1 and then underwent gastrectomy with lymph node dissection. 2. GC-0402: Patients with locally advanced gastric cancer, T3−4, N0−3, M0, for whom curative surgery was planned after NAC were included. Staging laparoscopy was not mandatory in this study. Patients received 2 courses of irinotecan and S-1 and then underwent gastrectomy with lymphadenectomy. In both study, patients resumed treatment with S-1 alone for 1 year after surgery. 3. Combined

analysis: To explore the prognostic factor in patients received surgery after NAC and in patients underwent R0 resection, Cox regression analyses (univariate and multivariate) were performed.
Results: GC0301: Fifty-one patients were enrolled and all patients were eligible. Surgery was performed in 44 patients. R0 resection was possible in 26 patients (51%). Median survival time (MST) was 19.2 months. Patients received R0 resection and those with Cy1 alone demonstrated a better survival. GC0402: Of 39 enrolled, 37 were eligible. Surgery was performed in 33 patients. R0 resection was possible in 17 (46%) patients. MST was 15.9 months. Overall survival was significantly better in patients underwent R0 resection. Combined analysis: In all patients received surgery, MST from surgery was 17.1 months. There was no significant difference of survival between the treatment arms. As independent prognostic factors, cN stage, histological type, final stage, and R-number were identified. In subgroup patients underwent R0 resection, only final stage was identified.
Conclusion: These results suggest that R0 resection is essential to achieve long-term survival and highly active regimen to obtain down staging is recommended.
No conflict of interest.

2507 POSTER

Efficacy and toxicity results of neoadjuvant gemcitabine-based combined chemoradiotherapy in patients with borderline resectable pancreatic adenocarcinoma: A single-institution experience

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Introduction: The management of borderline resectable pancreatic adenocarcinoma patients (pts) is challenging. A 1st-line surgical approach can lead to an unacceptably high rate of incomplete resections. Neoadjuvant protocols with chemotherapy (CT) and radiotherapy (RT) might improve response rates and allow a margin-free R0 resection, and could improve long-term survival rates.
Material and Methods: Pts with borderline resectable pancreatic adenocarcinoma according to the AHPBA-SSO-SSAT criteria were enrolled. Prediagnostic evaluation: dedicated pancreatic triple-phase CAT and endoscopic ultrasound. Histologic confirmation mandatory. EGOG PS 0−1. Normal blood, hepatic and renal function (bilirrubin levels <3 mg/dl).
2 cycles of gemcitabine-oxaliplatin q14 days followed by combined CT-RT: weekly gemcitabine 300 mg/m^2; 45 Gy of external-beam RT followed by 5 Gy tumour boost (1.8 Gy/ fraction). Staging CAT after neoadjuvant CT and after combined CT-RT. If feasible, surgery was performed 4 to 6 weeks after end of protocol.
Results: *Patient characteristics*: 16 ptsbetween 02.2008–02.2013. Mean age 55 years (r 37−70). 62 % males. 69% with pretreatment biliary drainage. All PS 0−1. 100%: histologic confirmation of malignancy. Reasons for borderline resectability: mesenteric-portal confluence in 75%, superior mesenteric vein in 19% and espleno-portal confluence in 6%. No arterial involvement.
Treatment: 7% of patients progressed systemically during the neoadjuvant CT; the remaining 93% all finished the protocol. Grade 3−4 toxicity observed (during CT-RT): diarrhoea (19%), abdominal pain (19%) and afebrile neutropenia (19%). Radiological response: 31% minor partial response, 44% stable disease, 25% progressive disease. In 9 patients (56%) a surgical exploration was performed: in 37% a complete resection was possible (cephalic duodenopancreatectomy in 31% and corporo-caudal resection in 6%); in 12% only a palliative derivative procedure was done and in 6% no surgical act was performed. 2 episodes of intestinal ischemia were seen after the end of CT-RT, with one patient death.
Pathologic classification: complete pathologic response in 6%, ypT1N1 in 6%, ypT3N1 in 6%, ypT4N0M0 in 6%; 12% with a neuroendocrine tumour. All R0 resections.
Survival: Median follow-up of 16 m (r 2−28 m). Relapses in 60%: systemic in 37%, local in 19% and both in 4%. Median overall survival (OS) of 8 m (r 5.6–10.8 m). OS according to surgical resection (excluding neuroendocrine): resection vs no resection, 10 months versus 7.3 months, p 0.230.
Conclusions: In our series of clearly defined borderline resectable patients, neoadjuvant CT-RT is feasible and it can identify a subgroup of patients (37%) who can benefit from a radical surgical procedure with clear margins. However, the protocol is technically challenging and should probably be restricted to fit patients who are candidates for radical surgery. The main site of relapse is systemic and improvements in systemic therapies are clearly necessary. Small pretreatment biopsies can be a problem.
No conflict of interest.

2508 POSTER

Prognostic indicators in gastric cancer after neo-adjuvant chemotherapy and surgery

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Background: The aim of this study was to identify reliable factors affecting the survival of locally advanced gastric cancer (LAGC) patients treated with neoadjuvant chemotherapy followed by surgery.
Material and Methods: We reviewed the data of 60 patients underwent gastrectomy after neoadjuvant chemotherapy for LAGC in a clinical trial setting. Univariate and multivariate survival analysis were performed in order to determine the independent prognostic factors. A scoring system was developed including these factors.The time-dependent receiver operating characteristic (ROC) curve was constructed and the area under the ROC curve (AUC) were employed to assess the performance of the score.
Results: On univariate analysis, multivisceral resection ($p < 0.001$), residual disease after surgery ($p < 0.001$), tumour diameter ($p < 0.001$), Lauren's histotype ($p < 0.001$), pT ($p = 0.023$), pN ($p < 0.001$) and T-downstaging ($p = 0.004$) were significantly associated with overall survival. Residual tumour, Lauren's histotype and pN were found to be independent prognostic factors at the Cox's regression. After rounding the regression coefficients, a score ranging from 0 to 4 was obtained. According to the survival estimates and the log-rank test differences, three groups were identified: group I (0 points), group II (1−1.5 points), group III (2.5−4 points). Time-dependent ROC curve analysis provided an AUC of 0.89, 0.90, 0.88 and 0.86 at 1-yr, 2-yrs, 3-yrs and 5-yrs of follow-up, respectively.
Conclusions: Residual disease after surgery, Lauren's histotype and nodal involvement are the most reliable prognostic indicators in patients treated with neoadjuvant chemotherapy. A score combining these variables could correctly predict survival in these patients.
No conflict of interest.

2509 POSTER

Nomogram prediction of overall survival in patients with extrahepatic bile duct cancer undergoing curative resection followed by adjuvant chemoradiotherapy

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Background: To develop a nomogram for predicting the overall survival in patients with extrahepatic bile duct cancer undergoing adjuvant chemoradiotherapy.
Material and Methods: From January 1995 through August 2006, 166 consecutive patients underwent curative resection followed by adjuvant chemoradiotherapy. Multivariate analysis using Cox proportional hazards regression was performed and this Cox model was used as the basis for the nomogram. We calculated concordance indices of the constructed nomogram and American Joint Committee on Cancer (AJCC) staging system.
Results: The overall survival rate at 2 years and 5 years was 60.8% and 42.5%, respectively. The tumor location, involved lymph node, and histologic differentiation were retained in the multivariate Cox proportional hazards model as independent prognostic factors for overall survival. The bootstrap-corrected concordance index of the nomogram and the AJCC staging was 0.63 and 0.50, respectively.
Conclusions: We developed a nomogram that predicted survival better than AJCC staging. It could be useful when counseling patients and choosing treatment strategies.
No conflict of interest.

2510 POSTER

Concurrent chemoradiation of patients with inoperable non-metastatic pancreatic cancer

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Background: Inoperable non-metastatic pancreatic cancer is a great challenge because the median survival is generally less than 1 year and the impact of standard therapies is so limited. All patients should be considered for protocol-based therapy. The aim of this study is to determine the tolerability and efficacy of Gemcitabine concurrent with 3D conformal

radiotherapy for locally advanced, unresectable, non-metastatic pancreatic cancer.
Methods: Thirty three patients received the following protocol in 3 phases; induction phase: weekly Gemcitabine at a dose of 1,000 mg/m^2 over 30 minutes infusion for 7 weeks, chemoradiotherapy phase: gemcitabine 600 mg/m^2 weekly for 5 weeks concurrent with 3 dimensional (3D) conformal radiotherapy for a total dose of 50.4 Gy in 28 fractions in 5.5 weeks, 5 days per week, and maintenance phase: Gemcitabine at a dose of 1,000 mg/m^2 weekly for 3 weeks with 1 week rest between 2 cycles.
Results: Forty eight patients with locally advanced unresectable pancreatic cancer were enrolled; only 33 patients completed the treatment protocol. After a median follow up period of 20 months 15 patients were alive. The median progression free survival (PFS) was 15 months; the median overall survival was 19 months. The estimated 12 months, 18 months and 24 months survival was 79%, 52%, and 18% respectively. Grade III toxicity were reported in 38% of patients with no grade IV toxicity, vomiting were the most common toxicity (35.5%) followed by fatigue (21.5%).
Conclusions: Gemcitabine concurrent with 3D conformal radiotherapy is active, well tolerated and associated with encouraging survival in patients with locally advanced pancreatic cancer.
No conflict of interest.

2511 POSTER

Reality of adjuvant treatment with chemoradiation in gastric cancer in non-selected patients. Is it possible to achieve the results of controlled trials?

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Background: Adjuvant treatment in cancer gastric is controversial. Postoperative chemoradiotherapy has been a standard since publication of the INT0116 trial (MacDonald, N Eng J Med, 2001). Toxicity and the difficulty to standardize surgery protocols are main weak points. Over the last years, perioperative treatment (MAGIC trial) has emerged as a valid strategy and minor toxicity. We present our results of patients treated with Macdonald schedule.
Material and Methods: Between 2001 and 2012 a total of 88 patient with advanced gastric cancer (T3−4 and/or N+), where treated. Treatment according Macdonald article. Survival was analysed by Kaplan–Meier method. The TNM version is the 6th edition, 1997.
Results: Median age: 59 (35−79). Performance status: ECOG 1 or 0 in all patients. TNM stage: IB (3, 3%), II (27, 31%), IIIA (20, 23%), IIIB (17, 19%), IV (21, 24%). Total gastrectomy: 53 patients (60%) and subtotal gastrectomy in 35 patients (40%). 77% of patients had D2 lymph node resection. Median number of lymph nodes resected: 20 (4−73) and median positive lymph nodes: 4 (0−55). Adjuvant treatment indication: T3−4 (22%), N1 (33%), N2 (24%), N3 (21%). Grade 3−4 toxicity achieved in 40% of patients: mucositis (20%), diarrhoea (20%), nausea (8%), asthenia (7%), febrile neutropenia (6%), thrombocytopenia (2%) and 20 patients (23%) were admitted to hospital. Treatment delayed in 26 patients (30%), dose of chemotherapy was reduced by 25% in 13 patients (15%) and 19 patients (22%) did not complete treatment, 13 (15%) of them due to toxicity, 1 due to progression in course of treatment. Two patients died due to toxicity. With a median follow-up period of 94 months (3–141), 32 (36%) patients are still alive, 31 (35%) of them with disease-free recurrence, 56 (64%) died, 47 (54%) of them due to disease relapse and 7 (8%) due to other causes. Median overall survival (OS) was 23 months with a median disease free survival of 12 months.
Conclusions: Our results are worse than in the INT0116 trial. Possible explanations must be: non-selected population, probably different to those in clinical trials. There are also a high percentage of patients with large number of lymph nodes affected (45% >7 nodes, 21% >15). D2 resection has been achieved in the majority of patients, the indication of postoperative treatment after D2 resection is not clear today. It is difficult to complete the whole treatment: 30% of delays, 25% dose reductions (these data are not reported in the INT0116 trial). We can conclude that due to the poor results, our clinical strategy has been changed to perioperative chemotherapy, similar to the MAGIC trial.
No conflict of interest.

2512 POSTER

Palliative treatment of malignant obstructive jaundice

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Palliation of malignant biliary tract obstruction is still associated with significant complications.Many techniques for the palliative management of patients with malignant obstructive jaundice have been developed,including endo-prosthesis,operative transtumor stenting and biliary-enteric by-pass,but the general prognosis remains poor.We review our experience with emphasis on therapeutic options.
From 1993 to 2012, 250 patients with malignant obstructive jaundice unsuitable for curative patients were treated in our unit.There were 150 men(60%)and 100 women(40%). With median age 64 years(43−87),60 patients (24%)had associated diseases.Diagnosis was based on ultrasound and computed tomography, supplemented when necessary by direct cholangiography and cytology. Clinical aspects, method of management,complications and mortality were assessed.
The principal sites of the lesion were the periampullary region in 80 patients(32%)and the upper -third-hilus in 40 patients(16%)the middle-third in 50((20%)the lower -third in 60(24%)and diffuse in 20(8%)patients.Surgical treatment was employed in 200(80%)cases,radiological in 50(20%)cases. Surgical therapy included hepaticojejunostomy, choledochojejunostomy and gastroenterostomy.Radiological treatment included percutaneously endo-prosthesis,transtumor stending by CT or US guided.The median hospital stay was 19 days,25 patients (10%)had complications and 10(4%)died.The morbidity was associated mainly with pulmonary complications.The main causes of death were renal dysfunction,sepsis and multiple organ failure,peritonitis.The median survival of the patients available was 11 months with (6%) of the patients alive at 2 years.
These results show that while short-term palliation is reasonable morbidity and mortality are high.The only significant factor influencing mortality was the pretreatment bilirubin level.Surgery for biliary tract obstruction is still associated with significant morbidity and mortality.
No conflict of interest.

2513 POSTER

Lean initiative to develop managed clinical network to improve outcomes for upper GI cancer patients in Saint Helens & Knowsley

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Background: The incidence of oesophagogastric cancer has risen in the north west of England. Since advanced cancer is associated with poor prognosis, early diagnosis can improve the patient care. The objective of our study was to assess the burden of disease in Saint Helen's & Knowsley trust and to help develop pathways for early diagnosis and improve outcomes.
Method: A retrospective cross-sectional study was conducted at Whiston Hospital and included all upper GI cancer patients diagnosed between Jan. 2010- Dec 2011. Data regarding demographics, type of cancer, staging, treatment, recurrence rate and follow-up was recorded in a specified proforma and analysed with SPSS.
Results: Total number of cancer patients was 187 (93/year, higher than national figures). Male were 61 % while rest were female (mean age: 71). Out of 187; 34% had oesophageal, 28% gastroesophageal junction and rest had carcinoma stomach (38%). Adenocarcinoma was the commonest histological type. The mean time from referral to diagnosis was 22 days. About 88 % had TNM staging; of which 67% were in advanced stage (III and IV). One third of the patients underwent surgery with a 30-day mortality of 5%, anastomotic leak rate of 11% and 5 year survival of 32%.
Conclusion: The incidence of Upper GI cancer in Knowsley is higher than national figures with more patients presenting with advanced disease. A collaborative strategy in the form of managed clinical network has been proposed involving primary care doctors by rationalisation of existing resources to ensure that all patients benefit from early diagnosis, the appropriate selection and delivery of treatment.
No conflict of interest.

2514 POSTER

Radiofrequency ablation (RFA) is the predominant locoregional treatment modality for elderly hepatocellular carcinoma patients; patterns of care study from Egypt

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Background: Hepatocellular carcinoma(HCC) in the older individual is an increasingly common problem facing the oncologist. Elderly patients often present with medical and physiological characteristics that make the selection of their optimal treatment more challenging. Moreover, these patients are rarely included in clinical trials. thus we have carried retrospective analysis of our HCC database to determine the patterns of care offered to this peculiar group of patients.
Methods: HCC patients treated at Cairo Oncology Centre (Cairo, Egypt) in the period between January 2012 and December2012 were reviewed.

Eligible patients were those who had complete information on date of diagnosis and radiological or histopathological confirmation of the diagnosis. We compared the difference in clinicopathological parameters between cases that are older than 65 years and cases that are younger. we revised the patterns of care and treatment modalities offered to the elderly group.
Results: 90 patients were included in the analysis fulfilling the inclusion criteria. 27 patients were confirmed to be older than 65 years whilst the rest of the cases were younger than 65 years. Elderly patients were more likely to present with ECOG PS >1 ($p = 0.001$), however, there was no difference between younger and older patients with regard to macrovascular invasion, extrahepatic disease, child class or CLIP score; BCLC stage distribution among our elderly patients were as follows: BCLC A 11%, BCLC B 22%, BCLC C 55%, BCLC D 12%; treatment modalities offered to our elderly patients were as follows: (surgery 4%, TACE 4%, R.F.A 74%, systemic treatment (Sorafenib) 11%, best supportive care 7%; choice of treatment modalities was guided primarily by the BCLC stage.
Conclusion: According to our data, performance status and organ function are more important considerations than age and chronological age alone should not impact our approach to HCC treatment. however, there is tendency among oncologists to recommend using less invasive local treatments (RFA) rather than surgical resection for elderly patients with HCC.
No conflict of interest.

2515 POSTER

Analysis of clinicopathologic prognostic patterns in patients with gastric and esophagogastric junction tumors: Experience of a single academic institution

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Background: Gastric (G) and esophagogastric junction (EGJ) tumors remain to be challenging aggresive diseases. Multidisciplinary approach has become the standard of care in this pathology, improving the management and prognosis of these patients.
Material and Methods: We retrospectively studied the data from 116 consecutive patients diagnosed of G or EGJ tumors and treated by surgery in our institution between March 2010 and March 2013. Data regarding clinical and pathological characteristics, staging, surgical and systemic therapy and survival were collected. Univariate analysis was performed using log-rank test, univariate Cox regression and Kaplan–Meier method for overall survival (OS) and relapse free survival (RFS). Cox regression was used for multivariate analysis.
Results: A majority of patients were men (68%). Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0 in 32.8% of pts, 1 in 56%, 2 in 9.5% of pts and 3 in 1.7%. 53 pts had intestinal-type gastric adenocarcinoma and 32 had diffuse-type gastric adenocarcinoma. Curative surgery was performed in 94.8% of pts. Complete resection (R0) counting for 84.5% of pts, 7.8% had a R1 resection and 7.8% had a palliative surgery (R2). About one third (31%) of pts had a D1 lymphadenectomy, 54.3% D2 lymph node dissection and 14.7% of pts had no lymphadenectomy. Pathologic stage status was: 26.7% had stage II disease, and 38% had stage III disease (21.6% stage IIIC). Adjuvant treatment was recieved for 43% of pts (28.4% chemoradiotherapy with 5FU-Leucovorin). With a median follow-up time of 13.3 months, 48.3% of patients have suffered disease progression and 38.8% have died. Median estimated OS in our series was 27.2 months (95% CI: 21.5–32.8). Diffuse-type adenocarcinoma had a worse RFS (p:0.012) and a worse OS (p:0.001) against intestinal-type adenocarcinoma. Pts with a better ECOG PS had a best OS, (HR: 1.66, 95% CI: 1.10–2.51) (p: 0.054) in the univariate Cox regression analysis. R0 resection was related with better RFS and OS ($p < 0.001$) with a median of 28.4 months (95% CI: 21.8–34.9). In multivariate analysis, a better OS was observed in patients with better ECOG (HR:1.62 95% CI:1.06–2.47, p:0.026) and R0 resection (HR:1.95 95% CI: 1.27–2.96, p:0.02).
Conclusions: In our experience, diffuse-type histology, worse PS at diagnosis and a non-accurate initial resection are independent factors for a poor prognosis in resected gastric adenocarcinoma. These data confirmed the heterogeneity of this pt population and the need of joining efforts between experienced institutions to improve pt care.
Conflict of interest: *Corporate-sponsored research: Jorge Barriuso runs clinical trials sponsored by Roche, Novartis, Taiho, AstraZeneca and Pfizer. Other substantive relationships: Jorge Barriuso is partly funded by Asociacion Española Contra el Cancer (AECC)*

2516 POSTER

Clinical, pathological characteristics and the effect on survival in elderly patients with gastrointestinal stromal tumours

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Background: Gastrointestinal stromal tumours (GIST) are common tumours of the gastrointestinal system (GIS). Their most frequent location is the stomach. Although the clinical and pathological characteristics of the disease are well-known, the clinical and pathological characteristics and the response to treatment are not clear in the elderly patients.
Materials and Method: In this study, clinicopathological characteristics, treatment evaluations and survival analyses were performed in patients at and above the age of 65 years whose data were registered via a web-based patient records system following admission to three centers.
Results: A total of 85 patients above the age of 65 years were included in the study. According to the risk classification, n = 24 (27.1%) were in low risk group, n = 20 (21.4%) were in moderate risk group, and n = 41 (51.4%) were in high risk group among the patients at and above the age of 65 years. The mean age at diagnosis in all cases was 59 years and the median was 60 years, respectively. At baseline, 69.9% of the patients had localised disease while 30.1% had metastatic disease. The tumour was located in the stomach in the majority (45.6%) of patients. Upon evaluation of tumour diameters, the most commonly seen tumour size was 5−10 cm, n = 85, 34.1%. A hundred seventy-four patients underwent surgery. Of the 67 patients, (26.5%) were treated with imatinib at 400 mg/d. Eight patients (2.4%) with metastatic disease switched from imatinib to sunitinib.
Discussion: These data are important with regards to revealing the clinicopathological characteristics and survival data of elderly patients with GIST. The prognostic factors in elderly patients are not different than that of young patients. However, the existence of comorbid conditions may worse the clinical course in elderly patients. The follow-up and treatment of patients in specialized centers lead to high survival rates.
No conflict of interest.

2517 POSTER

Double-Blind, placebo-controlled, randomized phase II study of TJ-14 (Hangeshashinto) for gastric cancer chemotherapy-induced oral mucositis

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Background: Oral mucositis is a common complication of cancer chemotherapy and/or radiotherapy, sometimes leading to dose reduction and/or interruption of the treatment. Despite many attempts to reduce those cancer chemotherapy-related mucositis, no standard efficacious prophylactic therapy has been established.
In this regard, an attempt to examine the safety and efficacy of TJ-14 (Hangeshashinto; one of the traditional Japanese medicines (Kampo) for prevention and treatment of chemotherapy-induced oral mucositis was investigated by a placebo-controlled randomized phase II trial.
Methods: We randomly assigned 94 patients with gastric cancer who had developed moderate to severe oral mucositis (NCI-CTC grade $\geqslant 1$) during any course of chemotherapy with S-1, S-1/CDDP, S-1/DTX and so on (regimen) to receive either TJ-14 or placebo. Patients received TJ-14 or placebo for 2−6 weeks according to chemotherapy regimen during the next course of chemotherapy, followed by TJ-14. Patients were assessed three times per week for safety and for oral mucositis incidence and its severity using the NCI-CTC grading.
Results: We analyzed 91 eligible patients (TJ-14; 45, placebo; 46) by a per protocol set analysis after the key-opening. The incidence of $\geqslant$grade 2 oral mucositis was 40.0% in the TJ-14 and 41.3% in the placebo group. In patients with oral mucositis at the start of the next course of chemotherapy (TJ-14; 33, placebo; 30), the median duration of mucositis was 12.0 days

vs. 16.5 days (HR; 1.15 95% CI; 0.61–2.16 p = 0.655). No difference in other treatment toxicity of was observed between the two groups, and patients exhibited high compliance regarding dosing administration.
Conclusion: TJ-14 demonstrated a favorable profile in the treatment of oral mucositis induced by chemotherapy in patients with gastric cancer. TJ-14 might be effective in reducing the duration of oral mucositis compared to the placebo control.
No conflict of interest.

2518 POSTER

Everolimus in combination with octreotide LAR as the first-line treatment for advanced neuroendocrine tumors: efficacy data in pNET and non-pNET patients: I.T.M.O. (Italian Trials in Medical Oncology) group

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Background: Everolimus has shown antitumor activity in patients (pts) with advanced neuroendocrine tumors (NETs). We aimed to assess efficacy and safety of everolimus in combination with octreotide long-acting repeatable (LAR) in patients with well differentiated NETs of gastroenteropancreatic and of lung origin.
Methods: We performed a phase II, multicenter trial using a Simon two-stage minmax design. Pts with advanced well differentiated, previously untreated NETs of the gastroenteropancreatic tract and of the lung received octreotide LAR 30 mg every 28 days in conjunction with everolimus 10 mg per day continuously. The primary endpoint was objective response rate (ORR).
Results: A total of 50 pts (58% males) were enrolled. The median age was 60.5 years (range 25−76). Primary tumor site was pancreas in 14 (28%), unknown in 14 (28%), lung in 11 (22%), ileum in 9 (18%) and jejunum and duodenum in 2 (4%) of pts. 13 (26%) pts had carcinoid syndrome. The ORR, calculated on the ITT population, was 20.0% (95% CI 8.9–31.1): 14. 3 % (2/14) in pNET pts and 22.2% (8/36) in non pNET pts. Thirty-six patients (72%) achieved stable disease (SD). All CR and all PR as well as 91.7% of SD had a duration $\geqslant$6 months. Clinical benefit (CR+PR+SD) was 92%. At a median follow-up of 277 days, the median time to progression (TTP) was 16.3 months (95% CI 10.7–20.1): 17.2 months in pNET pts. Overall survival could not be assessed. Treatment-related adverse events (AEs) were mostly of grade 1 or 2; the only grade 4 AE was mucositis in 1 patient, while grade 3 AEs included skin rash in 1 case, stomatitis in 4 cases (8%) and diarrhea in 11 cases (22%).
Conclusion: Everolimus in combination with octreotide LAR has shown to be active and well tolerated in advanced NETs, both in pancreatic and non -pancreatic primary sites.
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Conflict of interest: *Advisory board: Novartis. Corporate-sponsored research: Novartis*

2519 POSTER

Characteristics and treatment patterns of patients potentially eligible for further therapy after discontinuation of first-line sorafenib for advanced hepatocellular carcinoma (HCC): An EU perspective

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Background: Currently, sorafenib is the only agent indicated for the treatment of advanced HCC. There are no recommended therapies after sorafenib discontinuation, and little information is available to characterize this unmet need. Here we describe treatment patterns for a sample of such patients from France, Germany, Italy, and Spain.
Material and Methods: Physicians who treat patients with advanced HCC were asked to complete an internet-based survey detailing clinical and resource utilization data for 5 de-identified patients (3 patients in Germany) each. The aim was 50 patients per country. Medical records were eligible if the patients were $\geqslant$18 years old, had been diagnosed with advanced HCC, had initiated first-line sorafenib after 2008, had subsequently discontinued sorafenib, had survived $\geqslant$2 months after sorafenib discontinuation, and had $\geqslant$6 months of follow-up data (or had died). Data were summarized descriptively. Time-to-event measures were estimated using the Kaplan–Meier method.
Results: From August to October 2012, 200 physicians (50 per country) provided data for 900 patients. Patients' mean age was 61 years and 72% were male. The most common co-morbidities were cirrhosis 54%, hypertension 29%, and diabetes 23%. For those with cirrhosis, the most common etiologic factors were alcohol 47%, hepatitis C 29%, and hepatitis B 17%. Barcelona Clinic Liver Cancer stage was 31% B, 63% C, and 6% D. At sorafenib initiation, Child-Pugh status was 40% A, 40% B, and 19% C. At sorafenib discontinuation, Child-Pugh status was 17% A, 43% B, and 39% C; 59% had no change from sorafenib initiation. 82% of patients discontinued sorafenib due to HCC progression. 63% were documented as deceased, with 91% of deaths attributed to HCC. Median follow-up from sorafenib discontinuation was 3.8 months for those documented as deceased and 7.7 months for those known to be alive or with unknown status. 15% of patients received systemic anti-cancer therapy after sorafenib discontinuation and an additional 6% re-initiated sorafenib after $\geqslant$2 months of interruption. Procedures following sorafenib discontinuation included transarterial chemoembolization 6% and radiofrequency ablation 3%. 32% of patients were hospitalized and 23% had at least one emergency room visit. Physicians reported providing supportive care to 688 patients. Of these, 63% received routine pain management (most commonly oral opiates), 36% nutritional support (enteral or parenteral), and 17% transfusions. For all patients, median survival from sorafenib discontinuation was 6.5 months ($\geqslant$2 months required by design).
Conclusions: For this select group of advanced HCC patients, few received anti-cancer therapy after discontinuation of sorafenib. However, these patients continued to receive supportive care and many required hospitalization. Interventions that improve survival and reduce supportive care needs would be beneficial.
Conflict of interest: *Ownership: Dr Liepa, Ms D'yachkova,and Ms Taipale are stockholders of Eli Lilly and Company. Corporate-sponsored research: Dr Kaye is an employee of RTI Health Solutions and Dr. Mitra was an employee of RTI Health Solutions at the time of this research. RTI Health Solutions was contracted by Eli Lilly and Company. Other substantive relationships: Dr Liepa, Ms D'yachkova,and Ms Taipale are employees of Eli Lilly and Company*

2520 POSTER

Conditional survival in patients with advanced pancreatic cancer − improvement as time passes by?

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Background: Survival projections are usually estimated from the date of diagnosis to the date of death. However, these estimates can lose validity once a patient survives longer than predicted. Conditional survival (CS) probabilities provide guidance for such situations. We investigated conditional survival probabilities for patients with advanced pancreatic cancer.
Patients and Methods: Clinical data of all patients diagnosed with unresectable stage III or IV pancreatic cancer between 2000 and 2008 at 4 Swiss medical centres were retrospectively collected. We calculated overall survival (OS) as time from diagnosis until death. We used the landmark approach to calculate conditional survival estimates defined as the probability to survive another additional time given that the patient has already survived a certain time after diagnosis. For this analysis, we built four patient subsets according to landmark times at 6, 12, 18, and 24 months after diagnosis and calculated the probability to survive another 6 months. Patients who died before the respective landmark times were excluded from each following set.
Results: We included 483 patients (median age 66, 43% female; stage III and IV 19% and 81% respectively). 79% were treated with gemcitabine or gemcitabine plus capecitabine, 11% received other regimens. 448 patients have died; median follow-up for all patients was 8.8 months (inter-quartile range 5−15). Respective 6, 12, and 24-month OS probabilities were 67% (95% confidence interval [CI], 63% − 71%), 37% (95% CI, 33% − 42%), and 11% (95% CI, 8% − 15%). Overall conditional survival estimates are summarized in the TABLE. Patients surviving at least 24 months after diagnosis show a slightly improved 6-months OS probability of 71%.

Conclusions: The 6-months OS probabilities remain stable over time and increase only for those patients who survive at least 24 months after diagnosis. Our CS estimates provide additional information for counselling patients with advanced pancreatic cancer regarding therapy decisions and end of life planning.
No conflict of interest.

Table: 6-months OS probability conditioned on the time survived after diagnosis.

Time survived after diagnosis	6 months	12 months	18 months	24 months
Probability to survive another 6 months, % (95% CI)	56 (50, 61)	58 (51, 66)	52 (43, 63)	71 (58, 85)
Patients at risk in each set	317	170	97	48
Stage at diagnosis N (%)				
III	57 (18)	29 (17)	18 (19)	8 (17)
IV	259 (82)	138 (83)	77 (81)	40 (83)

CI, confidence interval.

2521 POSTER

Incidence of deep venous thrombosis detected by routine surveillance ultrasonography in patients with gastric cancer before operation

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Background: Pulmonary thromboembolism (PTE) is one of the serious postoperative complications of major surgery, and about 80% of PTE results from deep venous thrombosis (DVT) of lower extremity. However, the incidence of DVT in the patients with gastric cancer before operation is unknown. The aim of this study was to clarify the incidence and risk factors of DVT of lower extremity in the patients with gastric cancer before operation.
Patients and Methods: Between May 2010 and August 2011, 293 patients with gastric cancer who had routinely undergone doppler ultrasonography (DUSG) for the diagnosis of lower-extremity deep venous thrombosis before operation at Shizuoka Cancer Center, Japan were analyzed. The clinicopathological data of the patients were collected retrospectively.
Results: Of 293 patients, 25 patients (8.5%) were preoperatively found to have DVT, and all patients with DVT were asymptomatic. The anticoagulant drugs were administered or inferior vena cava filter were placed to prevent PE for the patients with DVT. As a result, no patients developed PE. Among these 25 patients, 9 patients were male and 16 patients were female. The rate of the patients who detected DVT were 30.0% of the patients of 80 years old or more, and 24.4% of the patients with East Cooperative Oncology Group (ECOG) Performance Status (PS) $\geqslant$1. Likewise, 18.2% of the patients with stage IV gastric cancer and 41.7% of the patients with central venous catheter (CVC) were found to have DVT. Atrial fibrillation, ischemic heart disease, congestive heart failure, and leg paralysis were not associated with DVT. In order to select the predictor of DVT before operation, some indicators were enumerated (age, gender, performance status, body mass index, tumor stage, and the presence or absence of previous chemotherapy, previous hormonal therapy, hypertension, hyperlipidemia, varicose vein of lower extremity, CVC). Multivariate logistic regression analysis demonstrated that female, age $\geqslant$80, PS 1 or 2, and the presence of CVC were significantly correlated with DVT before operation.
Conclusions: DUSG was a quite easily performed and non-invasive imaging examination and provide valuable information for thromboprophylaxis. Detection of the patients with asymptomatic DVT before surgery and appropriate prophylaxis for them in the perioperative period might reduce PE. Therefore, we consider that DUSG is useful for the preoperative screening of DVT in patients with gastric cancer.
No conflict of interest.

2522 POSTER

Clinical significance of HER2 overexpression in gastric and gastro-esophageal junction cancers: Is there any discordance between IHC and FISH

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Objectives: In this study, we investigated the rate of HER2 overexpression in gastric and gastroesophageal junction cancers (GC, GEJC), and the relationship with HER2 expression and clinical, pathological parameters and prognosis.
Materials and Methods: Surgery or biopsy specimen of 598 (436 male, 162 female) patients with GC or GEJC, the presence of HER2 overexpression by immunohistochemistry (IHC) and fluorosein insitu hybridization (FISH) were evaluated. The relationship between HER2 positivity and tumor size (TS), histopathology (H), grade (G), serosal invasion (SI), lenfovascular invasion (LVI), perineural invasion (PNI), Lauren and Borrmann type, tumor location (TL), TNM stage, local recurrence (LR) and metastasis (M) and survival (OS) and the presence of discordance between IHC and FISH results were investigated.
Results: HER2 IHC scores were; 418 (69.9%) IHC 0, 58 (9.7%) IHC +1, 50 (8.4%) IHC +2, 72 (12%) IHC +3. Fifty of 18 (38.2%) patients with IHC +2, FISH positive, and 29 (61.7%) patients FISH negative, 3 of patients not studied FISH because of unsufficient biopsy material. The number of patients evaluated with IHC +3 or IHC +2 and FISH positive, HER2 positivity was 14.6% (Figure 3). IHC and FISH discordance summarized in Table 1. There was no relationship between HER2 positivity and the age, gender, TNM stage, TS, TL, LR, M, LVI, PNI, and Borrmann type. HER2 positivity was higher in intestinal type tumors than in diffuse type (16.9% *vs* 6.6%, $p = 0.014$). HER2 positivity was significantly higher in well-moderately differentiated tumors than poorly differentiated tumors (24.2% and vs 7.3%, $p < 0.0001$). HER2 positivity was higher in adenocarcinomas than the other histologic subtypes; 17.6% of adenocarcinomas, 2.9% of signet-ring cell carcinomas, %11.6 of mixed carcinomas (adenocarcinoma+signet-ring cell carcinomas) were HER2-positive ($p = 0.002$). HER2 pozitivity was no significant effect on median OS (23.2 vs 19.1 months, $p = 0.44$). But in the early stage median OS of HER2-positive patients was shorter than HER2-negative patients (51.4 months vs not reach, $p = 0.047$)(Figure 4). However patients with advaced stage HER2-positive and -negative there was no significant difference between the median OS rates (16.2 vs 13.7 months, $p = 0.72$) (Figure 5).
Conclusion: HER2 positivity is associated with the degree of tumor differentiation and histopathology in GC and GEJC. Patients with early-stage, HER2 positivity is related to poor prognosis.
No conflict of interest.

2523 POSTER

Mediastinal drainage in the management of anastomotic major leakage after subtotal esophagectomy with posterior mediastinal gastric tube reconstruction for thoracic esophageal cancer

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Background: Although gastric tube reconstruction through posterior mediastinal route is considered to have less surgical procedure and lower risk for anastomotic complication compared to through retrosternal route or antethoracic route, major anastomotic complication will easily develop into severe status in mortal danger. The purpose of this study is to evaluate the efficacy and safety of naso-esophageal extra drainage (NEED) in the management of anastomotic major leakage after subtotal esophagectomy for thoracic esophageal cancer (TEC).
Material and Methods: A total of 342 consecutive TEC patients who underwent subtotal esophagectomy with thoraco-abdominal lymphadenectomy and with gastric tube reconstruction through posterior mediastinal route were investigated. All patients received prophylactic thoracic drainage. Forty-one had a complication of anastomotic leakage. In postoperative course, gastro-esophagography was performed when anastomotic complication was suspected with following episodes: fever

(>38ºC) more than 3 days, an increase in WBC or CRP, right back pain or chilling. Leakage was diagnosed when contrast agent flow out through the gastro-esophageal tract into the mediastinum or pleural cavity, and were classified into two types: minor type with linear shaped and narrow abscess cavity and major type with round shaped and expansive cavity. Only naso-gastric tube drainage was performed in minor type, and patients of major type underwent extracorporeal drainage. Patients were divided into two groups as non-NEED group (non-ND, N = 17) and NEED group (ND, N = 24). If extracorporeal drainage is considered ineffective in major type, NEED procedure was performed by inserting continuous aspiration tube from naso-esophageal route through perforation hole into mediastinum or peritoneal cavity. Patients were treated concomitantly with enteral alimentation. We compared both groups about reoperation rate, hospital mortality and cure rate which means the possibility of both oral uptake and independent life.
Results: Reoperation rate was 18% in non-ND and 0% in ND (P = 0.064). There was a significantly difference between non-ND and ND in hospital mortality (29% vs. 0%, P = 0.010) and cure rate (53% vs. 100%, P<0.001). 47% of non-ND could not take oral feeding due to death in hospital, bedridden in residence and status of esophagostomy for years using enteral feeding. Postoperative fasting duration was 52 days in non-ND recover cases and 45 days in ND with no significant difference (P = 0.753). All of major type could survived and live an independent life.
Conclusions: NEED treatment is a noninvasive and very effective procedure in the management of complication of major leakage after subtotal esophagectomy through posterior mediastinal route reconstruction.
No conflict of interest.

2524 POSTER

Changes in body composition in primary oesophageal cancer: Does it affect immediate and long-term clinical outcomes?

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Background: Changes in body composition may influence oncological outcomes. We examined the changes in body composition in patients who received neoadjuvant chemotherapy (NAC) followed by surgery for oesophageal cancer and its association with clinical outcomes.
Material and Methods: IRB approval was obtained for this retrospective study. 37 patients (median age 66 years; 31 males; clinical stage II/III; 32 adenocarcinoma) who received NAC followed by oesophagectomy, and who had pre- and post-treatment CT available for analysis were identified from our institutional database. Body composition analysis was performed on the CT images using a previously described method: Pre- and post-treatment fat-muscle ratio (FMR), fat-free mass (FFM) and skeletal muscle mass (SMM) were obtained, and percentage change for each parameter was calculated. Overall survival (OS), disease-free survival (DFS) and length of hospital stay (LOS) were calculated. Post-operative complications such as wound dehiscence, infection, chyle leak or haematemesis were recorded. Pre- and post-treatment parameters were compared using Wilcoxon signed-rank test. Correlation between LOS and each parameter was done using Pearson's correlation. Median value was used to dichotomise each parameter. Fisher exact and chi-square tests were used to assess for significant association between each dichotomised parameter, and presence of post-operative complications and resection margin status. Survival analysis was performed using Cox proportional hazards model treating each parameter as a continuous variable. Kaplan–Meier survival analysis was done using dichotomised parameters. A p-value<0.05 was deemed significant.
Results: Median follow-up was 24.0 months (range 0.7–54.5) and median LOS was 13 days (range 7–182). Twenty-three (62%) and 14 (38%) patients had R0 and R1 resection, respectively. Thirteen (35%) patients had post-operative complications. Two (5%) and 6 (16%) patients had locoregional and distant recurrence respectively. There were weak and non-significant correlations between each parameter and LOS (r = −0.150–0.226; p = 0.273–0.835). FMR decreased (mean and median changes: −6% and −3%, p = 0.242) whereas FFM (14% and 3%, p = 0.013) and SMM (16% and 3%, p = 0.013) increased following NAC. Post-treatment FMR was associated with resection margin status (p=0.045). There was no significant association between presence of post-operative complications and each parameter. There was no significant association between each parameter, OS and DFS.
Conclusions: FFM and SMM increased following NAC in oesophageal cancer, likely due to improved nutritional care in our institution. However, changes in body composition did not seem to affect post-operative complications and survival outcomes, although this could be attributed to our relatively small sample size and short median follow-up.
No conflict of interest.

2525 POSTER

An early phase II study of salvage photodynamic therapy (PDT) using talaporfin sodium and a diode laser for local failure of esophageal cancer (EC) after chemoradiotherapy (CRT)

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Background: While we reported that PDT has a curative potential for local failure after CRT for EC, porfimer sodium (Photofrin)-based PDT has some problems such as long light shielding and skin phototoxicities. Talaporfin sodium (Laserphyrin), the second generation photosensitizer, has less phototoxicity. In our phase I study, we identified the optimum irradiation dose (100J/cm^2) for Laserphyrin-based PDT. We conducted an early phase II study to evaluate the efficacy and safety of Laserphyrin-based PDT as a salvage treatment after CRT or radiotherapy (RT) for EC (UMIN000003970).
Material and Methods: Patients with histologically proven local failure limited to the T2 after definitive CRT or RT (⩾50 Gy) for EC were enrolled in the study. PDT was applied with an intravenous administration of 40 mg/kg of Laserphyrin followed by a diode laser irradiation of 100J/cm^2 4−6 hr later. The primary endpoint was a complete response (CR) of the primary site, and the secondary endpoints were adverse event, adverse reaction, and device failure related to PDT, progression-free survival (PFS) and overall survival (OS).
Results: Thirteen patients were enrolled in the study. Nine cases were estimated as T1 and 4 cases were T2 by endoscopic ultrasound. Eight cases achieved CR (CR rate, 61.5%:one side 95% CI, 40.2%-). Severe phototoxicities and adverse events greater than grade 3 related to PDT were not observed in all patients. Also, adverse events, such as perforation and hemorrhage were not associated with PDT. We experienced two patients with esophageal pain (Grade2). One year overall survival was 82.5%.
Conclusions: Laserphyrin-based PDT is a safe and potentially curative treatment for local failure after CRT or RT for EC.
No conflict of interest.

2526 POSTER

Multidisciplinary care in the management of oesophagogastric cancer audit − a single institution quality assurance project

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Background: Peri-operative chemotherapy has demonstrated a survival benefit in early stage oesophagogastric cancer and is a recommended standard of care. Post-operative chemoradiotherapy also has a survival benefit compared to surgery alone. Pre-operative assessment (CT scan +/− PET scan and laparoscopy) remains critical to ensure futile surgical procedures are not performed. We sought to a) demonstrate that by focusing on multidisciplinary care and adhering to guidelines, our institution can deliver best practice outcomes; and b) identify reasons for deviations from recommended standard of care.
Materials and Methods: This is a retrospective cohort of patients diagnosed with oesophagogastric cancer at our institution between 1st July 2007 and 20 June 2012. Patient files were audited for basic demographics including age, sex, histology and stage. Patients with early stage disease were audited for completeness of pre-operative investigations including biopsy, CT scan, laparoscopy and PET scan. Patients presenting to our institution but primarily treated elsewhere were excluded. Descriptive statistics were used to illustrate patient characteristics. These included number (n) and percentages for categorical variables, and arithmetic means, medians and range for continuous variables. These outcomes were compared to the 'gold standard' trials.
Results: Between 2007 and 2011* 181 patients were diagnosed with oesophagogastric cancer at our institution. Of these 60 (33%) had early

stage disease. Median age at diagnosis was 70.2 years. For early stage disease compliance with recommended investigations was 100% for CT, 81% for PET scanning and 62% for laparoscopy. One year survival was 93%, 2 year survival was 76%. From 2007 there was an increased uptake of pre-operative treatment (33%, 40%, 60% and 63% from 2007–2011). Reasons for not receiving pre-operative chemotherapy were: age, early stage tumour, need for emergency surgery. Of those who completed pre-operative chemotherapy 53% commenced post-operative chemotherapy.
Conclusion: This data demonstrates that our small institution can deliver outcomes equivalent to the gold standard trials, which we attribute in part to a strong multidisciplinary care framework and diligence with best practice guidelines. An appreciation of current standards of care and an understanding of reasons for incomplete staging will allow directed strategies to improve outcomes in the future.
* Updated data including 2012 will be presented.
No conflict of interest.

2527 POSTER

Time to health-related quality of life score deterioration as a modality of longitudinal analysis using propensity score method to deal with missing data: A phase II trial in patients with metastatic non pre-treated pancreatic adenocarcinoma

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Background: To investigate the time to Health-related Quality of Life (HRQoL) score deterioration (TTD) approach as a modality of longitudinal analysis in a phase II trial of pancreatic cancer using the propensity score to deal with the non-random missing data profile.
Material and Methods: A randomized multicentre phase II trial was performed to assess the sequential treatment strategy using FOLFIRI.3 and gemcitabine alternately in one arm and gemcitabine alone in the other arm, in patients with metastatic non pre-treated pancreatic adenocarcinoma.
HRQoL was evaluated using the EORTC QLQ-C30 at baseline and every two months until the end of the study or death. Several definitions of TTD were investigated. The main definition was the time from baseline to a first QoL score deterioration with a minimal clinically important difference of 5 points as compared to the baseline score with no further improvement of more than 5 points or death. In order to deal with the non-random missing data profile, analyses were repeated with inverse probability weighting (IPW) using the propensity score. Profiles compared were patients with at least one missing HRQoL score during the follow-up versus patients with all scores available. Univariate and Multivariate Cox regression analyses were performed to identify independent factors influencing TTD.
Results: Between October 2007 and May 2011, 98 patients were included with a median age of 63 years. At baseline, 64 patients (65%) completed the QLQ-C30 questionnaire. Adjusting on the IPW score, patients who received FOLFIRI.3 and gemcitabine alternately presented a longer time to Global Health Status score deterioration than those who received gemcitabine alone (Log-rank p = 0.008) with an Univariate Hazard Ratio (HR) of 0.52 [95% CI 0.31–0.85]. The same trend was observed for role functioning (HR: 0.41 [0.25–0.69]), emotional functioning (HR: 0.35 [0.21–0.59]) and fatigue (HR: 0.61 [0.38–0.97]).
Conclusions: Patients who received FOLFIRI.3 and gemcitabine alternately presented a longer TTD than those who received gemcitabine alone for most of HRQoL scores. The TTD method as the advantage to provide meaningful longitudinal HRQoL results for clinicians. Moreover, the IPW method allows to take into account the non-random missing data profile.
No conflict of interest.

2528 POSTER

Concurrent chemoradiation with mitomycin C and continuous vs non-continuous 5-fluorouracil infusion for anal squamous carcinoma

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Background: Concurrent chemoradiation with 5-fluorouracil (5-FU) and mitomycin-C (MMC) is the standard of care for anal squamous cell carcinoma (ASCC). The best schedule of 5-FU with radiotherapy (RT) is still subject to debate. Continuous 5-FU has been used with shortened irradiation schemes. No comparison between continuous vs non-continuous 5-FU has been done. We aim to compare pts with ASCC treated with RT and MMC with continuous vs non-continuous infusion of 5-FU in a single institution.
Material and Methods: 51 pts treated for ASCC from 2004 to 2010 were retrospectively reviewed. 9 pts were excluded (1 died before completing treatment and 8 had a different RT scheme). Two chemoradiation regimens were used: Group A (24 pts) was treated with MMC (10 mg/m^2 on d1 and d29) and 5-FU (1000 mg/m^2 d1−4 and d29−32) concomitant with external beam radiation (45 Gy 5w) followed by a 15 Gy boost; Group B (18 pts) was treated with MMC (10 mg/m^2 d1 of each RT course), 5-FU (200 mg/m^2/day continuously) with split-course RT (36 Gy and a 23.4 Gy boost with 2w interval). Primary endpoint (at 36 months) was progression-free survival (PFS). Secondary endpoints (at 36 months) were complete response rate (CRR), overall survival (OS) and toxicity.
Results: The groups were well-balanced in age, gender, histology, stage and tumor location. CRR was 62.5% in group A and 94.4% in B (P = 0.016). 3-year PFS was 79.2% in group A and 55.6% group B (P = 0.101). Median PFS was 29.2 months (95% CI: 23.7–34.6) in group A and 28.8 months (95% CI: 23.0–34.6) in B (P = 0.276). 3-year OS was 54.2% in group A and 83.3% group B (P = 0.047). Median OS was 23.4 months (95% CI: 21.1–31.6) in group A and 33.3 months (95% CI: 30.4–36.3) in B (P = 0.045). Grade III/IV toxicity was present in 57.9% in group A and 42.1% in group B. One pt in group A died of cardiac toxicity after completing chemoradiotherapy.
Conclusions: Continuous infusion of 5-FU in ASCC treatment was associated with higher complete response rates and 3-year overall survival, although lower progression-free survival rates require further analysis with longer follow-up. Results of continuous 5-FU should also be compared between split-course vs shortened conformal irradiation scheme.
No conflict of interest.

2529 POSTER

Is the Lean Six Sigma methodology applicable in a multidisciplinary outpatient clinic for gastro-intestinal cancer?

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Introduction: Long waiting times are the main source of prolonged run through time (RTT) in healthcare systems. In the Academic Medical Centre in Amsterdam, a one-stop fast-track multidisciplinary outpatient clinic was founded to shorten waiting times and reduce run through times for patients with a gastro-intestinal malignancy. The Gastro-Intestinal Oncology Centre Amsterdam (GIOCA). At GIOCA, the week has a standard layout, where days are limited to specific tumors, i.e. hepatocellular carcinoma, upper gastro-intestinal (GI) tumors, lower GI tumors and hepatobiliary tumors, Our aim is to admit patients to the outpatient clinic, within one week of referral and to initiate treatment within three weeks after the first appointment.
Lean Six Sigma (LSS) is a combination of Lean-management and the Six Sigma methodology. LSS incorporates means to systematically identify and address suboptimal performance of a process. Lean and Six Sigma have their origins in the manufacturing industry, like the Toyota factory, with largely homogenous products.
A complex high care medical facility deals with heterogeneous patients and human emotions, rather than a production site with largely homogeneous products. Our aims are to explore the possibility to implement LSS in a high care medical facility and thereby identify obstacles that prevent an admission time of less than one week.
Methods: We have applied the DMAIC-cycle (Define Measure Analyse Improve Control) to the referral process of new patients. The DMAIC-cycle is the management cycle of Six Sigma.
Results: Our preliminary results indicate that Lean Six Sigma methodology is applicable in a complex high care medical facility. We have identified obstacles that prevent an admission time of less than one week, inter alia, the division of the tumors into different days, and failure to diagnose the patient in our Multidisciplinary meeting.
Conclusion: Lean Six Sigma is applicable in a high care medical facility, like the Academic Medical Centre and its outpatient clinic. Obstacles in the logistics of a high care medical facility can be identified with LSS. Our next investigative step will explore the applicability of LSS to remove the obstacles and solve the problems surrounding admission time.
No conflict of interest.

2530 POSTER

A study of growth factor receptor expression and their clinicopathological correlation in gallbladder carcinoma

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Background: North India reports one of the highest incidence of gallbladder cancer (GBC) in the world. There are very few studies evaluating differential growth factor receptor expression in GBC and non-malignant gallbladder specimens and study correlation of biomarker expression with clinico-pathological attributes of tumor.
Material and Methods: Present study determines immunohistochemical expression of growth factor receptors (Her-2/neu and EGFR-1) in GBC and the control group (cholelithiasis), which was quantified in accordance with guidelines as followed in *ToGA study* evaluating Her-2/neu expression in gastric cancer. Study evaluated correlation of these biomarkers expression with clinicopathological parameters as histological type and grade, T stage, lymph node status, response to chemotherapy, disease progression and survival.
Results: Study evaluated 75 patients of GBC and 25 in control group (cholelithiasis). Increased expression of Her 2/neu [31/75 positive (41%)] and EGFR-1 [30/75 positive (40%)] observed in GBC patients was statistically significant (p=<.0001) as compared to control group [Her-2 and EGFR-1 positive in 8% each (2/25)]. Increased expression of Her-2/neu (p=.126) and EGFR-1 (p = 0.006) was observed in locally advanced/metastatic GBC patients (Stage IVA-IVB; n = 43) as compared to early stage disease (Stage I−IIIB; n = 32). No observed correlation of biomarker expression with age, cholelithiasis, histological type & grade. EGFR-1 and Her-2 coexpression was associated with poor disease outcome in both palliative (n = 43; p = 0.006) and curative resection subgroups (n = 32; p = 0.086). Statistically significant correlation of EGFR-1 expression with Disease Free Survival (DFS) at 12 months was observed in Radical cholecystectomy subgroup (p = 0.030). Her-2/neu expression was associated with poor Disease Control rate (DCR) and Overall Response rate (ORR) in palliative treatment subgroup.
Conclusions: GBC is characterized by late diagnosis, poor response to treatment and genarally a dismal prognosis. Clearly, newer and more effective therapeutic regimens are the need of the hour, based on our evolving understanding of molecular biology of GBC. Her-2 and EGFR-1 expression in GBC could be predictive of aggressive disease biology, marker of response to chemotherapy and also serve as potential therapeutic targets. Data presented here, from the region with one of the highest incidence of GBC in the world, represents the largest ever such analysis. It presents a case for exploring the use of Her-2/neu specific monoclonal antibodies or EGFR tyrosine kinase inhibitors in combination with Gemcitabine based regimens for treatment of GBC and could prove to be the holy grail in the treatment of GBC.
No conflict of interest.

2531 POSTER

TWIST1 gene expressions in gastric adenocancer

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Background: Recent studies have shown that TWIST1 is one of the main regulatory proteins that promote epithelial–mesenchymal transition (EMT). EMT is pivotal for morphogenesis and in the transformation of early stage tumors into invasive malignancies. TWIST1 plays distinct roles in regulating the expression of downstream genes, acting either as activators or repressors. In the present study we aimed to elucidate the expressions of TWIST1 gene in the gastric mucosa of different histopathological variety: normal gastric mucosa (NGM), chronic active gastritis (CAG) and gastric adenocancer (GAC).
Material and Methods: In order to evaluate the utility of TWIST1 as marker associated with increased gastric cancer risk, we investigated gene expression by reverse transcription polymerase chain reaction. Premalign and malignanat gastric samples were obtained from 93 untreated patients.
Results: We evaluated gastric tissues of 93 patients [43 (46.2%) female, 50 (53.8%) male] between the ages of 18−70. According to histopathological groups NGM (32; 34.4%), CAG (33; 35.5%), GAC (28; 30.1%) TWIST1 gene expression levels using RT-PCR method were evaluated prospectively.In univariate analysis, gastric mucosal TWIST1 mRNA expressions were increased in CAG compared to NGM. TWIST1 mRNA expressions were found to have a significant increase in GAC. The relative expression level of TWIST1 mRNA was low to absent in NGM, and aproximately six times less than that of the CAG, whereas it was significantly (P <0.0001) higher in GAC (~200 times). The relative expression ratio of TWIST1 >12.5 is a risk factor for adenocancer development and an augmented TWIST1 expression causes a 10^9 fold increase in adenocancer development risk (OR=1.8X10^9, %95 CI=3.2X10^8-10^9, P=10^{-7}). In advanced stages TWIST1 expression was significantly higher (p = 0.0265).
Conclusion: TWIST1 is found to be an independent risk factor in the prediction of adenocancer development.
No conflict of interest.

2532 POSTER

Perfusion CT in assessing tumor blood flow as an imaging biomarker for gastric cancer

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Background: Intratumoral hemodynamics or tumor perfusion is useful in understanding the pathological background of the cancer. A parameter for a non-invasive, preoperative assessment of tumor perfusion has yet to be developed. The purpose of this study is to evaluate the correlation between tumor blood flow calculated with perfusion CT and clinicopathological status of gastric cancer.
Material and Methods: This study included 50 patients who underwent surgery for advanced gastric cancer. A total or distal gastrectomy with regional lymphadenectomy was performed in 40 patients. In the remaining 10 cases, the tumors were unresectable due to invasion of surrounding tissues (8 cases) and/or peritoneal dissemination (5 cases) and biopsy specimens from preoperative endoscopy were used for the pathological analysis. According to the UICC Stage, patients were classified as stage Ib in 5, stage II in 8, stage III in 12, and stage IV in 25. Out of the 25 patients, 21 were categorized as stage IV for their M1 status. All of these patients possessed peritoneal dissemination, and 2 had metastases to the liver. Perfusion computed tomography (PCT) was performed using a 16-row multidetector CT following intravenous injection of contrast materials, and tumor blood flow (BF: ml/min/100g tissue) values were measured. We compared BF with histopathological characteristics, with microvessel density and tumor stromal density and postoperative outcome.
Results: None of the specimens possessed any necrotic tissue. No significant correlation was found between BF and the tumor location, macroscopic appearance or size. There was a significant decrease in BF in advanced tumor depth (P = 0.0027), peritoneal dissemination (P = 0.0411). Cases with Lauren's diffuse type carcinoma were found to have decreased BF compared to the mixed or intestinal type (34.5 vs. 67.8, P<0.0001). As for the stromal structure, BF significantly decreased with increased stromal density (R=0.861, P<0.0001), despite the lack of correlation with microvessel density (R=0.261, P = 0.266). The 5-year survival rate of high BF group (50<) is significantly better than that of low BF group (<50), 50.8% and 26.5% (P = 0.0367), respectively.
Conclusions: The BF value of the gastric cancer acquired from perfusion CT may reflect the histopathological structure of the tumor, which include the tumor vascularity and the volume of extracellular matrix components of the tumor. In addition, BF value was correlated with 5-year survival rate. This radiological imaging procedure is a valid modality to visualize the decreased tumor blood flow for assessing the malignant level of gastric cancer, especially in those with high-grade malignancy.
No conflict of interest.

2533 POSTER

Real world data on patients with neuroendocrine tumors treated with octreotide LAR

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Background: Octreotide LAR (OCT) has been proven effective in controlling the symptoms and delaying disease progression in patients (pts.) with neuroendocrine tumors (NET). Recent real world medical data on OCT use for the treatment of NET are limited. This retrospective study focuses on treatment history, symptom control and disease progression in NET pts. treated with OCT.
Methods: A retrospective chart audit was conducted in the UK, Spain, Germany, Italy, and France (data collected in January 2013). 78 physicians

completed 158 structured case report forms for pts. treated with OCT in the past 12 months. Demographics, treatment history, symptoms and tumor control data were collected.
Results: Of the 158 NET pts., 57% were male, age (mean[SD]) was 60[10] yrs. and mean time since diagnosis 3[2] yrs. 27%, 46% and 22% of pts. had tumor grade 1, 2 and 3 respectively (WHO classification); 67% of pts. had tumors with secretory symptoms; 61% had metastatic disease. Initial tumor site was: 47% small intestine, 23% stomach, 14% appendix, 10% colon and 6% rectum. Site of metastases: 91% liver, 23% pulmonary, 23% peritoneal, 11% other. Besides OCT, prior treatment history included surgery in 64%, chemotherapy in 9% and targeted therapy in 3%. Concomitant treatments included surgery in 8%, chemotherapy in 7% and targeted therapy in 11%. On average, pts. in this review have received OCT for 33 months. Reasons for prescribing OCT were mostly: efficacy in controlling symptoms (69%) and stabilizing/shrinking the tumor (75%). Most prevalent doses were 20 mg (44%) and 30 mg (44%). OCT injections were administered monthly in the majority of pts. (66%), however dose intervals varied from 2 to 6 weeks. 37% of OCT was administered by nurses at pts. home, 59% at doctors' offices and 8% by a family member. 69% of pts. experienced stabilization or shrinkage of the tumor over the last 12 months. Disease progression was reported in 15% of OCT pts. in the last 12 months, as assessed by Chromogranin A levels, CT-scan, MRI, endoscopy, sonography and other diagnostic tests and procedures.
Conclusions: Most of the NET pts. treated with OCT in this study had advanced metastatic disease. This real-world sample showed that majority of OCT-treated patients where on treatment for several years, any form of disease progression was reported in only 15% of study patients over the last 12 months.
Conflict of interest: *Other substantive relationships: Novartis Pharmaceuticals Corporation*

2534 POSTER

The influence of income status on survival after chemotherapy in patients with advanced gastric cancer

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Introduction: It is well-known that socio-economic (SE) inequalities can influence the survival of cancer patients. The association between SE factors and the survival of cancer has been explained by disease extension at diagnosis and different treatment procedures. However, there are few studies that report the influence of income status on survival of advanced gastric cancer patients treated with similar chemotherapy. In South Korea we have Medical Aid Program (MAP) for the poor. For advanced gastric cancer, the patients with MAP can receive same chemotherapeutic agents including trastzumab (Herceptin®) as patients with National Health Insurance Program (NHIP) in South Korea. We think that disease extension at diagnosis is not quite different by income status of patients with advanced gastric cancer. So we planned to study the influence of income status on results of systemic chemotherapy in patients with advanced gastric cancer.
Patients and Methods: One hundred thirty-eight patients with advanced gastric cancer were admitted for chemotherapy at the Korea University Ansan Hospital between March 2004 and February 2011. Chemotherapy was provided based on physician's decision for performance of patients and consideration for benefit of treatment and risk of toxicity. We reviewed clinical information by the electronic medical records of the patients.
Results: One hundred five patients with NHIP and thirty three MAP patients participated in this study. The median age of the patients was fifty-nine. There were 86 men (62.3%) and 52 women (37.7%). The median number of chemotherapeutic agents was five. Patients with HNIP had a median survival time of 9 months (95% CI, 7.8–10.2 months), which was not significantly different from that of patients with MAP (11 months, 95% CI, 8.6–13.4 months, $p = 0.14$). More than five chemotherapeutic agents were used 52% in patients with MAP (17/33) and 33% (35/105) in patients with NHIP. The patients with MAP showed tendency to receive more chemotherapeutic agents than the patients with NHIP ($p = 0.07$).
Conclusions: Because of welfare system, the survival of advanced gastric cancer patients with MAP seems to be not inferior to that of the patients with NHIP in this study. Further prospective large scale studies are warranted to confirm these results.
No conflict of interest.

2535 POSTER

Assessing the prognostic effect of HER3 (mRNA) in gastric cancer

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Introduction: The epidermal growth factor receptors (EGFR) family stimulates a number of signal transduction cascades that regulate diverse cellular processes, such as proliferation, differentiation, survival, migration and adhesion. These signaling pathways are important in normal cellular homeostasis, but aberrant activation of the EGFR members can cause carcinogenesis. The carcinogenic role of HER3 and HER4 has been seen gastric cancer. In this study, the prognostic effect of HER3 is evaluated in gastric cancer patients.
Material and Methods: Tumoral and free tumoral borders of gastric tissues were freshly obtained from 40 patients with primary gastric adenocarcinoma who underwent a surgical procedure. The patients who underwent gasterectomy did not get any neoadjuvant therapy. Histopathological features including tumor size, location, and grade of differentiation were defined, and surgical stage was determined on the basis of the Union International Cancer TNM classification.
RNA was extracted from normal and cancerous tissue of gastric samples using the RNeasy Mini kit (Qiagen, Hilden, Germany), and then the cDNA was synthesized by using synthesis kit (Fermentas, Lithuania), after that Quantitative Real-time PCR was performed by using SYBR green PCR Master Mix (Fermentas, Lithuania) to determine the expression of HER3 in species. for determining the prognosis, we followed the patients' situation for 6 and 12 months after OR, then the correlation between HER3 (mRNA) with prognosis was determined. Statistical analysis was done by spss ver19, for assessing the correlation between HER3 and clinicopathologic factors used Independent sample t test and Kaplan–Meier curves were generated for overall survival, and statistical significance was determined using the log-rank test.
Results: 77.5% of patients were male and 22.5% were female, 52.5% of patients were older than 65 years whereas, 47.5% were less than 65. 35% of patients have HER3 overexpression. HER3 expression was significantly associated with factors involved with tumor progression, including depth of tumor invasion T1-T2 versus T3-T4 ($P = 0.000$); involved lymph nodes ($P = 0.001$); stage ($P = 0.000$); recurrent disease ($P = 0.000$) and CA19-9 ($P = 0.000$). The significant relationship between mRNA and protein of HER3 was seen. ($P = 0.000$) HER3 overexpression was associated with a significantly worse survival. ($P = 0.000$). The protein of HER3 was an independent prognostic factor in the multivariate analysis. ($P = 0.007$) 95% confidence interval, 0.006–0.454.
Conclusion: HER3 is an independent prognostic factor which can cause tumor progression and poorer survival rate of patients, in cellular and molecular study is demonstrated that anti agents which target HER2 can cause compensatory overexpression of HER3,so that the unexpected result would be gained and prognosis would be poor, therefore, we suggest assessing the expression of HER3 in patients and use regimen which target the band between HER2 and HER3 to get proper results and improve the prognosis.
No conflict of interest.

2536 POSTER

Influence of cytokine gene expressions on development of gastric cancer and chronic active gastritis

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Background: There have been many studies of cytokine expressions in the gastric mucosa of Helicobacter Pylori (H.pylori) infected patients with chronic gastritis and gastric adenocancer. Alterations of these cytokine genes are associated with individual differences in gastric mucosal cytokine mRNA level, which results in differences in gastric mucosal inflamation, gastroduodenal disease risk in response to H.pylori infection. In the present study we aimed to elucidate the expression of cytokines in the gastric mucosa and the immunopathological roles played by these cytokines in normal gastric mucosa (NGM), chronic active gastritis (CAG) and gastric adenocancer (GAC). The cytokines examined were IFN-γ, TNF-α, IL-4, IL-6, IL-10, TGF-β, IL-17A, IL-32, FGF1 and FGF2.
Material and Methods: In order to evaluate the utility of cytokine mediators as markers associated with increased gastric cancer risk, we investigated cytokine gene expression by reverse transcription polymerase chain reaction in gastric biopsy specimens obtained from 93 patients.

Results: We evaluated gastric tissues of 93 patients [43 (46.2%) female, 50 (53.8%) male] between the ages of 18−70. According to histopathological groups (NGM (32; 34.4%), CAG (33; 35.5%), GAC (28; 30.1%)] cytokine gene expression levels using RT-PCR method were evaluated prospectively. IFN-γ, TNF-α, IL-6, IL-10, IL-17A, FGF1 m RNA were increased in CAG group and TNF-α, IL-6, IL-10, IL-17A, TGF-β, FGF1 mRNA were increased in GAC group. The relative expression ratio of IL-6>22 was found to be an independent predictive factor for adenocancer development with referance to control (NGM) group (OR=43.47, %95 CI=3.79–498.82, p = 0.002). The relative expression ratio of IL-6>22 was shown to have increased risk of CAG development with referance to control (NGM) group (OR=10.63, %95 CI=1.70–66.57, p = 0.012).
Conclusion: Our findings suggest that immune response of gastric mucosa to H.pylori differs from patient to patient. Finally IL-6 expression might be useful as an independent molecular marker for early diagnosis of pre-neoplastic changes might be used for follow up. Its utility and cost-effectiveness must be investigated in further studies.
No conflict of interest.

2537 POSTER

Multi-disciplinary team decisions in hepatocellular carcinoma − process and compliance evaluation

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Introduction: It is recommended worldwide that treatment decisions concerning oncological patients should be made in a multi-disciplinary team (MDT). However, few studies have analyzed these decisions and their implementation.
The purposes of this study are the evaluation of the MDT decisions concerning hepatocellular carcinoma (HCC), their implementation, and to analyze the reasons for non-compliance.
Methods: All treatment decisions made by a hepato-bilio-pancreatic MDT of a referral Center in Portugal were prospectively recorded during a 3-year period (January 2010 to December 2012). Implementation of decisions and reasons for non-compliance concerning HCC patients were identified and analyzed.
Results: During this period 2071 MDT consultations were performed, 399 (19%) of them in HCC patients. The 399 MDT decisions analyzed concern 149 HCC patients (sex distribution: 127M/22F; median age of 67 years [25−90]). Two hundred and nine therapeutic decisions were proposed. Non-therapeutic attitudes were proposed in 74 instances (best supportive care − 21, follow-up − 53). In 109 situations the MDT decided not to take a treatment decision and proposed further study due to insufficient information.
Fifteen percent of the decisions (58) were not implemented. Factors associated to non-compliance were: progression of the disease or previously undetected anatomical abnormalities that altered the indication or contra-indicated the proposed treatment, patient option or clinical option. In the cases of non-compliance alternate treatment options were more conservative, with the exception of one patient that had a more aggressive approach.
During this period 21 (14%) patients were proposed to a multimodal approach.
Conclusion: The vast majority of MDT decisions in hepatocellular carcinoma were implemented and changes were mostly related to patient or disease factors that had not been taken into account. Systems for evaluating team effectiveness are immature and methods to monitor performance, teamwork and outcomes are required. Analysis of the implementation of team decisions is an informative process to monitor the quality of MDT decision-making.
No conflict of interest.

2538 POSTER

Sann-Joong-Kuey-Jian-Tang could inhibit human pancreatic carcinoma BxPC-3 cells through inducing autophagy

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Background: Pancreatic cancer is the fourth leading cause of cancer death in the USA, remains a challenging disease. Sann-Joong-Kuey-Jian-Tang (SJKJT), a traditional Chinese medicinal prescription, with cytotoxic effects in many human cancer cell lines, has been used as complementary medicine in Taiwan. But the molecular mechanisms have not been elucidated. Our previous studies showed that SJKJT can inhibit colon cancer colo 205 cells through inducing autophagy in vitro. In the present study we evaluated the efficacy of SJKJT in human pancreatic carcinoma BxPC-3 cells.
Material and Methods: The cytotoxic activity of SJKJT in BxPC-3 cells was measured by MTT assay. The autophagy related protein expressions (such as: BECN1, ATG3, ATG 7, ATG12-ATG5 and LC3-II) were measured by Western blotting.
Results: The results showed that SJKJT could inhibit the proliferation of BxPC-3 cells with time and dose dependent manner. The protein expressions of LC3-II were increased, but BECN1, ATG3, ATG 7 and ATG12-ATG5 were increased at first 24 hrs then decreased at 48 to 72 hrs in BxPC-3 cells were treated with SJKJT.
Conclusions: These finding indicated that SJKJT can inhibit the proliferation of a BxPC-3 cells through inducing Autophagy in vitro. The therapeutic potential of SJKJT in human pancreatic cancer need further in vivo study in the future.
No conflict of interest.

2539 POSTER

Clinical significance of serum M30 and M65 levels in metastatic pancreatic adenocarcinoma

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Background: M30 and M65 are relatively new assays that detect different circulating forms of the epithelial cell structural protein cytokeratin18. This study was conducted to investigate the serum levels of M30 and M65 in patients with metastatic pancreatic adenocarcinoma and the relationship with tumor progression and known prognostic parameters.
Material and Methods: Twenty-six patients with metastatic pancreatic adenocarcinoma were investigated. Serum samples were obtained on first admission before treatment and follow-up. Both serum M30 and M65 levels were determined using enzyme-linked immunosorbent assay (ELISA).
Results: The median age at diagnosis was 59 years, range 32−80 years; 14 patients were male. All patients had metastatic stage and most (n = 21, 81%) had hepatic metastasis. The baseline levels of both serum M30 and M65 levels were significantly higher in patients with metastatic pancreatic adenocarcinoma than the control group (p < 0.001, for both assays). Serum M65 level was significantly higher in the patients with elevated serum LDH (lactate dehydrogenase) levels than those with normal serum LDH levels (p = 0.03). However, serum M30 levels were not corralated with LDH levels. The significant relationship was found between the serum levels of M30 and M65 (r_s = 0.926, n = 26, p < 0.001, Spearman's correlation). Median survival for all patients was 31.7±2.2 weeks (%95 CI=27.31–36.08). Only the serum LDH level was found to be significant for prognosis (p = 0.01). Neither serum M30 nor serum M65 had significant impact on survival (p = 0.28, and p = 0.15, respectively).
Conclusions: Although both serum levels of M30 and M65 assays were found to be diagnostic value, no predictive and prognostic value was determine in metastatic pancreatic adenocarcinoma patients.
No conflict of interest.

2541 POSTER

Clinical significance of coagulation assays in metastatic pancreas adenocarcinoma

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Background: Activated coagulation and fibrinolytic system in cancer patients are associated with tumor stroma formation and metastasis in different types of cancer. The aim of this study is to explore the correlation of blood coagulation tests for various clinicopathologic factors in patients with metastatic pancreatic adenocarcinoma (MPA).
Material: A total of 17 MPA patients were enrolled into the study. All the patients were treatment-naive. Pretreatment blood coagulation tests including PT (prothrombin time), APTT (activated partial thromboplastin time), INR (international normalized ratio),D-dimer, fibrinogen levels and platelet counts were evaluated. Control group was comprised with age 50 and sex- matched individuals without history of malignancy and coagulation disorder.
Results: Median age of diagnosis was 59 years old (range: 35−72). The plasma level of all coagulation factors were revealed statistically significant difference between patient and control group (p < 0.001). Anemic patients had associated with higher D-dimer levels (2996 vs. 505 IU/ml, p = 0.001). Similarly, the ones with elevated serum CA199 exhibited significantly higher D-dimer values (1650 vs. 505 IU/ml, p = 0.01). For APTT, significant differences were found in both between gender of patients (p = 0.01) and response to chemotherapy (p = 0.01). The patients with elevated erythrocyte sedimentation rates had associated with lower INR (1.12 vs. 1.24, p = 0.05). Univariate analysis of survival revealed that the patients with

responsive to chemotherapy (25.7 vs. 34.9 month, p = 0.06) and higher INR (25.6 vs. 33.9 month, p = 0.078) had poor overall outcome.
Conclusion: Coagulation assays can be utilized as predictive factors of MPA. Plasma D-dimer level is also elevated among MPA patients with higher serum CA199. The correlection of D-dimer and CA199 is supposed to reflect hyperactivation of fibrinolytic pathway in presense of higer tumor burden. APTT level is elevated among MPA patients to predict the response to chemotherapy. Higher INR levels seem to be poor prognostic factor in MPA.
No conflict of interest.

2542 POSTER

Prognostic factors in metastatic pancreatic cancer: Older patients have poorer prognosis

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Background: Despite all efforts at management, prognosis of metastatic pancreatic cancer is extremely poor, with median survival of a few months. Pancreatic cancer is mainly a disease of the elderly. Incidence of pancreatic cancer increases with age and 60% of patients are older than 65 years. The aim of this study was to identify and evaluate the impact of different clinicopathologic factors, especially age on the prognosis of metastatic pancreatic cancer.
Material and Methods: The data about 154 metastatic patients with histologically confirmed diagnosis of pancreatic cancer who were treated and followed up in our clinic were recorded from their medical charts.
Results: The group included 102 (66%) male patients and median age was 58 years (25−88 years). Majority of the patients had poor performance status (64%), weight loss more than 10% (74%), larger (>3 cm) tumor size (75%), and elevated tumor markers including CEA (66%) and CA19.9 (85%). The distribution of prognostic factors according to the age of patients were generally identical. The median survival of patients was 179 days, and the 1-year survival rate was 7%. The median survival time of the elderly patients was significantly lower than younger ones (148 days *v* 198 days, p = 0.039). The 1-year survival rates in elderly and younger patients were 3% and 10%, respectively. In both univariate and multivariate analyses, elderly patients had poorer outcome than younger ones (p = 0.04, p = 0.05, respectively). In the whole group, univariate analyses showed similar prognostic factors on survival, including performance status and tumor markers (CEA and CA 19.9). In multivariate anaysis, younger patients with poor performance status had a significantly shorter overall survival than those with good performance status (p = 0.008). However, no significant prognostic factor on outcome was found in the elderly patients.
Conclusions: Age of patients is one of the major prognostic factors influencing survival in metastatic pancreatic cancer. In this regard, elderly patients should be evaluated for different treatment options carefully.
No conflict of interest.

2543 POSTER

SWV, elastometry and elastography of autopsy liver tumor specimen in differential diagnostics of hepatocellular carcinoma

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Objective: Ultrasound diagnostics of liver tumors is still a difficult problem in many cases.
Goal: To improve hepatocellular cance rdiagnostics using elastometry and elastigraphy of the autopsy liver tumor specimens.
Materials and Mmethods: 20 aoutopsy liver tumor specimens with a histologically verified hepatocellular carcinoma were examined. The structure of the tumor and of the normal liver parenchyma were analyzed. Elastography of autopsy liver tumor specimen was focused on tumor tissue softness/rigidity qualitative criteria (soft, solid ormixed type of tissue rigidity depending on the structure of the tumor lesion as compared to the normal liver parenchyma).
Results: Mean values of shear wave velocity (SWV) during the elastometry were as follows: in normal liver parenchyma was 2.44 m/s(1.91 m/s − 2.81 m/s), whereas in the tumor tissue was 2.18 m/s (1.62 m/s to2.73 m/s) (p = 0.45). The analysis of the mean SWV value of tissue deformation in this 20 patients before surgery showed that it was 2.28 m/s in the normal liver parenchyma and 2.20 m/s in the tumor tissue (p = 0.7).
According to ARFI data, we invented classification of the tumors rigidity: 1st type − soft consistency, 2nd type − solid, and 3rd type − mixed consistency (soft with solidparts). Using the ARFI technology in gross specimen, it was explored that type 1 was in 9 cases (45.0%), type 2 − in 3 cases (15.0%), and type 3 − in 8 (40.0%). Based on data of the elastography with manual compression, we divided all liver tumors into 4 groups: group 1 − soft, group 2 − soft central parts with solid edges, group 3 − soft with isolated solid inclusions, group 4 − solid with isolated soft inclusions. Examinations of the liver tumor in a gross specimen showed that group 1 included 2 patients (10.0%), group 2−8 (40.0%), group 3−4 (20.0%), and group 4−6 patients (30.0%). That means, that only 30% of tumors could be considered as rigid and 70% − as soft.
Conclusion: According to ARFI data, the hepatocellular cancer with together with severe liver fibrosis has a soft consistency in most of the cases. Elastography and elastometry showed the same results. SWV didn't show significant difference in the value of normal and tumor liver tissue. Therefore, SWV, elastometry and elastography cannot be used for differential diagnostics of the hepatocellular carcinoma.
No conflict of interest.

2544 POSTER

Recurrence after complete resection of gastrointestinal or pancreatic neuroendocrine tumors: Single institution analysis

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Background: Adjuvant therapy is not currently indicated in patients (pts) with completely resected neuroendocrine tumors (NETs). Additional data regarding time to progression (TTP) and overall survival (OS) of pt with resected NETs are necessary to design adequately powered studies in this setting. Whenever possible, complete surgical resection with curative intent of the primary tumor should be performed; however, many pts don't develop disease recurrence. The probability of recurrence may vary depending on tumor site and biologic aggressiveness. Design and completion of definitive studies evaluating adjuvant regimens is challenging, and no adequately controlled studies have been performed. The aims of this study were to evaluate TTP and OS after complete resection of carcinoid (GI NET) or pancreatic NETs (PNET).
Material and Methods: We analyze retrospectively 28 PNET pts and 36 GI NET pts (3 stomach, 4 duodenum, 18 ileum, 7 appendix, 4 colon) with completely resected disease followed at our center between January 1995 and February 2013, evaluating TTP and OS.
Results: Between 28 PNET pts group, 15 pt experience relapse with mTTP 25.43 (3.57–141.00+) months and mOS 123.86 (4.57−77.17+) months, while 13 pts still not present relapse and are still alive (median OS 50.11 m+). Between 36 GINET pts group, 14 pts experience relapse with mTTP 16.92 (0.8–133.40+) months and mOS 150.67 (31.8–1199.3+) months, while 22 pts still not present relapse and are still alive (median OS 95.13 m+). Between 36 GI NET pts resulted in not evidenced disease after surgery, median OS was 119.3 month (5.7–1199.3+): of these, 22 pts still not present relapse and are still alive (median OS 95.13 m+) 14 pts experience relapse with median PFS 16.92 (0.8–133.40+) months, mOS 150.67 (31.8–1199.3+) months. Pts with not evidenced disease after metastatic site completely resected mTTP and MOS were 3.95 (1.93−50.77+) and 36.68 (16.8–55.33+) months in the PNET group (4 pts), 9.03 (5.1−32.77+) and 150.37 (83.8–172.37+) months in the GI NET group (3 pts). Between pts with primary tumor completely resected without synchronous metastasis, mTTP and mOS were 68.83 (7.16–1238.6+) and 38.57 (6.1–1376.87+) months in the PNET group (24 pts), 56.37 (9.2–1112.9+) and 59.93 (5.7–1199.3+) in the GI NET group (34 pts).
Conclusion: P NET and GI NET G1 and G2 have comparable PFS and OS when radically resected. Pts radically resected who have undergone complete resection of metastases seems to have poorer PFS.
No conflict of interest.

2545 POSTER

Clinical significance of serum LDH, CEA and CA19-9 levels in metastatic pancreatic cancer

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Background: To evaluate the clinical significance of serum LDH, CEA, and CA19-9 levels in metastatic pancreatic cancer (MPC).
Material and Methods: In this retrospective study, we analyzed the outcome of 196 MPC treated and followed up in our clinic.
Results: Positivity rates of serum LDH, CEA, and CA19-9 were 22%, 40%, and 83%, respectively. Likewise, the rates of very high serum levels of tumor markers were correlated with these positivity rates (2/22, 9% for LDH; 12/40, 30% for CEA; and 46/83, 55% for CA19-9). The serum LDH levels were significantly higher in older patients (p = 0.05) and also in the patients with large tumors (p = 0.05), hepatic metastasis (p = 0.01),

hypoalbuminemia (p = 0.01), unresponsive to chemotherapy (p = 0.04). The distribution of prognostic factors depend on both serum CEA and CA19-9 were identical; no relation was found. The significant relationships were found between the serum levels of CEA and CA19-9 (rs = 0.24, p = 0.004), and serum LDH and CEA (rs = 0.193, p = 0.02). No correlation between serum LDH and CA19-9 levels (p = 0.39). 1-year overall survival rate was 12.8% (95% CI =8−18). Increased serum levels of all the tumor markers significantly adverse affect on survival (p = 0.001 for LDH, p = 0.002 for CEA, and p = 0.007 for CA19-9). No difference was observed in between high levels and very high levels of serum markers for all tumor markers. Patients with normal serum levels of all three tumor markers had better outcome than others (p = 0.002) and with normal serum LDH and CEA levels and whatever CA19-9 levels had associated with better survival compared with other possible alternatives (p < 0.001).
Conclusion: Serum levels of LDH, CEA, and CA19-9 significantly affect on survival in MPC patients.
No conflict of interest.

2546 POSTER

Prognostic significance of FDG-PET in locally advanced pancreatic cancer treated with carbon-ion radiotherapy and concurrent full-dose gemcitabine

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Background: The aim of this study was to evaluate the prognostic significance of positron emission tomography using 18-fluorodeoxyglucose (FDG-PET) in patients with locally advanced pancreatic cancer (LAPC) treated on a prospective trial of carbon-ion radiotherapy (CIRT) dose escalation with concurrent gemcitabine.
Material and Methods: Forty patients with unresectable LAPC were treated in our institution on a phase I/II trial of CIRT dose escalation with concurrent full-dose gemcitabine. On the FDG-PET before CIRT and concurrent gemcitabine, the maximum standardized uptake value (SUVmax) on primary tumor was calculated. Cox models were used to assess the effect of prognostic factor on freedom from local progression (FFLP), progression-free survival (PFS), and overall survival (OS).
Results: The median SUVmax was 5.2 (range 1.5–13.2). In the univariate analysis, SUVmax predicted FFLP (HR 1.31 $p = 0.014$), PFS (HR 1.18 $p = 0.020$), and OS (HR 1.28 $p = 0.009$). For all 40 patients, the 2- year FFLP rate, PFS rate, and OS rate were 48%, 14%, 36%. The 2-year FFLP rate, PFS rate, and OS rate in patients with SUVmax <5.2 were 63%, 26%, 80%.
Conclusions: In patients with LAPC undergoing CIRT with full-dose gemcitabine, SUVmax was independently prognostic factor.
No conflict of interest.

2547 POSTER

FDG-PET/CT during chemo-radiotherapy for esophageal cancer: Planning higher radiotherapy doses to reduced target volumes

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Background: The standard treatment of oesophageal cancer is a concomitant combination of cis-platinum-based chemotherapy and radiotherapy (RT) to a total dose of 50.4 Gy. Higher RT doses are likely to improve the poor results of concomitant chemo-radiotherapy (CRT). We investigated whether RT target volumes reduction, as assessed on FDG-PET/CT before and during CRT, would allow RT dose escalation to 66 Gy without compromising normal tissue tolerance.
Methods and Materials: A prospective study (RTEP3, NCT 00934505) included 57 patients with stage IIB, III or IVA (TNM 2002) oesophageal squamous cell carcinomas. FDG-PET/CT was performed before (PET_1) and at 21 days (PET_2) of CRT. The present analysis is restricted to 13 patients in whom FDG-PET/CTs were acquired in radiotherapy position. The Gross Target Volume (GTV_{PET}) was delineated by a nuclear physician and a radiation oncologist on PET_1 and PET_2. Adequate margins were added to account for microscopic disease around GTV_{PET} (Clinical Target Volume CTV) and set-up uncertainties around CTV (Planning Target Volumes PTV). An initial PTV, to be treated up to 40 Gy, was defined on PET_1. Then, the PTV was reduced to receive 50 or 66 Gy (ICRU 83 report), based on either PET_1 or PET_2. The Organs At Risk (OAR) were the spinal cord, the lungs, and the heart. The RT plans were compared in terms of PTV coverage and doses received by the OARs.
Results: 13 patients had a PET in radiotherapy position. GTV_{PET-2} could not be delineated in 3 patients with acute esophagitis. In the 10 remaining patients, GTV_{PET} decreased by 61% (p = 0.01) between PET_1 and PET_2. The $PTV_{66\,Gy-1}$ and $PTV_{66\,Gy-2}$ were $149 \pm 18\,cm^3$ and $102 \pm 8\,cm^3$, respectively, i.e. a 31% reduction (p = 0.05). The dose objectives to the PTV were achieved for all the plans without impairing PTV coverage. Despite PTV dose escalation, significant reductions in dose to the spinal cord (p = 0.01) and to the lungs ($V_{20\,Gy}$, p = 0.005) were achieved with adaptive radiotherapy based on PET_2.
Conclusion: Target volume adaptation using FDG-PET/CT during CRT allows radiotherapy-dose escalation with improved protection of the OAR's, without compromising target volume coverage. This approach needs clinical validation in a prospective trial.
No conflict of interest.

2548 POSTER

Identifying the optimal criteria for radiotherapy in patients with intermediate and advanced hepatocellular carcinoma

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Purpose: We evaluated the clinical outcomes of radiotherapy (RT) for patients with Barcelona Clinic Liver Cancer (BCLC) intermediate and advanced stage hepatocellular carcinoma (HCC) and established the optimal criteria for RT in these stages.
Methods and Materials: A total of 103 patients were enrolled in this study. All patients received RT delivered using the TomoTherapy Hi-Art system (TomoTherapy Inc., Madison, WI, USA), at Incheon St. Mary's Hospital and Seoul St. Mary's Hospital between March 2006 and February 2012. The planning target volume (PTV) was $330.1 \pm 275.1\,cm^3$, and the non-target normal liver (NTNL) volume was $1209.7 \pm 426.9\,cm^3$. The dose per fraction to the PTV was 1.8−5 Gy, and the total dose was 40−60 Gy (median, 50 Gy). We evaluated the factors associated with the deterioration of hepatic function and the local progression-free survival (PFS) in order to identify the optimal criteria for RT.
Results: A PTV of 225 cc, a total dose of 60 Gy_{10}, and an NTNL-V_{BED20} of 40% were identified as factors associated with the deterioration of hepatic function and local PFS. On the basis of these factors, patients were divided to a favorable group or unfavorable group. The differences in median local PFS, overall survival, and the incidence rate of deteriorated hepatic function between the 2 groups were 10.4 months, 11.2 months, and 66.2%, respectively, all of which were statistically significant (p < 0.001 in each case).
Conclusions: We suggest that the optimal criteria for RT in patients with BCLC intermediate and advanced stage HCC were a PTV <225 cc, a total dose >60 Gy_{10}, and an NTNL-V_{BED20} <40%.
No conflict of interest.

2549 POSTER

The role of postoperative or definitive three-dimensional chemoradiotherapy in pancreatic cancer: A single institution experience

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Purpose: To evaluate the effect of radiotherapy (RT) in the curative treatment of patients with pancreatic cancer.
Materials and Methods: We retrospectively evaluated the medical records of 176 patients treated in our department between July 2009 and October 2011. RT was delivered as an adjuvant treatment in 98 patients and as a definitive treatment in 78 patients. Median age was 57 years old (range, 30−80 years) and 114 (65%) of the patients were male. The disease was located in the pancreatic head in 78% of the patients. According to AJCC staging system tumor stage was T3 in 36% and T4 in 45% of the patients. Pathological/radiological regional lymph nodes (LN) were involved in 48% of the cases. The median total dose of 50.4 Gy was delivered conformally to the tumor bed and regional LNs. The median daily fraction dose was 1.8 Gy.

A total of 154 patients received concurrent gemcitabine (126 patients) or 5-FU (28 patients) chemotherapy (CT).
Results: Median follow up was 15 months (range, 2–158 months). Median survival in the adjuvant treatment group was 26 months and definitive treatment group was 16 months ($p = 0.004$). Progression free survival (PFS) in the adjuvant and definitive treatment groups were 9 and 6 months respectively ($p = 0.045$). Gender, location of the tumor, CT regimens, tumor and node status did not affect the overall survival (OS) and PFS. In both groups OS and PFS were affected by the ECOG performance status ($p < 0.001$). In the adjuvant group, OS was superior in patients <60 years old ($p = 0.028$). In this group PFS was also superior (12 months vs. 7 months, $p = 0.05$). The patients generally well tolerated our treatment regimen. The most common toxicity was grade 1 emesis according to RTOG acute toxicity criteria (55%).
Conclusions: In this retrospective study we found that ECOG performance status was an important factor that affects OS and PFS in both adjuvant and definitive treatment groups. Postoperative adjuvant radiotherapy seems to be more effective than definitive setting.
No conflict of interest.

2550 POSTER

Adjuvant chemoradiotherapy after distal pancreatectomy for pancreatic cancer

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Background: To evaluate the outcome of adjuvant chemoradiotherapy (CRT) after distal pancreatectomy (DP) in patients with pancreatic adenocarcinoma, and to identify the prognostic factors for these patients.
Methods and Materials: We performed a retrospective review of 66 consecutive patients who underwent curative DP followed by adjuvant CRT between 2000 and 2011. There were 34 males and 32 females, and median age was 64 years (range, 38−80). Adjuvant radiotherapy was delivered to the tumor bed and regional lymph nodes with median dose of 50.4 Gy (range, 40–55.8). All patients received concomitant chemotherapy and 55 patients (83.3%) also received maintenance chemotherapy. The median follow-up period was 20 months.
Results: Forty patients (60.6%) experienced relapse. Isolated locoregional recurrence (LRR) developed in 5 patients (7.6%) and distant metastasis (DM) in 35 patients (53.0%), of whom 13 had both LRR and DM. Median disease-free survival (DFS) was 16.5 months. On univariate analysis, splenic artery (SA) invasion, resection margin (RM) involvement, tumor size $\geqslant$3 cm, lymph node metastasis, angiolymphatic invasion, venous invasion, and perineural invasion were identified as significant adverse prognosticators. Multivariate analysis revealed that SA invasion ($p = 0.032$) and RM involvement ($p = 0.005$) were independent prognostic factors for DFS. Grade 3 or higher hematologic and gastrointestinal toxicities occurred in 21.2% and 4.5% of patients, respectively.
Conclusions: Adjuvant CRT resulted in a low rate of isolated LRR with acceptable toxicity, but DM was still frequent despite maintenance chemotherapy. Our results indicated that SA invasion was a significant factor predicting inferior DFS as was RM involvement. When SA invasion is identified preoperatively, neoadjuvant treatment may be considered.
No conflict of interest.

2551 POSTER

Clinical characteristics and prognostic factors of brain metastases from hepatocellular carcinoma

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Background: To evaluate clinical features and prognostic factors of brain metastases from hepatocellular carcinoma.
Materials and Methods: Medical records of 95 patients who have been diagnosed of brain metastases from hepatocellular carcinoma between Jan. 2000 and Dec. 2011 were retrospectively reviewed.
Results: The median age at diagnosis of brain metastases is 56.1 years. Eighty-two patients were male. Median interval from diagnosis of hepatocellular carcinoma to brain metastases was 29.5 months. Eighty eight patents had extracranial metastasis, and the lung was the most frequent involved organ. Motor weakness was the most frequent presenting symptom (49.5%). Intracranial hemorrhage was present in 71 patients (74.7%). Brain metastases were treated with surgery alone in 3 patients, radiosurgery alone in 18 patients, whole brain radiation therapy (WBRT) alone in 57 patients, surgery and radiosurgery in 3 patients, surgery and WBRT in 6 patients, radiosurgery and WBRT in 2 patients, conservative management only in 6 patients. Median overall survival was 3.0 months. Multivariate analysis showed ECOG performance status, AFP level, Child-Pugh class, number of brain lesions, and treatment modality were associated with survival ($P < 0.05$). Diagnosis Specific Graded Prognostic Assessment(DS-GPA) could be suggested with four factors (ECOG performance status, AFP level, Child-Pugh classification, number of brain lesions). We calculated DS-GPA for each patients by scoring individual factors with 0 or 1. Median survival of the patients with DS-GPA score 0 or 1 was 0.6 month (95% CI 0.50–0.70), score 2 was 2.5 months (95% CI 1.90–3.15), and score 3 or 4 was 5.8 months (95% CI 5.21–6.40).

DS-GPA variables	Point 0	Point 1
ECOG PS	>2	$\leqslant$2
Child-Pugh class	B/C	A
AFP (ng/ml)	>1400	$\leqslant$1400
No. of brain metastases	>1	1

Conclusions: Although overall prognosis of patients with brain metastases from hepatocellular carcinoma is poor, we can estimate the survival of patients by employing DA-GPA using four prognostic factors (AFP level, Child-Pugh Class, ECOG PS, number of brain lesions).
No conflict of interest.

2552 POSTER

Benefits of stereotactic body radiotherapy after incomplete transcatheter arterial chemoembolization in inoperable hepatocellular carcinoma

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Background: To analyze the effects of additional stereotactic body radiotherapy (SBRT) after incomplete transcatheter arterial chemoembolization (TACE) in inoperable hepatocellular carcinoma (HCC), the treatment outcomes of TACE followed by SBRT and TACE followed by treatment modalities other than SBRT were compared retrospectively.
Material and Methods: Between January 2006 and December 2008, 497 patients with HCC were treated with TACE as a primary treatment. In order to compare the effects of SBRT following incomplete TACE with those of modalities other than SBRT, the following criteria were imposed. The eligibility criteria included the following; (1) single tumor, (2) tumor size $\leqslant$10 cm, (3) no extrahepatic metastases, (4) Child-Pugh score $\leqslant$7, (5) no major vessel invasion, (6) Eastern Cooperative Oncology Group performance status $\leqslant$2. The exclusion criteria were as follows; (1) diffuse infiltrative tumor type, (2) tumor occupying $\geqslant$2/3 of the liver volume, (3) liver cirrhosis-associated complications, (4) severe co-morbidity, (5) previous radiation therapy to the upper abdomen, (6) presence of other malignancies within 5 years. One hundred and four patients were evaluated for TACE failure. Complete response was shown in 19 patients (complete TACE group), and incomplete in 85 patients. Among the incomplete TACE group, 39 patients had additional SBRT (TACE+SBRT group), and the remaining 46 patients received repeated TACE (incomplete TACE group).
Results: The patient characteristics were similar among the three groups except for the size of the tumor. The complete TACE group, in which none of the tumors were larger than 5 cm, contained tumors of smaller size compared to other groups. With a median survival time of 34 months, the overall survival (OS) at 2 years for the complete TACE group, incomplete TACE group and TACE+SBRT group were 84.2%, 45.7%, and 76.8%, respectively. The OS at 5 years for the complete TACE group, incomplete TACE group and TACE+SBRT group were 47.4%, 28.3%, and 63.5%, respectively. Compared with the incomplete TACE group, the TACE+SBRT group and the complete TACE group showed significantly improved survival rates ($p = 0.006$ and $p = 0.023$, respectively). Although the complete TACE group was composed of smaller tumors than the TACE+SBRT group, survival appeared to be statistically equivalent in the two groups ($p = 0.948$).
Conclusions: A significantly improved survival benefit was found in the TACE+SBRT group compared to the incomplete TACE group. Therefore, SBRT is strongly recommended for patients with incomplete TACE in inoperable HCC.
No conflict of interest.

2553 POSTER

YTTRIUM-90 (y-90) radioembolization in patients with unresectable liver metastases: Determining the factors that lead to treatment efficacy

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Introduction: Locoregional treatments, such as radioembolization, can be used to treat patients with unresectable liver metastases. These treatments have been shown to reduce tumor size, lower the risk of recurrence, and increase survival time in these patients. In this study, we aimed to determine the progression-free survival and factors that predict survival of patients with liver metastases whose response to selective internal radiation therapy (SIRT) with Y-90 was assessed by positron emission tomography − computed tomography (PET CT).
Patients: Seventy eight liver cancer patients who were treated with Y-90 radioembolization in the Departments of Medical Oncology, Invasive Radiology and Nuclear Medicine at Akdeniz University Hospital between February 2010 and November 2012 were included in this report.
Results: The post-treatment response rates were as follows: 7 patients (9%) had stable disease (SD), 26 patients (33.3%) had a partial response (PR), 4 patients (5.1%) had a complete response (CR), and progressive disease (PD) was observed in 28 patients (35.9%). The median hepatic progression-free survival (HPFS) was 4.4 months (95% Confidence Interval (CI): 2.5 to 6.3), while median overall survival was 10.1 months (95% CI: 7.4 to 12.9). Univariate analysis revealed that HPFS is significantly affected by international normalized ratio (INR) levels and age (hazard ratio (HR) = 0.54 (95% CI: 0.30–096), P = 0.034, HR = 1.03 (95% CI: 1.00–1.05), P = 0.051, respectively). However, only INR levels retained significance with multivariate analysis (HR = 0.53 (95% CI: 0.30–0.93), P = 0.028), while age had limited significance (HR = 1.02 (95% CI: 1.00–1.05), P = 0.051).
Conclusion: We determined that Y-90 radioembolization is effective as a salvage therapy in patients with predominant liver metastases. For the first time, we showed that age and INR values reflecting the functional hepatic reserve can be used as positive predictive factors for hepatic progression-free survival.
No conflict of interest.

2554 POSTER

High-dose stereotactic body radiotherapy improves local control and overall survival in patients with inoperable hepatocellular carcinoma

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Background: The purpose of this study is to determine whether high-dose stereotactic body radiotherapy (SBRT) improves survival in patients with inoperable hepatocellular carcinoma (HCC).
Material and Methods: Between March 2003 and February 2011, 108 patients with 122 lesions were treated with SBRT for HCC. The indications for SBRT were unsuitability for surgery or local ablative therapies and incomplete response to transarterial chemoembolization. The inclusion criteria of this study were SBRT in 3 fractions and a longest diameter (LD) $\leqslant$7.0 cm. Eighty-two patients with 95 lesions were analyzed. Seventy-four patients had Child-Turcotte-Pugh class A and 8 had B7. The median LD was 3.0 cm (range, 1.0−7.0 cm). The median dose was 51 Gy (range, 33−60 Gy).
Results: Local control (LC) and overall survival (OS) rates at 2 years after SBRT were 87% and 63%, respectively, with a median follow-up duration of 30 months for all patients. The 2-year local control (LC)/overall survival (OS) rates for patients treated with doses of >54 Gy, 45−54 Gy, and <45 Gy were 100%/71%, 78%/64%, and 64%/30%, respectively ($p = 0.009/p < 0.001$). The 2-year overall survival rates for patients with and without local failure were 27% and 68%, respectively ($p < 0.001$). Multivariate analysis revealed that SBRT dose ($p = 0.005$) and Barcelona Clinic Liver Cancer stage ($p = 0.015$) were significant prognostic factors for OS. Correlation analysis revealed that there was a positive linear relationship between SBRT dose and LC ($p = 0.006$, R=0.899) and OS ($p = 0.002$, R=0.940) at 2 years. Five patients experienced grade 3 or higher gastrointestinal toxicity, and 6 experienced worsening of CTP score by $\geqslant$2 within 3 months of SBRT. Patients with dose >54 Gy had LC and OS rates of 100% and 67%, respectively, at 4.5 years. The estimated SBRT dose to achieve 90% LC at 2 year was 54.8 Gy in 3 fractions.
Conclusions: The present study revealed dose-control and survival relationships in SBRT for HCC. Excellent local control rates were achieved with SBRT dose of more than 54 Gy. Higher local control rates resulted from increasing dose may be survival benefit for inoperable HCC. High-dose SBRT may be as effective and safe a treatment modality as radiofrequency ablation. We suggest SBRT dose of more than 54 Gy in 3 fractions, if normal tissue constraints allow.
No conflict of interest.

2555 POSTER

Radiation dose does not influence anastomotic complications in patients with esophageal cancer treated with neoadjuvant chemoradiation and transhiatal esophagectomy

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Background: According to the Dutch guidelines the preferred curative treatment for non-metastatic esophageal cancer is neoadjuvant chemoradiation followed by surgery. Surgical treatment is associated with high rates of anastomotic leakage and stenosis. Neoadjuvant chemoradiation might increase anastomotic leakage and stenosis. The aim of this study was to determine the influence of radiation dose on leakage and stenosis in patients with esophageal cancer undergoing neoadjuvant chemoradiation followed by a transhiatal esophagectomy.
Material and Methods: A retrospective review was performed of 53 consecutive patients with distal esophageal cancer (C15.5) or gastro-esophageal junction cancer (C16.0), who received neoadjuvant chemoradiation (23 x 1.8 Gy, (41.4 Gy) combined with Paclitaxel and Carboplatin) followed by a transhiatal esophagectomy and a left cervical anastomosis between 2009 and 2011. On the preoperative planning CT the future anastomotic region was determined and the mean radiation dose, V20, V25, V30, V35 and V40 were calculated. Logistic regression analysis was conducted to examine determinants of anastomotic leakage and stenosis.
Results: Anastomotic leaks occurred in 13 of 53 patients (25.5%) and anastomotic stenosis occurred in 24 of 53 patients (45.3%). Median follow up duration was 20 months (range 0.2−25). Logistic regression analysis showed that mean dose, V20 − V40, age, co-morbidity, method of anastomosis, operating time and interval between last radiotherapy treatment and surgery were no predictors of anastomotic leakage and stenosis.
Conclusion: This study demonstrates that the radiation dose of 23 x 1.8 Gy on the future anastomotic region has no influence on the occurrence of anastomotic leakage and stenosis in patients with esophageal cancer treated with neoadjuvant chemoradiation followed by transhiatal esophagectomy.
No conflict of interest.

2556 POSTER

Adjuvant radiochemotherapy in completely resected gastric cancer: Experience of National Cancer Institute of Chile

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Purpose: Cancer in Central America, Caribbean and South America, is the 2º leading cause of death, where gastric cancer (GC) for men is the 3º most frequent and the 3º most deadly, for women is the 3º most common and the 3º most deadly. In the case of Chile, the GC for men is the 2º most common and 1º most deadly, for women is the 4º most common and 3º most deadly. Given its importance, it was necessary for us to review the results obtained in our institution in patients treated with adjuvant radio-chemotherapy.
Material and Methods: From Aug 2004 to Dec 2011, 168 patients, 99 men and 69 women with loco-regionally advanced GC (pT1−4, N0−3, M0), completely resected were treated with concomitant Radiotherapy (RT) and Chemotherapy (CT) based in 5FU (INT0116 scheme) in the National Cancer Institute of Santiago. The median age of diagnosis was 62 years, 99% of patients ECOG 0−1. Treatment consisted of total gastrectomy, subtotal gastrectomy or esophageal-gastrectomy plus D1 lymphadenectomy (14 patients), D2 (153 patients) and D3 (1 patient) respectively, followed by 3DRT, doses of 45 Gy in 25 fractions to tumor bed, regional nodes and anastomoses. The CT consisted of 5 FU (425 mg/mt2/day) and leucovorin (20 mg/mt2/day) for 5 days beginning

on day 1 and then RTCT 5FU (400 mg/mt2/day) and leucovorin (20 mg/mt2/day) for 4 days during the first week and for 3 days at RT the fifth week, then two separate monthly cycles than 1 month 5FU (425 mg/mt2/day) and leucovorin (20 mg/mt2/day) for 5 days or only RTCT 5FU (400 mg/mt2/día) and leucovorin (20 mg/mt2/day) for 4 days during the first week and three days the fifth week of RT. The dosage was adjusted according to toxicity.
Results: With a median follow up of 58 months (minimum 12 months), the median survival was 41 months. The median interval from surgery to start CT was 12 weeks and start RT was 17 weeks. The greater toxicity during RT was grade 3 in 3.5% of patients, mainly gastro-intestinal. Overall survival at 1, 2, 3, 4, 5 years was 88%, 64%, 53%, 47% and 41% respectively. Univariate analysis showed statistically significant factors associated with poor prognosis for overall survival were tumor site in antrum + fundus (p 0.007), presence of signet ring cells (p 0.0061), + LVI (p 0.014), N + (0.0008) with a HR of 1.32 for every stage of N increases and a HR of 1.05 for each positive found node (p 0.001), >15 positive nodes (p 0.001) and pathological increase of stage group (p 0.017). At multivariate analysis, statistically significant factors associated with poor prognosis for overall survival were tumor location in antrum+fundus (p 0.002), presence of signet ring cells (p 0.044), >15 positive nodes (p0.015).
Conclusion: Adjuvant RTCT at our institution has shown to be effective and safe, even at 12 weeks of delay in initiation of CT or 17 weeks to RT after surgery, with results in survival at 3 and 5 years of 53% and 41% respectively, comparable results with INT 0116 and its last update in 2012, with survival at 3 and 5 years of 50% and 41% respectively, this maybe due to the better quality of surgery offered, 91% with D2 lymphadenectomy vs. 10% in the INT 0116 respectively.
No conflict of interest.

2557 POSTER

Treatment of hepatocellular carcinoma with stereotactic body radiation: Experience from two institutions

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Background: Hepatocellular carcinomas (HCC) are aggressive liver tumors arising in patients with already limited liver. Treatment options for localized disease include surgery and ablative therapy. Our objective is to review our 4 year experience of stereotactic body radiation therapy (SBRT) for HCC patients ineligible for further local therapy.
Material and Methods: A population of 16 patients diagnosed with HCC and treated with SBRT between January 2007 and December 2011 was collected from two Montreal institutions. Patient characteristics and tumor features, as well as treatment details were obtained from chart review. Eight patients were treated by Cyberknife with synchrony fiducial tracking. The other eight patients treated were treated using conventional isocentric linear accelerators with fiducial-aided respiratory gating. The tolerance dose for the liver used in plan design was the biological equivalent of 700 cc of liver irradiated to less than 15 Gy in 3 fractions.
Results: The mean age of patients treated was 68 years old (range 49−83). Mean follow-up period from time of SBRT was 5.5 month (range 0.97–45.5). Nine patients were classified as a Child-Pugh class A, 4 were class B, and 1 patient was class C. Previous ablative treatments had been attempted in 46% of patients. The mean maximal tumor dimension was 3.75 cm (range 1.4−8.0 cm) and mean gross tumor volume was 52 cc. Nine patients received SBRT administered in 3 fractions (dose 30−45 Gy), four patients received 5 fractions (dose 24−50 Gy), one patient received 6 fractions (total dose 30 Gy), and one patient received 10 fractions (total dose 40 Gy) due to proximity to the stomach. Four patients developed acute SBRT-related toxicity, with two patients complaining of transient abdominal pain, one patient had grade I nausea, and one patient developed grade III dermatitis at the sites of beam entry. Actuarial two-year overall survival was 63%. Two-thirds of deaths were related to intra-hepatic progression. One patient is alive following liver transplant (with complete pathological response) and 2 patients had no residual HCC seen on repeat biopsy. So far, only 2 patients have had progression of the treated lesion.
Conclusion: Although our series is limited in size and follow-up, it confirms that SBRT is a well-tolerated treatment for HCC with the potential for complete response and long-term control in patients ineligible for surgery or other local ablative therapies.
No conflict of interest.

2558 POSTER

IMRT in carcinoma anal canal: Initial dosimetric analysis of a prospective study

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Background: The cornerstone for the treatment of carcinoma anal canal remains concurrent chemo radiotherapy (CTRT). The conventional radiotherapy technique is associated with higher acute toxicity and treatment interruptions, thereby obscuring local control. We are presenting the dosimetric data of IMRT for carcinoma anal canal from a prospective study.
Methods: We prospectively enrolled patients with carcinoma anal canal to undergo CTRT. The radiation was planned by IMRT technique. The CTV-A has been delineated as the GTV with a 3 cm expansion limiting from the bones and uninvolved muscles. The nodal CTV (CTV-B) included the internal iliac, Obturator, External Iliac, Presacral and B/L inguinal group of lymph nodes. 1 cm expansion was used to form the PTV. The PTV-A received 54 Gy in 30 fractions over a period of 6 weeks, except for T2N0 where the dose was delivered in 28 fractions. The dose for PTV-B varied, with T2N0 recieving42 Gy in 28 fractions, while T3-T4 with N0, a dose of 45 Gy, while for Node<3 cm dose of 50.4 Gy and node >3 cm dose of 54 Gy, were given in 30 fractions. All patients were planned with Eclipse planning system version 6.5 with 7 field IMRT using 6 MV photon beam. All patients received concurrent chemotherapy with InjCisplatin and Inj 5FU. Grade III and Grade IV toxicity was taken as indication for admission. All patients were assessed for response and salvage APR done after 6 weeks.
Results: We analyzed data from four patients. All but one patient was female. Median age at diagnosis 52 years (Range: 50−65 years). Bleeding Per rectum (2) and local pain (2) were the most common presenting symptom. Smoking history was associated with three patients. Three patients were in stage II and One in stage III. Treatment plan remained CTRT (2) or NACT followed by CTRT (2). Median V35, V40, V50 for bladder was 55.32%, 42.13%, 21.92%. Median V30, V40, V44 for Left Femur was 97%, 25.16%, 0.71% and Right femur 100%, 43%, 2.26%. Median V30, V35, V45, V50 for small intestine was 164.7 cc, 123.95cc, 53.61 cc, and 1.21 cc. Median V30,V35,V45 and V50 for large intestine was 88.78 cc,39.96 cc,71.95 cc. Median Conformity and homogeneity index were 1.26 (Range: 1–1.55) and 1.1 (Range: 1.09–1.11).
Conclusion: The dosimetric data shows good sparing of critical normal organs and conformal dose distribution. This can predict reduced radiation side effect and treatment interruption with better local control.
No conflict of interest.

2559 POSTER

Noncoplanar three-dimensional radiation therapy for advanced hepatocellular carcinoma

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Background: Standard treatments for patients with hepatocellular carcinoma (HCC) are surgery, radiofrequency ablation (RFA) and transcatheter arterial chemoembolization (TACE). However, for patients limited use of these treatments, the efficiency of radiation therapy (RT) has been indicated. In our institution, noncoplanar three-dimensional radiation therapy (NC3DRT) had been performed to increase the efficiency of RT without damaging of the normal liver for advanced HCC from 2010. The purpose of this retrospective study was to evaluate the feasibility and safety of NC3DRT for the treatment of advanced HCC with/without tumor thrombosis.
Material and Methods: From July 2010 to January 2013, 17 patients with advanced HCC were treated with NC3DRT at our institution. Eleven men and six women ages 54 to 86 years (median, 72 years) were included in the study. Of these patients, 11 presented with tumor thrombus in the portal vein (10 patients) or inferior vena cava (one patients). The longest diameter of the lesions ranged in size from 30 mm to 80 mm (median, 45 mm). A total dose of 60 Gy in 30 fractions over the 6 weeks was delivered with noncoplanar three-dimensional technique to a target volume that encompassed the HCC with/without tumor thrombus.
Results: Fifteen patients were local progression-free during a median follow-up period of 8 months (ranging from 3 to 26). Two patients experienced progressive disease. Of these patients, one had tumor progression during treatment and died 3 months after the beginning of

NC3DRT, remaining one patient suffered marginal recurrences 2 months after NC3DRT and died of progressive disease 6 months after the beginning of NC3DRT. Eight patients died and the remaining nine patients were alive as of March 2013. Two patients died of multiple tumors in the liver, two of distant metastases, two of progressive primary tumor as mentioned above, and two of liver failure, respectively. Local progression-free survival rates were 54% at 1 year and 27% at 2 years. No toxicity forced the patients to discontinue the treatment. According to the National Cancer Institute's Common Toxicities Criteria for Adverse Events, version 3.0 (CTCAE v3.0), no acute and late toxicities of grade 3 or higher were observed.
Conclusions: NC3DRT of 60 Gy in 30 fractions seems a safe and effective for patients with advanced HCC.
No conflict of interest.

2560 POSTER

Brain metastases from stomach cancer − the role of different treatment modalities and efficacy of palliative radiotherapy

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Introduction: Brain metastases from stomach cancer are usually late manifestation of the disease and patients are often in severe cachexia and in bad performance status. There are few literature studies concerning this group of patients, thus the authors decided to evaluate the efficacy of palliative radiotherapy and to describe different treatment modalities and sequences − surgery plus SRS and WBRT, surgery plus WBRT, SRS plus WBRT and WBRT only.
Materials and Methods: Between 2002 and 2011 a total of 16 patients were diagnosed with brain metastases from stomach cancer at Centre of Oncology Institute Maria Sklodowska-Curie Memorial in Gliwice. The data of all the patients were collected and retrospectively analyzed. The patients ranged in age from 51 to 75 years (median 68.5 years). There were 11 men (69%) and 5 women (31%). All patients had histologically verified gastric cancer. Primary metastatic gastric cancer was diagnosed in 6 patients (37.5%), and in 3 cases (18.75%) it was metastasis to the brain.
Results: Median time to brain metastases (TBM) was 12.3 months. Median TBM was shorter for patients with pretreatment metastases to other organs compared with patients without metastases (5.5 months vs. 12.6 months, $p = 0.042$). Median TBM were 12.8 months (range, from 0.8 month to 52 months) and 5.4 months (range, from 0.8 month to 52 months), respectively for 9 patients after R0 resection and for 7 remaining patients. The following clinical features were not prognostic for TBM: gender, age, number, location and largest size of brain metastases, location of other metastases.
The 1- and 2-year OS were 19% and 12.7%, respectively (median OS was 2.8 months). Amongst different clinical factors influencing OS, performance status, number of metastases, pattern of metastases, type of treatment, were statistically significant.
There was no statistically significant effect noted on OS for gender, grade, types of neurological symptoms, or location and largest size of brain metastases. However, patients under the age of 60, and patients with TBM less than 6 months tend to have a more favorable prognosis ($p < 0.1$).
Conclusions: Brain metastases from gastric cancer are very rare and difficult to treat. The response to radiotherapy is worse than in brain metastases from other cancers and the survival is also shorter. Therefore very aggresive treatment schemes are needed to improve the outcome.
The results of this study show that combining neurosurgery with adjuvant radiotherapy and chemotherapy is improving the survival. Our study also indicates the prognostic factors which may be helpful in considering the best treatment options.
No conflict of interest.

2561 POSTER

Radiochemotherapy with capecitabine after surgery for adenocarcinoma of the stomach or gastroesophageal junction

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Background: Surgical resection of adenocarcinoma of the stomach is the only curative modality. After surgery alone, more than 60 % of the patients will develop distant metastasis or local recidiv.
The Intergroup Study INT-0116 reported significant improvent in survival in patients with resected adenocarcinoma of the stomach or gastro esophageal junction with adjuvant radiochemoterapy.
In the Republic of Macedonia, patients are treated with adjuvant radiochemotherapy, 5-fluorouracyl and leucovorin and 2D radiotherapy since 2002.
In this study we replace 5-fluorouracyl, leucovorin chemotherapy with oral Capecitabine, and instead of 2D we used 3D radiotherapy.
Patients and Method: During 2011–2012, 32 patients with the mean age of 56 years were treated with chemo radiotherapy after surgery for adenocarcinoma of the stomach or gastro esophageal junction. Patients were staged Ib-IIIC, with R0 or R1 resection, (26 patients with R0, and 6 patients with R1 resection).
Patients were treated with one cycle chemotherapy with Capecitabine ($1250\ mg/m^2$) twice daily on day 1−14. After 3 weeks we started with 3D radiotherapy to total dose 45 Gy delivered in 5 weeks, daily dose 1.8 Gy. Computer tomography- based 3 dimensional RT planning was previously performed and radiotherapy was delivered with 15-MV photons, generally by 3 field technique. CTV was defined using preoperative computer tomography, endoscopic findings, stapler. LNs as described in Intergroup 0116 study. Anastomotic regions and safety margin around the former tumor 3 sm. PTV was calculated with 1 sm margin over CTV. The design of the treatment field was individualized according to tumor stage, localization and the type of surgery.
Chemotherapy during irradiation was administered with daily dose $825\ mg/m^2$ twice daily, 5 days per week. First dose was taken 1 hour before irradiation and the second dose 12 hours lately. After finishing irradiation three more cycle chemotherapy were added in 3-week intervals.
Results: The treatment was completed according to the protocol in 26 patients. No death occurred due to the therapy.
Nausea and vomiting, diarrhea, hand foot syndrome, stenocardia, dysphagia grade three occurred in 2, 6, 1, 2, and one patient respectively.
10 patients lost more than 10% body weight (range 10−18%).
At the firs follow up visit, 3 months after completion of treatment all 26 patients were alive, with no side effects of radio chemotherapy.
Conclusion: Adjuvant 3D radio chemotherapy with capecitabine in patients with gastric cancer is feasible and toxicity is low.
No conflict of interest.

2562 POSTER

Quality assurance in lymphadenectomy for gastric cancer in the Dutch randomized gastric cancer trial

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Background: After a median follow up of 15 years a D2 lymphadenectomy was associated with lower local recurrence and lower gastric cancer related death rates rather than D1 surgery. Several Japanese authors, of high volume institutions with better survival results, argued that a proper a D2 dissection is technically demanding that learning curves had not reached the plateau at the end of the trial. In order to assess the impact of quality assurance prospectively, non-compliance and contamination in both the study arms was investigated with respect to recurrence and survival.
Methods: 1078 patients were included in the trial. 711 patients with potentially curative resections were evaluated. Location and numbers of lymph nodes detected at pathological investigation were compared according to the guidelines of the Japanese Research Society for the study of Gastric Cancer. *Non-compliance* was defined as inadequate removal of lymph node stations and *contamination* was defined as lymph nodes removed outside the intended level of resection. The dissection groups D1 and D2 were divided into non compliant, compliant and contaminated. Long term overall survival was calculated for minor ($\leqslant$2 lymph nodes) and major ($\geqslant$3 lymph nodes) non-compliance and minor ($\leqslant$2 lymph nodes) and major ($\geqslant$3 lymph nodes) contamination in the D1 and D2 group, using Kaplan–Meier plots.
Results: Overall noncompliance was 80.6% in the D1 and 81.5% in the D2 group. In the D1 group minor non-compliance was present in 65.3% and for the D2 group 55.6%. Long-term survival for the correct dissected D1 group (minor non compliance + compliance, $n = 319$) and correct dissected D2 group (minor non compliance + compliance, $n = 245$) was 23.2% versus 32% ($P = 0.259$). When all patients with a accidental spleen resection were excluded the survival was 23.3% for the D1 group versus 39% for the D2 group. ($P = 0.004$) In the D2 dissection group contamination also leads to better survival. In both groups compliance leads to better survival rates.
Conclusion: After 15 years of follow up quality assurance by compliant D2 dissection leads to better survival.
No conflict of interest.

2563 POSTER

Interim analysis of a phase II trial of neoadjuvant chemoradiation therapy followed by conventional resection for cholangiocarcinoma

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Background: Cholangiocarcinoma has one of the worst prognoses among GI tract cancers. To improve the prognosis of cholangiocarcinoma patients, we have applied neoadjuvant chemoradiation therapy followed by conventional resection for possibly resectable cholangiocarcinoma. We published the phase I study (Hepatogastroenterology. 2011;58:1866−72) and showed that neoadjuvant chemoradiation with conventional resection was safe and tolerable. Then, we proceeded Phase II study (P-2). Here, we evaluated P-2 as an interim analysis and compared the P-2 group and 99 patients who were operated on using conventional resection at the same stage and same period as the P-2 group in terms of the perioperative factors and effectiveness.
Material and Methods: Regimen of P-2 was 600 mg/m^2 of gemcitabine (day 1 and 8 x 2 courses) with external beam radiation therapy (1.8-Gy daily fractions to a total dose of 45 Gy). Patients with histologically or cytologically confirmed adenocarcinoma of the extra- and hilar cholangiocarcinoma were enrolled from 2008 to June 2012 at Tohoku University Hospital. The primary endpoint was the R0-resection rate. We thought the R0-resection rate was 60% referring to our previous data, assumed that it would increase to 80% with neoadjuvant chemoradiation treatment and calculated that the number of samples would be 36 cases under the condition that α was 0.05 and the power of the test was 0.8 (β was 0.2). We determined that the enrolment should be 40 cases assuming 10% of the patients would drop out.
Results: 22 patients were enrolled in P-2. 21 patients received complete chemoradiation. Only one case was not completed because of the adverse event of Grade 3 appetite loss. 19 cases were operated on, and 18 cases were resected. 3 cases were not operated on. 2 cases were progressing disease, and one was heart failure. The R0-resection rate of the P-2 group and conventional resection group was 62%(13 cases out of 22 cases) and 36%(36 cases out of 99 cases), respectively ($p < 0.05$). Intraoperative bleeding, operative duration and hospital stay after surgery were not significant (Table 1), and surgical site infection (SSI) was also not significant.
Conclusions: Neoadjuvant chemoradiation therapy with conventional resection appears to be effective and well tolerated. The study is continuing as scheduled to further evaluate the benefits of this regimen.
Trial registration: UMIN Clinical Trials Registry (UMIN-CTR) UMIN UMIN000000992 and UMIN000001754.
No conflict of interest.

Table 1. Perioperative factors

	P-2 Group	non-P-2 Group	p value
Operative bleeding (median)	1426 ml	1486 ml	n.s.
Operative duration (median)	618 min	622 min	n.s.
Hospital stay after operation (median)	30 days	31 days	n.s.

2564 POSTER

Risk factors for non-curative resection of early gastric neoplasms performed endoscopic submucosal dissection: Analysis of 1123 lesions

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Background: The frequency of residual disease and recurrences after endoscopic submucosal dissection (ESD) has markedly decreased compared with conventional endoscopic mucosal resection because ESD procedure facilitates *en bloc* resection. However, a few cases of residual disease and recurrences have been observed after non-curative resection by ESD.
Materials and Methods: We investigated 1123 early gastric neoplasm lesions treated by ESD at three institutions. Non-curative resection was defined as histological positivity of the resected margins, vascular invasion, or failure of *en bloc* resection. Initially, the reasons for non-curative resection were classified as inadequate technique, pre-procedural misdiagnosis, or problems in histological diagnosis. Following this, a comparison between cases of non-curative and curative resection was made on the basis of following patient characteristics: size, type, and location of lesions; as well as procedure time. Statistical analyses were performed using the chi-square test and logistic regression analysis. Statistical significance was deemed at $p < 0.05$.
Results: The frequency of non-curative resection was 16% (182 lesions). The reasons for non-curative resection were as follows: inadequate technique for 59 lesions (32%), pre-procedural misdiagnosis for 88 lesions (48%), and problems in histological diagnosis for 35 lesions (19%). Univariate analysis indicated that the risk factors for non-curative resection due to inadequate technique were large lesion size, lesion complicated with an ulcer scar, long procedure time, and inexperienced endoscopists. Multivariate analysis revealed that large lesion size [odds ratio (OR): 1.05, 95% confidence interval (CI): 1.03–1.07], long procedure time (OR: 1.01, 95% CI: 1.00–1.01), and inexperienced endoscopist (OR: 1.63, 95% CI: 1.18–2.26) were associated with a significantly higher risk of non-curative resection due to inadequate technique. Univariate analysis indicated that the risk factors for non-curative resection due to pre-procedural misdiagnosis included lesions located in the upper area of the stomach, large lesion size, cancer with submucosal invasion, and inexperienced endoscopists. Multivariate analysis revealed that lesions located in the upper area of the stomach (OR: 1.74, 95% CI: 1.02–2.97), and cancer with submucosal invasion (OR: 24.4, 95% CI: 13.9–41.7) were associated with significantly higher risk of non-curative resection due to pre-procedural misdiagnosis.
Conclusions: This study demonstrated that the major reasons for non-curative resection were inadequate technique and pre-procedural misdiagnosis. Furthermore, risk factors for these were clarified. These results highlight the need to conduct ESD procedures more accurately in cases of early gastric neoplasms.
No conflict of interest.

2565 POSTER

Failure-to-rescue after gastric and oesophageal cancer resection: Results of the Dutch Upper GI Cancer Audit (DUCA)

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Background: In the Dutch Upper GI Cancer Audit (DUCA), as well as other recent studies in the Dutch setting, mortality after surgery with curative intent appears to be higher in gastric cancer patients than oesophageal cancer patients. The purpose of this study was to evaluate differences in postoperative mortality after gastrectomy and oesophagectomy in relation to casemix and failure-to-rescue (FTR) from complications.
Methods: All patients who underwent gastrectomy or oesophagectomy for cancer and registered in the nationwide Dutch Upper GI Cancer Audit in 2011–2012 were selected. FTR was defined as mortality among patients with postoperative complications.
Results: In total, 663 gastric cancer and 1210 oesophageal cancer patients underwent potentially curative surgery in 46 and 25 hospitals, respectively. Patients undergoing gastrectomy were older (mean 68 vs. 64 years), and had more comorbidity (16 vs. 8.4% Charlson comorbidity index of 3 or higher) as compared to oesophageal cancer patients.
The postoperative complication rate was lower after gastrectomy than oesophagectomy (38% versus 59%; $p < 0.001$), but postoperative mortality was higher: 6.6% versus 4.2% ($p < 0.001$). FTR after gastrectomy was significantly higher than after oesophagectomy: 18% versus 7.2% ($p < 0.010$). FTR and associated mortality rates were highest after partial gastrectomy (table 1).

Table 1. postoperative complication-, failure to rescue (FTR)- and mortality rates per type of resection

	Postoperative complications	FTR	Postoperative mortality
Transhiatal oesophagectomy	50%	7.4%	3.7%
Transthoracic oesophagectomy	66%	7.0%	4.6%
Total gastrectomy	39%	13%	4.9%
Partial gastrectomy	35%	22%	7.8%

FTR was significantly higher after gastrectomy than after oesophagectomy when associated with clinical anastomotic leakage (40% for gastrectomy vs 12% for oesophagectomy patients, $p < 0.001$), pulmonary complications

(25% vs. 9.5%, p < 0.001) and cardiac complications (38% vs. 12%, p < 0.001).
Adjusted for age, Charlson comorbidity score, American Society of Anesthesiologists score, body mass index, TNM stage, neoadjuvant therapy and medication use, the difference in mortality after gastrectomy versus oesophagectomy lost statistical significance (Odds ratio 1.16 [95% CI 0.59−2.3]), while the difference in FTR remained (Odds ratio 2.1 [95% CI 1.02–4.01]).
Conclusions: Gastrectomy patients had a 2-fold higher risk of dying from a postoperative complication than oesophagectomy patients. Adequate management of postoperative complications as well as strict patient selection for surgery appears to be crucial in this vulnerable patient group.
No conflict of interest.

2566 POSTER

Long-term outcomes and prognostic factors of T1 squamous cell carcinoma of the esophagus after esophagectomy

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Background: Although superficial (T1) esophageal cancer has been separated into mucosal (T1a) and submucosal (T1b) cancer, T1a and T1b esophageal squamous cell carcinoma (ESCC) have often been analyzed together and are staged as the same category in the UICC/TNM staging system. The difference in surgical outcomes between T1a and T1b ESCC therefore remains unclear. The purpose of this study was to examine the differences in surgical outcomes between T1a and T1b ESCC, and to investigate the prognostic factors in T1 ESCC.
Methods: A prospectively maintained database identified 145 previously untreated patients with pT1 ESCC who underwent radical transthoracic (n = 134) or transhiatal esophagectomy (n = 11). Median follow-up was 108 months.
Results: All patients received R0 resection. Of the 145 patients, 35 (24%) had pT1a cancer and 110 (76%) had pT1b cancer. Lymph node metastasis was present in 45 patients (31%): 3 patients with pT1a cancer and 42 patients with pT1b cancer (P = 0.003). Lymphovascular invasion and Grade 2/3 were also more frequent in pT1b cancers than pT1a cancers (P <0.0001, P = 0.0258) The overall 5-year survival rate for the whole group was 77%. The 5-year survival rate of the pT1a patients was 94% compared with 72% for the pT1b patients (P = 0.282). In multivariate analysis, only the depth of tumor invasion (pT1a vs pT1b) was an independent prognostic factor (hazard ratio, 2.358; 95% confidence interval, 1.009–5.513; P = 0.0477).
Conclusions: The prognosis of patients with pT1b ESCC is significantly worse than that of patients with pT1a ESCC after esophagectomy. Submucosal invasion is the only independent prognostic factor affecting survival in patients with pT1 ESCC. These findings suggested that T1a and T1b ESCC could be staged separately in the next version of UICC/TNM staging system.
No conflict of interest.

2567 POSTER

More pathologically complete responders after a longer interval between chemoradiotherapy and surgery for oesophageal cancer

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Background: The tumor regression grade (TRG) in the resection specimen has been recognised as a valuable prognostic factor for survival in patients who underwent neoadjuvant chemoradiotherapy (CRT) for oesophageal cancer. Little is known about the influence of the length of the interval between neoadjuvant CRT and surgery on the TRG observed in the resection specimen. Aim of this study was to determine the correlation between this interval and TRG.
Methods: Patients treated with neoadjuvant CRT (5 weekly courses of Carboplatin and Paclitaxel with 41.4 Gy concurrent radiotherapy) for resectable oesophageal cancer between 2002 and 2009 were identified. Patients with irresectable tumors were excluded. The interval between the end of neoadjuvant CRT and surgery, and the TRG in the resection specimen, including adjacent lymph nodes, were determined for each patient.
Results: Two hundred and forty-seven patients were included. Median age was 59.8 years and the majority of patients (74.5%) had an adenocarcinoma. A microscopically radical resection was performed in 234/247 (95%) patients. The median interval between CRT and surgery was 47 days [p25-p75: 39−56]. No significant differences were found in TRG distribution between patients with intervals above and below the median interval length. The percentage of pathologically complete responders (TRG1) was 43% in patients with an interval of more than 55 days (>p75) vs. 24% in patients with an interval of less than 56 days (<p75) (p = 0.005) There was no significant difference in the proportion of adeno- and squamous cell carcinomas between the 4th and the remaining quartiles. Median follow-up for surviving patients was 50.7 months. Disease free survival (DFS) was not significantly different between patients with intervals above and below the median interval (HR 2.1; 95% CI 0.6−7.2). There was no significant difference in DFS between patients with an interval above or below the 75Th percentile (HR 1.01 95% CI0.63–1.62).
Conclusion: In patients with a relatively long interval (>p75) between CRT and surgery, more pathologically complete responders were observed. These results suggest that prolonging the interval between CRT and surgery might increase the pathologically complete response rate.
No conflict of interest.

2568 POSTER

Anti-reflux hand-sewn esophago-jejuno anastomosis following total gastrectomy for gastric cancer

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Background: Gastrointestinal tract reconstruction is a key procedure in surgery for gastric cancer. Hand-sewn anastomosis after total gastrectomy accompanied relatively high frequency anastomotic leakage. Stapling devices reduce the leakage rate of digestive tract anastomoses, but they increase the risk of strictures, reflux esophagitis and frequency of dumping syndrome. Quality of life in patients after gastrectomy is largely dependent on the method of formation of the esophago-jejuno anastomosis.
Aim: The aim of our study is to evaluate the results of the anti-reflux hand-sewn esophago-jejuno anastomosis by the method of Bondar Gr.V. after total gastrectomy.
Materials and Methods: The Donetsk regional anticancer center has experience in treating 15 000 patients with gastric cancer. We retrospectively reviewed 1477 consecutive patients who underwent total gastrectomy using hand-sewn esophago-jejuno anastomosis at our center between January 1986 and December 2005. There were 65.9% male, mean age was 58.5 years. 81.0% of patients had stage III−IV disease. In all cases applied the anti-reflux hand-sewn esophago-jejuno anastomosis by the method of Bondar Gr.V. Multivisceral en bloc resection were performed in 23.5% of patients, palliative gastrectomy occurred in 20.3% of cases. Functional results and quality of life were studied in terms of 1–240 months after surgery.
Results: There were no technical problems with the technique of forming an anastomosis. The overall morbidity and mortality were 19.1% and 3.7% respectively. Anastomotic leakage occurred only in 1.1%. Five-year survival rates were 35.0%. Anastomotic stricture occurred in 6.4% patients and reflux esophagitis was observed in 6.7% cases. Incidences of dumping syndrome were 7.7%.
Conclusion: Anti-reflux hand-sewn esophago-jejuno anastomosis by the method of Bondar Gr.V. after total gastrectomy led to a reduction in the incidence of anastomotic leakage. The use of this method can minimize the risk of anastomotic stricture, reflux esophagitis and dumping syndrome.
No conflict of interest.

2569 POSTER

Adjuvant endoaortic regional chemotherapy in treatment of extraorgan retroperitoneal tumors

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Background: To improve the results of combined treatment of extraorgan tumors of retroperitoneal space.
Materials and Methods: The research was carried out on 96 patients with extraorgan retroperitoneal tumors during 1996–2009. Patients ranged in age from 18−68 years old, 62 men (63.3%), 34 women (34.7%). According to histological classification 26 patients (26.5%) were diagnosed angiosarcoma, 38 patients (38.8%) fibrosarcoma, 25 patients (25.3%) liposarcoma and 9 patients (9.2%) neurosarcoma. All patients underwent tumor removal, from them in 44 cases (42.8%) were performed combined resections, which include except tumor removal resection of small and large intestines, nephrectomy, tubovarectomy, splenectomy, resection and prosthetics of main vessels, resection of the bladder and others. Depending on the methods of chemotherapy patients were divided into 2 groups: Group 1−53 patients after retroperitoneal space tumor removal were conducted 2 courses of systemic chemotherapy with an interval of 21 days. Group 2−45 patients after tumor removal were conducted 2 courses of prolonged endoaortic regional chemotherapy with an interval of 21

days. For the implementation of prolonged endoaortic chemotherapy was performed catheterization of aorta through the femoral artery by Seldinger and catheter was placed at the level of diaphragm, above the celiac trunk. Establishing at this level provides wide distribution of chemotherapy drugs to the visceral branches of the abdominal aorta, which are the source of blood supply to the tumor and possible regional metastases. Both groups used Doxorubicin 60 mg/m^2, 500 mg/m^2 Ifosfamide and Vincristine 1.5 mg/m^2. Treatment in the first group was held for 3 days and in the second group for 72 hours continuously.
Results: Complications associated with adjuvant chemotherapy in both groups were not observed. Within 5 years in the first group relapses and metastases occurred in 42% and 41% of the patients respectively. Moreover, the combination of relapses and metastases were observed in 33.9% of the patients. In the second group for the same period the relapses appeared in 31.7% of the patients, metastases in 26.6% of the patients, combined relapses with metastases were observed in 31.1% of the patients. 5-year survival rate is 26.9±2.5 in the first group and 25.5±1.9 in the second group. Observations for 10 years has shown that in the first group 73.6% of the patients died from relapses and metastases, and 9.4% died from other causes unrelated to the tumor. 10 years survival was 17±1.4%. In the second group within 10 years 67.8% of the patients died because of relapses and metastases and the percentage of the patients who died because of other causes unrelated to the tumor was 8.8% and 10 years survival rate was 24.4±1.8% in this group.
Conclusion: Prolonged adjuvant endoaortic regional chemotherapy in the cases of extraorgan retroperitoneal tumors significantly reduces the incidence of relapses and metastasis and increases 5 and 10 years survival.
No conflict of interest.

2570 POSTER

Adequacy and impact on survival of lymph node harvesting in gastric cancer

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Background: According to the TNM classification, 16 or more lymph nodes are required for appropriate staging of gastric cancer. The aim of this study was to evaluate whether this number of resected lymph nodes affects survival as well.
Materials and Methods: This is a multicentric retrospective study based on an analysis of 992 patients with gastric adenocarcinoma who underwent curative resection (R0) between January 1980 and December 2009. Patients were classified according to the number of resected lymph nodes in <16 lymph nodes and those with >16, the anatomical extent of lymph node dissection (D2 vs D1) and according to the VII edition of the UICC/AJCC TNM staging rules. Survival estimates were determined by univariate and multivariate analyses.
Results: At univariate and multivariate analysis, resection of 16 or more lymph nodes was associated with significantly better survival results [p = 0.002; HR (95% CI): 0.519 (0.345–0.780)]. We modified the pN-TNM stage including the lymph node count obtaining eight new subgroups. Patients with a lymph node count <16 had significantly worse survival rate than >16 group in pN0 (p = 0.001), pN1 (p = 0.007) and pN2 (p = 0.001) but no differences in pN3 stage. In the majority of cases >16 lymph nodes were retrieved when D2 dissection was performed.
Conclusions: In gastric cancer, removal of 16 or more lymph nodes accomplished through a D2 lymph node dissection, significantly affected survival.
No conflict of interest.

2571 POSTER

D1-extra lymphadenectomy for gastric carcinoma; high yield, low morbidity and mortality

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Background: The surgical treatment of gastric cancer consists of a (partial) gastric resection with a lymphadenectomy with a recommended yield of at least 15 lymph nodes, a yield which is normally not met in the Netherlands. Studies conducted in the West comparing a D1 versus a D2 resection did not show an improved survival due to high morbidity and mortality rates in the D2 group. In the southern part of the Netherlands a multicenter phase II study has been conducted investigating the feasibility of, besides neoadjuvant chemotherapy, an extended standardized lymphadenectomy, the so-called D1-extra lymphadenectomy.
Methods: Patients with curable gastric carcinoma (including Siewert 2 and 3 tumours), were treated with 4 cycles of docetaxel (60 mg/m^3 IV day 1), cisplatin (60 mg/m^3 IV day 1) and capecitabine (1.875 mg/m^3 PO day 1−14) every three weeks, followed by standardized (partial) gastric resection and lymphadenectomy. Lymph node stations 3−9 were removed and depending on location of the tumour, stations 1, 2, 10 and 12 (Japanese classification). Pathologic investigation was performed according to a set protocol and all specimens were revised by one pathology center. Descriptive statistics were used to evaluate nodal yield and rates of adverse events.
Results: In total, 51 patients were included, 47 proceeded to surgery. At the time of submission of this abstract data on 37 patients who underwent surgery were available. A mean of 27 nodes was harvested (30 after revision). The median number of harvested nodes was 26 (range 4−52); after revision 30 (range 13−58). Ten serious adverse events (SAE) after surgery were reported. One patient died due to small bowel necrosis and one patient died within 30 days after surgery in a hospice due to his own wish; the other SAE's resolved without sequelae.
Conclusion: Due to the introduction of a standardized D1-extra lymphadenectomy a high yield of lymph nodes was achieved was meeting the threshold as stated by guidelines according to the UICC/AJCC. Morbidity and mortality seem to be very acceptable.
No conflict of interest.

2572 POSTER

Evaluation of aortic non-involvement of esophageal squamous cell cancer by electrocardiogram-gated 320-row area detector computed tomography

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Background: However preoperative assessment of T4b to adjacent structures of esophageal squamous cell cancer (eSCC) is very important, pericardial invasion is difficult to evaluate precisely because of cardiac pulsation. The purpose of this study is to assess aortic eSCC invasion using electrocardiogram-gated area detector computed tomography (Gate CT) to eliminate the influence of motion artifact and to verify the impact of Gate CT on postoperative outcomes.
Material and Methods: Two-hundred and twenty eSCC consecutive operative patients were enrolled. Depth of tumor invasion was evaluated by routine contrast enhanced 64-row MDCT and revealed 81 pts were T3 and 139 were T4. Treatments were as follows: 50 only with surgery, 43 chemotherapy prior to surgery, 36 chemoradiotherapy prior to surgery and 91 no surgery only with chemoradiotherapy (CRT). Gate CT was performed with a 0.5-mm slice thickness following intravenous injection of contrast material. Images were obtained with retrospective ECG-gated reconstruction at early arterial phase using computer-assisted automatic bolus-tracking technique and were reconstructed every 5% of the R-to-R interval. If a hypodensity layer between the tumor and the thoracic aortic wall is observed by Gate CT animation image, the case is diagnosed as resectable non-T4 and surgical treatment was performed. We compared Gate CT findings with histological results and estimated the impact of Gate CT on postoperative survival rate.
Results: In a total of 129 surgical treated pts, who were diagnosed as clinical non-T4 by Gate CT, 124 underwent radical surgical resection of subtotal esophagectomy with lymphadenectomy and result in histological non-T4. Probe thoracotomy was performed in remaining 5. The negative predictive value (NPV) of non-T4 detection was 96% in all surgical cases. According to the neoadjuvant treatment the NPV were as follows: no treatment 98% (49/50), chemotherapy 93% (40/43) and CRT 97% (35/36). In 127 CRT pts (36+91), 36 were considered to be downstaging by Gate CT and the operation was performed and 1 result in probethoracotomy, remaining 91 were estimated as T4b by Gate CT. The five-year survival rate of these two groups were 69% and 14% (P<0.0001), respectively, with a significant difference.
Conclusions: Histological results can be proved only in clinical non-T4b cases because operations are performed for these cases. Therefore only the NPV can be assessed for T4b. Gate CT can eliminate the influence of pericardial artifact and yield a high predictive power for aortic invasion. It is a valid imaging tool for assessing aortic invasion of esophageal cancer, and patients who were suspected aortic involvement may experience a better survival benefit from Gate CT by discriminating non-T4b from T4b.
No conflict of interest.

2573 POSTER

Oesophageal cancer as a difficult clinical problem

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Background: Oesophageal cancer remains a complex clinical problem, and the results of its treatment − both surgical and combination- are still unsatisfactory. The aim of this research is a clinical analysis of a group of oesophageal cancer patients who have undergone surgical and combination therapy.
Material and Method: A group of 130 patients with diagnosed oesophageal cancer was analysed, with a special consideration to those, who have undergone resection surgery (type I and type II according to the Siewert classification). The following methods, such as an interview, measurement and analysis of medical documentation are used in research procedures.
Results: Within the group of 130 patients with diagnosed oesophageal cancer, 50 people (38.5%), have undergone resection surgery. The average age of having become ill was 59. Resection of the upper stomach and resection of the lower part of the oesophagus with the 'end-to-end' esophagogastric anastomosis was performed without opening the thorax in 8 patients; resection of the upper stomach and surgical removal of the lower part of the oesophagus with the 'end-to-side' esophagogastric anastomosis was performed through a left thoracotomy in 8 patients, a full surgical removal of the stomach and the lower part of the thoracic segment of oesophagus with the esophago-intestinal anastomosis using the Roux-en-Y method was performed without opening the thorax in the mediastinum in 11 patients, a full removal of the stomach and the lower half of the thoracic segment of the oesophagus with the esophago-intestinal anastomosis using the Roux-en-Y method in the thorax (through left thoracotomy) was performed in 8 patients; nearly full removal of the oesophagus using the Akiyama method through a right-side/right thoracotomy (esophagogastric anastomosis in the neck) was performed in 15 patients. The most numerous group (n = 21) comprised patients in $T_3N_1M_0$ stage. In all cases where the cancer was located in the lower ? of the oesophagus, *adenocarcinoma* tissue was diagnosed in histopalogical examination; whereas in the case of cancers located in one third of the middle part of the thoracic segment of the oesophagus and one third of the upper part of this segment − *carcinoma planoepitheliale* tissue. Leakiness of the anastomoses occurred in 7 patients (7/50−14%), after the Akiyama procedure in 3 patients, after resection of the upper stomach with thoracotomy in 2 patients, after gastrecotomy with thoracotomy in 2 patients. Six old patients (6/50−12%), susceptible to cardiovascular disease and in the highly advanced stage of neoplastic disease died in the post-surgery period. The average survival time in the study group of patients was two years.
Conclusions: An oesophageal and esophagogastric junction cancer is endowed with low resectivity, a high risk of complications after surgical treatment and bad oncological results. It is necessary to seek new methods of treatment.
No conflict of interest.

2574 POSTER

Minimally invasive esophagectomy: Preliminary results after introduction of intrathoracic anastomosis

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Introduction: An intrathoracic anastomosis after esophagectomy has recently been associated with a reduced incidence of recurrent laryngeal nerve palsy, anastomotic leakage and anastomotic strictures compared to a cervical anastomosis, without compromising other morbidity and mortality.
Material and Methods: From January 2011 until August 2012, all operable patients were planned to undergo MIE with creation of an intrathoracic anastomosis. Patient characteristics, anastomosis related complications, morbidity and mortality were prospectively registered and were analyzed retrospectively.
Results: Forty-five patients underwent MIE with intrathoracic stapled end-to-side anastomosis. Major changes in operative technique and perioperative care were made two times due to non satisfactory results, dividing the patients into three groups: group 1 (n = 9): creation of the anastomosis with a double stapling technique, group 2 (n = 18): creation of the anastomosis with a single stapling technique with application of a large omental wrap and group 3 (n = 18): creation of the anastomosis in the same way as group 2, but with a reduced volume of the omental wrap and addition of pre-operative intravenous injection of 1 mg/kg dexamethasone. One patient died in group 1. The anastomotic leakage rate decreased from 44% in group 1 to 0% in groups 2 and 3 ($p = 0.007$). The pulmonary complication rate decreased from 67% in group 1 to 44% in group 2 (NS) and 22% in group 3 ($p = 0.04$) and the overall complication rate decreased from 89% in group 1 to 78% in group 2 (NS) and 33% in group 3 ($p = 0.01$). The median ICU stay decreased from 9 days in group 1, to 7 days in group 2 (NS) and 2 days in group 3 ($p < 0.001$) and the median hospital stay decreased from 17 days in group 1 to 14 days in group 2 (NS) and 8 days in group 3 ($p < 0.001$).
During a median follow up of 11 months, there were no stenoses, no dilatations and no patients with recurrent laryngeal nerve trauma.
Conclusions: The introduction of an intrathoracic anastomosis after MIE led to favorable functional results but was initially associated with considerable morbidity. Results improved after changes in operative technique and perioperative care were made, but a learning curve may be partially responsible for the improved outcome.
No conflict of interest.

2575 POSTER

Treatment and prognosis for young patients with esophageal cancer

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Background: The incidence of esophageal cancer is rising among all age groups. Hence, esophageal cancer is increasingly recognized in younger patients. In young patients probably diagnosis is often delayed, tumors are more aggressive and survival is worse. We compared clinicopathological characteristics, treatment and subsequently survival of patients aged $\leqslant$50 years with patients aged >50 years diagnosed with esophageal cancer.
Material and Methods: From the nationwide Netherlands Cancer Registry we identified all patients diagnosed with esophageal cancer between January 2000 and December 2010 (n = 18,118). Patients with mesenchyme tumors (n = 618) and patients aged $\geqslant$75 years (n = 4,169) were excluded. Proportions were compared using the $\chi 2$ test for categorical variables. Relative survival was calculated as the ratio of the observed rates in cancer patients to the expected rates in the general population.
Results: Eleven percent of the patients (n = 1,466) were aged $\leqslant$50 years and 89% (n = 11,865) were aged >50 years. Adenocarcinoma was the most common tumor type in both age groups (73.6%). Grade of tumor differentiation was comparable between both age groups ($p = 0.460$), as well as T-stage ($p = 0.058$). Younger patients presented more often with tumor positive lymph nodes (70.1 vs. 66.4%, $p = 0.010$) and distant metastasis (50.5 vs. 44.7%, $p < 0.001$). Younger patients diagnosed with an adenocarcinoma were treated with curative surgery more often (40.6 vs. 37.9%, $p = 0.047$). However, 5-year relative survival after surgery was comparable between both age groups (36.8 vs. 34.4%, NS). Among the patients not qualified for surgery, younger patients were treated with palliative chemotherapy more often (44.8 vs. 32.7%, $p < 0.001$), nevertheless this resulted in a comparable 5-year relative survival with their older counterparts (4.7 vs. 5.9%, NS).
Conclusions: A considerable proportion (11%) of the patients diagnosed with esophageal cancer were aged $\leqslant$50 years. Approximately 80% of the tumors were histologically classified as adenocarcinomas. Younger patients presented with advanced disease stage more often, but received a more aggressive treatment. This resulted in a comparable 5-year relative survival rate with the older patients.
No conflict of interest.

2576 POSTER

Incidental finding of gallbladder carcinoma

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Background: Carcinoma of the gallbladder is the fifth most common gastrointestinal malignancy (and the most common of the biliary tract) and is usually discovered accidentally. Gallbladder carcinoma is diagnosed pathologically in 0.3−1.5% of cholecystectomy specimens.
Aim and Objectives: To evaluate the impact of incidental gallbladder cancer on surgical experience and to establish the overall rate of gallbladder carcinoma.
Methods: We retrospectively evaluated all consecutive cholecystectomies performed in our ward from (2007–2012) in order to determine the incidence of gallbladder carcinoma and to identify common characteristics of this particular group of patients.

Results: Of the 580 cholecystectomies performed in our ward from 2007–2012, gallbladder carcinoma was diagnosed in six patients (1.03%) but was not suspected prior to surgery in any of them. In accordance with the literature, the occurrence in women (4/6) was higher than in men (2/6). The mean age was 64 years (range 55−90). The most common symptom was abdominal pain; the majority (5/6) had cholelithiasis, and the pathologic report confirmed the diagnosis of adenocarcinoma in all six patients.
Conclusions: The overall incidence of unsuspected gallbladder carcinoma in our series was 1.03%. We could not find any common characteristics for this particular group of patients when compared to patients with non-malignant pathology.
No conflict of interest.

2577 POSTER

Positron emission tomography (PET) response from a randomized phase III trial (MPACT) of weekly nab-paclitaxel (nab-P) plus gemcitabine (G) vs G alone for patients (pts) with metastatic adenocarcinoma of the pancreas

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Background: *nab*-P + G demonstrated superior efficacy vs G alone in the MPACT phase III study of pts with metastatic pancreatic cancer (PC). A significant correlation was observed between overall survival (OS) and complete metabolic response (MR; $P = 0.01$) by PET in the initial phase I/II study. Here we present PET analyses of the MPACT trial, including efficacy in pts with a baseline (BL) PET scan (PET cohort).
Methods: A total of 861 previously untreated pts with metastatic PC were randomized 1:1 to receive *nab*-P 125 mg/m^2 + G 1000 mg/m^2 days 1, 8, and 15 every 4 weeks or G alone 1000 mg/m^2 weekly for 7 weeks followed by 1 week of rest (cycle 1) and then days 1, 8, and 15 every 4 weeks (cycle $\geqslant$2). Tumor responses were evaluated every 8 weeks by computed tomography (CT) using RECIST v1.0. PET scans at BL (n = 257), week 8 (n = 222), and week 16 (n = 134) were evaluated, using EORTC criteria; PET and CT were evaluated by blinded independent radiological review.
Results: PET was evaluable at BL in 252 pts. More than 60% of pts had 5 or 6 PET avid sites at BL, and the median standard uptake values were 18.0 and 19.7 in the *nab*-P + G and G arms, respectively. BL characteristics were well balanced in the PET cohort. The rate of MR (complete or partial) was significantly higher for *nab*-P + G vs G (63% vs 38%; response rate ratio [RRR], 1.67; $P = 0.000051$). The overall response rates (ORRs) by CT scan in the PET cohort were 31% and 11%, respectively ($P = 0.0001$). Concordance of ORR by CT scan with MR was 55% in the *nab*-P + G arm and 67% in the G arm. Both ORR and MR significantly predicted OS. Response by PET correlated with overall survival (median 13.1 months). *nab*-P + G was superior to G in the PET cohort for all efficacy endpoints (Table).

Table: Efficacy in the PET cohort

	nab-P + G (n = 130)	G (n = 127)	RRR or HR (95% CI)	*P* value
ORR by CT, %	31	11	2.79 (1.599–4.874)	0.0001
Median PFS, months	6.7	4.3	0.62 (0.443–0.862)	0.0041
Median OS, months	10.5	8.3	0.71 (0.542–0.920)	0.0096

Conclusions: PC is a PET avid tumor. This is the largest cohort of patients from an international PC trial evaluated for PET. More pts in the *nab*-P + G vs G arm achieved an MR. In the PET cohort, all efficacy endpoints favored *nab*-P + G, consistent with results from the intent-to-treat population. PET response rates were higher than those by CT and should be further tested as a potential improvement upon CT as a marker of efficacy.
Conflict of interest: *Ownership: XW, BL: Stock ownership (Celgene). Advisory board: RKR, DVH, MM, LT, SS, JT, DG (Celgene). Corporate-sponsored research: RKR, DVH, MM, DG (Celgene). Other substantive relationships: XW and BL are emplyees of Celgene*

2578 POSTER

Randomized phase II study comparing S-1 plus Leucovorin (SL) versus S-1 alone in patients with gemcitabine-refractory advanced pancreatic cancer (APC)

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Background: Gemcitabine (Gem)-based chemotherapy is a standard first-line treatment for advanced pancreatic cancer (APC). There is no consensus on second-line therapy in patients (pts) with disease progression (PD) in Gem-based chemotherapy. Randomized phase III study in Japan and Taiwan showed non-inferiority of S-1, an oral fluoropyrimidine, to gemcitabine in terms of OS for pts with unresectable APC (Ueno et al, JCO in press). Therefore, S-1 is one of the key drugs for APC in Japan. S-1 plus oral leucovorin (LV) showed promising activity with well-tolerated toxicities for metastatic colorectal cancer (Denda et al, ASCO GI 2012). We conducted a randomized phase II study to evaluate the efficacy and safety of S-1 plus LV (SL) compared with S-1 alone in the second-line setting for APC.
Material and Methods: The main inclusion criteria were; 1) pathologically confirmation of adenocarcinoma or adenosquamous carcinoma, 2) received one prior chemotherapy containing Gem and developed PD or recurrence, 3) at least one target lesion by RECIST ver1.1, 4) ECOG Performance Status 0−1, 5) age 20−79 years, 6) written informed consent. Pts were randomized to receive either S-1 (40−60 mg bid) and oral LV (25 mg bid) for one week, repeated every 2 weeks in the SL group, or oral dose of S-1 twice daily for 4 consecutive weeks, repeated every 6 weeks in the S-1 group. The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS), response rate (RR), disease control rate (DCR), and safety. Tumor response was assessed by independent review committee. This study was supported by Taiho Pharmaceutical CO.,LTD. (JAPIC Clinical Trials information Identifier: JapicCTI-111554).
Results: From August 2011 to August 2012, 142 pts were enrolled, and 140 were eligible (SL, 69; S-1, 71). There were no imbalances in patient characteristics between the two arms with the exception of some subgroups (e.g., pancreatic resection and the sum of diameter of target lesion). SL significantly improved PFS compared with S-1 (median PFS, 3.8 vs. 2.7 months, HR = 0.56; [95% CI: 0.37–0.85], p = 0.003). Pre-planned multivariate analysis confirmed the result of PFS (adjusted HR = 0.50; [95% CI: 0.33–0.76], p = 0.001). The incidences ($\geqslant$5%) of grade 3/4 adverse drug reactions in the SL and S-1 groups were anemia (9.9% vs. 11.3%), leucopenia (7.0% vs. 4.2%), neutropenia (8.5% vs. 5.6%), lymphopenia (12.7% vs. 11.3%), hyponatremia (5.6% vs. 2.8%), anorexia (14.1% vs. 4.2%), fatigue (7.0% vs. 0%), and diarrhea (5.6% vs. 4.2%), and one patient in the SL group died of treatment-related sepsis.

PFS (SL vs. S-1)	OS (SL vs. S-1)	RR (SL vs. S-1)	DCR (SL vs. S-1)
Median 3.8 vs. 2.7 months Event 42 vs. 55 HR = 0.56, p = 0.003 Adjusted HR = 0.50, p = 0.001	Median 6.3 vs. 6.1 months Event 45 vs. 50 HR = 0.82, p = 0.463 Adjusted HR = 0.72, p = 0.114	27.5 vs. 19.7% p = 0.322	91.3 vs. 71.8% p = 0.004

Conclusions: SL significantly improved PFS compared with S-1 alone, and the primary endpoint of this study was met. This study showed that SL had promising activity with well-tolerated toxicities for unresectable APC refractory to gemcitabine containing regimen. A phase III study is planned to ensure the survival benefit of SL.
Conflict of interest: *Ownership: None. Advisory board: Taiho Pharmaceutical Co., Ltd. Board of directors: None. Corporate-sponsored research: Taiho Pharmaceutical Co., Ltd. Other substantive relationships: Taiho Pharmaceutical Co., Ltd.*

2579 POSTER

Intraperitoneal CDDP administration chemotherapy with S-1 and paclitaxel for peritoneal metastatic gastric cancer

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Background: The phase III chemotherapy trials for gastric cancer have showed the median survival time is prolonged up to 13 months by SPIRITS trial (addition of cisplatin to S-1)and START trial (addition of docetaxel to S-1).
Meanwhile the efficacy of intraperitoneal (IP) administration of taxanes or platinum agents has been verified in ovarian cancer.
We reported the efficacy of the metronomic combination chemotherapy with S-1 and Paclitaxel (PTX) for advanced gastric cancer, which achieved 21.9 months as the median overall survival time. We aimed to evaluate the efficacy of the intraperitoneal CDDP administration chemotherapy with S-1 and Paclitaxel for peritoneal metastatic gastric cancer.
Patients and Methods: Gastric cancer patients with peritoneal dissemination and/or cancer cells on peritoneal cytology were enrolled. The surgical interventions such as gastrectomy, enterostomy, or colostomy with IP port implantation were done for all patients before this chemotherapy.
PTX was administered i.v. at 80 mg/m^2 on days 1 and 15. S-1 was administered at 80 mg/m^2/day for 7 consecutive days, followed by 7 days rest, repeatedly. CDDP was administered i.p. at 40 mg/body on day 8. This treatment was repeated every 4 weeks until disease progression or unacceptable toxicity was seen.
We estimated the overall survival (OS), the efficacy, and safety of this treatment.
Results: Fifty patients were enrolled, including 36 peritoneal metastatic cases with gastrectomy, 9 cases with peritoneal recurrence and 5 non-resectable cases with peritoneal metastasis. The median number of courses was 8.1 (range 1−29). The median time to treatment failure was 9.9 months. The 1-year and 3-year OS rates were 77.2% and 34.3%, respectively. The median OS was 18.2 months.The median survival times according to Performance Status (PS) were 21.2 months in PS0, 15.4 months in PS1, and 10.9 months in PS2, respectively.
CDDP allergic reactions occurred in 5 cases (10%), and at the median 7.8 times CDDP administrations. The major adverse reactions were leucopenia and neutropenia. Adverse reactions as gastrointestinal symptoms were few.
Conclusion: Intraperitoneal CDDP administration with S-1 and Paclitaxel for peritoneal metastatic gastric cancer appears to be highly efficacious and safe.
No conflict of interest.

2580 POSTER

Efficacy and safety of nintedanib vs sorafenib in Asian patients with advanced hepatocellular carcinoma (HCC): A randomised Phase II trial

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Background: Nintedanib is an oral angiokinase inhibitor targeting VEGFRs, PDGFRs, and FGFRs. This multicentre, open-label, randomised, Phase I/II study (NCT00987935) evaluated the efficacy and safety of Nintedanib vs Sorafenib in Asian patients (pts) with advanced HCC. Phase I data established the recommended dose of Nintedanib. Early Phase II data comparing Nintedanib vs Sorafenib are presented.
Methods: Previously untreated pts with advanced HCC not amenable to curative/locoregional therapy, a Child-Pugh score of 5−6, an ECOG PS of $\leqslant$2, and AST/ALT $\leqslant 2 \times$ ULN were enrolled. Pts were randomised 2:1 to receive Nintedanib 200 mg bid or Sorafenib 400 mg bid continuously in 28-day cycles. Treatment beyond disease progression (PD) was allowed. Primary endpoint was time to progression (TTP) by central review (RECIST 1.0). Secondary endpoints included objective response rate (ORR) by central review, overall survival (OS), and AEs. All analyses were descriptive and exploratory in nature.
Results: Ninety-five eligible pts from 16 sites in Taiwan and Korea were treated with Nintedanib (n = 63) or Sorafenib (n = 32). Arms were balanced except for macrovascular invasion (Nintedanib 48% vs Sorafenib 28%). As of Sept 28, 2012, 86 pts had discontinued the study due to PD (n = 67), AEs (n = 13), or other reasons (n = 6). Median time to discontinuation of Nintedanib or Sorafenib was 3.0 and 3.8 mo, respectively (HR 1.19 [95% CI: 0.76–1.88]). TTP (primary endpoint) was comparable in the Nintedanib and Sorafenib arms (median, 2.7 [95% CI: 1.8−3.7] vs 3.7 [95% CI: 2.6−7.3] mo; HR 1.36 [95% CI: 0.80–2.30]), as was ORR (3.2 vs 3.1%) and OS (median, 10.7 [95% CI: 8.1–14.8] vs 9.5 [95% CI: 7.4–11.0] mo; HR 0.77 [95% CI: 0.42–1.41]). CTCAE Gr 3 (32 vs 56%) and Gr 4 (8 vs 16%) AEs were less frequent with Nintedanib than Sorafenib. Any-grade (Nintedanib vs Sorafenib) HFSR (6 vs 50%), diarrhoea (44 vs 56%), hypertension (14 vs 22%), abdominal pain (22 vs 34%), AST increases (14 vs 28%), and ALT increases (11 vs 19%) were more common with Sorafenib; vomiting (30 vs 13%), decreased appetite (37 vs 25%), fatigue (22 vs 13%), and ascites (21 vs 9%) were more common with Nintedanib. 11 pts (18%) in the Nintedanib arm and 18 (56%) in the Sorafenib arm had a dose reduction due to AEs.
Conclusion: Nintedanib appears to be active and show similar efficacy to Sorafenib, with a more favourable and manageable AE profile, in Asian pts with advanced HCC. Further studies of Nintedanib in HCC are warranted.
Conflict of interest: *Advisory board: Cheng AL: Bayer Schering Pharma Inc. and Eisai Inc. Other substantive relationships: Studeny M: Employee, Boehringer Ingelheim RCV GmbH & Co KG Hocke J: Employee, Boehringer Ingelheim GmbH & Co KG Huang DCL: Employee, Boehringer Ingelheim Taiwan Limited*

2581 POSTER

Analysis of sorafenib starting dose and outcomes from the European subset of GIDEON (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of its Treatment with Sorafenib [SOR]) in >1000 patients (pts)

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Background: GIDEON is the largest (>3200 pts), global, prospective, non-interventional study of unresectable (u) HCC patients treated with SOR under real-life practice conditions. These data allow for the evaluation of the safety and efficacy of SOR in a diverse range of settings and pt groups where the data are currently limited, including patients with Child-Pugh B disease and those with poor prognostic factors. Here we describe the safety and efficacy in uHCC pts, treated in Europe, according to the initial SOR dose.
Methods: Patient demographics, disease characteristics (including stage according to Barcelona Clinic Liver Cancer [BCLC], tumor node metastases [TNM] and Child-Pugh [CP] score) and treatment history, were recorded at enrolment; SOR dose, concomitant medications, performance status, liver function, adverse events (AEs) and efficacy were recorded at follow-up visits.
Results: 1113 pts in 22 European countries were evaluable for safety. The majority of pts (82%) started SOR therapy at the full prescribing dose of 800 mg/day. Pts who started on 400 mg/day tended to have characteristics consistent with a poorer prognosis, including higher ECOG performance status and worse CP score and BCLC and TNM staging. The incidence of reported AEs was greater in the group starting on 400 mg/day compared to the group starting on 800 mg/day (96% vs 88%), as was the incidence of drug-related AEs (74% vs 69%) and serious AEs (57% vs 45%). The incidence of drug-related serious AEs was 11% in both groups). Hand foot skin reaction (HFSR) was reported by more pts started on 800 mg/day (21% vs 15%). Median duration of treatment was longer in the 800 mg/day starting dose group (18.0 weeks vs 13.0 weeks), as was median overall survival (26 months vs 18 months, whereas time to progression was similar (6.5 vs 6.2 months).
Conclusions: These data suggest that in real-life clinical practice physicians tend to start uHCC pts with poorer prognostic factors on the lower SOR dose (400 mg/day). However, the similar incidences of AEs with both Sor starting doses of r 800 mg/day and 400 mg/day suggest that this may not be necessary. Patients started on 800 mg/day tend to

continue Sor treatment longer and achieve better overall survival, with a slight higher HFSR rate. Further evaluation and analysis with appropriate statistical methods for dosing are ongoing.
Conflict of interest: *Advisory board: Bayer HealthCare Pharmaceuticals. Corporate-sponsored research: Bayer HealthCare Pharmaceuticals*

2582 POSTER

SLCO1B1 gene single nucleotide polymorphism is a drug response marker for pancreatic cancer patients treated with gemcitabine

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Background: We conducted an exploratory pharmacogenomics study to search for genetic factors, which influence overall survival (OS) in 69 stage IV pancreatic cancer patients treated with gemcitabine (GEM) monotherapy. A systemic candidate gene approach was employed by genotyping 5,438 single nucleotide polymorphisms (SNPs) in 219 genes encoding a wide category of drug-metabolizing enzymes and transporters (https://gemdbj.nibio.go.jp/dgdb/PharmaSearch.do). During the first screening, 4 SNPs were found to be associated with OS using statistical criteria ($P \leqslant 0.0005$).
Material and Methods: We validated these SNPs in part of the GEST study, which was a randomized phase III study conducted in 834 patients with unresectable advanced pancreatic cancer who were treated with GEM, S-1 or GEM plus S-1 (GS) (Ueno et al., J Clin Oncol 2013). One hundred eighty-eight patients from the GEST study were enrolled in the present study. Written informed consent was obtained from all the patients. DNA was isolated from peripheral blood and was typed for the 4 SNPs identified during the first screening. The associations between OS and the SNPs were investigated using the log-rank test and the Cox proportional hazards model. Potential treatment-SNP interactions were also evaluated using the Cox model.
Results: The SNP rs4149086 in the 3'UTR of the solute carrier organic anion transporter family, member 1B1 (SLCO1B1) gene exhibited a significant statistical interaction between the treatment and the SNP ($P = 0.02$). In the GEM group, the SNP was significantly associated with a shorter OS (median OS for AG+GG [n = 4] and AA [n = 63] were 6.7 and 9.6 months, respectively; $P = 0.008$; HR = 3.7 [1.3–10.8]) even after adjustment for multiple comparisons. On the other hand, the SNP was not associated with a shorter OS in the S-1 group (median OS for AG+GG [n = 6] and AA [n = 53], 14.4 and 10.7 months, retrospectively; $P = 0.35$; HR = 0.7 [0.3−1.8]) or the GS group (median OS for AG+GG [n = 5] and AA [n = 55], 15.9 and 10.8 months, respectively; $P = 0.72$; HR = 1.1 [0.4−3.0]). The observed interaction with treatment suggests that the SNP is predictive rather than prognostic.
Conclusions: The SLCO1B1 gene SNP may be a drug response marker for pancreatic cancer patients treated with GEM.
Conflict of interest: *Advisory board: Taiho Pharmaceutical. Corporate-sponsored research: Taiho Pharmaceutical, Eli Lilly*

2583 POSTER

Evaluation of peripheral neuropathy in a phase III trial (MPACT) of weekly nab-paclitaxel (nab-P) plus gemcitabine (G) vs G alone for patients with metastatic adenocarcinoma of the pancreas

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Background: *nab*-P + G demonstrated superior efficacy vs G in the phase III MPACT trial of patients (pts) with metastatic pancreatic cancer (PC). *nab*-P + G was associated with a higher rates of some adverse events, including peripheral neuropathy (PN). Here we further evaluate the frequency, duration, and severity of PN.
Methods: 861 previously untreated pts with metastatic PC were randomized 1:1 to receive treatment with *nab*-P 125 mg/m^2 + G 1000 mg/m^2 days 1, 8, and 15 every 4 weeks or G alone 1000 mg/m^2 weekly for 7 weeks followed by 1 week of rest (cycle 1) and then days 1, 8, and 15 every 4 weeks (cycle $\geqslant$2). PN was evaluated globally by a broad-spectrum group of standardized MedDRA queries (SMQ) and graded by NCI CTCAE v3.0. In addition, a case-report form was completed by physicians on day 1 of each cycle (also graded by NCI CTCAE v3.0).
Results: By SMQ evaluation, the rates of any-grade (54% vs 13%) and grade 3 PN (17% vs 1%) were higher for *nab*-P + G vs G. No grade 4 PN was reported in either arm. Most early-onset PN events (ie, occurring within the first 3 cycles) were grade 1. Treatment-related grade 3 PN occurred in 7% of pts who received up to 3 cycles of *nab*-P (the median number of cycles received in that arm). PN led to *nab*-P dose reduction in 6%, delay/omission in 8%, and treatment discontinuation in 8% of patients in the *nab*-P + G arm. Of the pts who had grade 3 PN in the *nab*-P + G arm (n = 70), the median time to onset was 140 days (4 cycles), 44 (63%) improved by 1 grade (median 21 days), and 30 (43%) pts improved to grade $\leqslant$1 (median 29 days); 44% of pts resumed treatment with *nab*-P. The rates of grade 3 PN by physician-completed case report forms were similar to those of the assessment by SMQ terms: 14% for *nab*-P + G vs <1% for G; no grade 4 neuropathy was observed. There were no noted differences in baseline characteristics between pts who developed PN vs those who did not.
Conclusions: The rate of grade 3 PN for patients in the *nab*-P + G arm who received up to the median of 3 cycles was 7%, and overall, was 17%, consistent with prior *nab*-P studies. Grade 3 PN was manageable by dose reduction or delay and reversible to grade $\leqslant$1 for almost half of those patients within a median time of approximately 1 month.
Conflict of interest: *Ownership: BL: Stock ownership (Celgene). Advisory board: JT, DG, MM, DVH, RR (Celgene). Corporate-sponsored research: DG, MM, EG, DVH, RR (Celgene). Other substantive relationships: AK, BL: Employees of Celgene Corporation*

2584 POSTER

Compassionate use of everolimus in advanced neuroendocrine tumors

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Background: Everolimus has been approved for treatment of advanced Pancreatic Neuroendocrine Tumors (pNETs). However, no data are available outside the setting of clinical trials designed for drug approval.
Aim: To determine, in a real world setting, tolerability and efficacy of Everolimus in advanced NET.
Patients and Methods: Retrospective analysis of patients (pts) treated with Everolimus given by compassionate use programme. Inclusion criteria: advanced, unresectable, sporadic NET, progression after failure of previous treatments, performance status $\leqslant$2, life expectancy >3 months. Safety assessed according with the CTCAE. Efficacy assessed by evaluation of best response rate during treatment, progression-free survival (PFS), overall survival (OS).
Results: 169 pts enrolled (55.5% male, median age 63 yr), including 85 PETs (50.3%), and 84 non-pancreatic NET (non-PETs) (49.7%). Tumor grading was: G1, 40 pts (23.7%); G2, 114 pts (67.4%); G3, 15 pts (8.9%). Most frequent prior treatments were peptide-receptors radionuclide therapy (PRRT) (50.3%) and systemic chemotherapy (49.7%); 38 pts (22.5%) received both treatments before Everolimus. During a median treatment period of 6 months (range 1−46), 109 pts (64.5%) reduced dose or temporarily discontinued treatment due to toxicity. 144 pts (85.2%) experienced adverse events (AEs), which were grade 3−4 in 78 of them (46.1%). Significantly higher proportion of pts previously treated with both PRRT and chemotherapy had grade 3−4 AEs when compared with other patients (33/38, 86.8% vs 45/131, 34.3%; p < 0.0001). Overall, most frequent grade 3−4 AEs were: pneumonitis, 14 pts (8.3%); thrombocytopenia, 13 pts (7.7%); anemia, 9 pts (5.3%). Tumor response was observed in 128 pts (75.7%) (stable disease: 67.4%, partial response 7.7%, complete response 0.6%). Overall, PFS was 12 months (11 and 12 months in PETs and non-PETs, respectively; p = 0.789). A total of 46 pts died during follow-up (27.2%). Median OS was 32 months (not reached and 32 months in PETs and non-PETs, respectively; p = 0.295).

Conclusions: In real world setting (clinical practice), Everolimus efficacy was similar to that reported by phase 3 trials, with equal results in both PETs and non-PETs. A two fold increase of severe toxicity incidence was observed in patients previously treated with PRRT and chemotherapy. These data rise the question on the influence of previous treatments on the severity of adverse events expectable during Everolimus treatment.
No conflict of interest.

2585 POSTER

Second-line chemotherapy for advanced biliary tract cancer: Results of a multicenter survey

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Background: There is no established standard chemotherapy for second-line treatment of patients with advanced biliary tract cancer (BTC). However, with the improvement of first-line treatment, many patients remain in good clinical conditions and maintain a normal liver function after progression to first-line chemotherapy and therefore are suitable for second-line chemotherapy.
Material and Methods: We retrospectively reviewed data of consecutive patients who received second-line chemotherapy for BTC at 8 Italian institutions from 2006 to 2012, and described clinic-pathological characteristics of disease and the outcome of second-line treatment.
Results: A total of 247 evaluable patients were identified. At the beginning of second-line chemotherapy, median age was 65 years with a range of 28 to 85 years; 135 patients were of female sex and 112 male; ECOG performance status was 0 in 154 patients (64%), 1 in 66 (27%) and 2 in 23 patients (9%). The site of primary tumor was gallbladder in 44 patients (18%), intrahepatic in 129 (52%), extrahepatic in 55 (22%), ampullary in 19 patients (8%). The majority of patients had metastatic disease; the median number of metastatic site was 2.
The majority of patients had received a platinum-containing first-line chemotherapy (71%); 19.8% of patients responded to first-line chemotherapy with a median progression-free survival (PFS) was 6.3 months.
Second-line chemotherapy consisted of platinum-based combinations in 84 patients (34%), fluoropyrimidines in 50 patients (20%), gemcitabine in 16 (7%), combinations of fluoropyrimidines and gemcitabine in 41 patients (17%), taxanes containing regimen in 11 patients (4%), irinotecan containing regimen in 22 (9%), other regimens in the remaining 23 patients (9%).
Twelve partial responses (5%) and 77 stable diseases (31%) have been observed with a disease control rate of 36%; 7% of patients have not been evaluable for response.
Median PFS was 3.3 months (95% confidence interval-CI: 2.9−3.7) and median overall survival from the beginning of second-line was 8.2 months (95% CI: 6.8−9.6).
One hundred and thirteen patients (45%) received further local or systemic treatment after second-line therapy.
Conclusions: Second-line chemotherapy is active for a group of patients with advanced BTC progressed to first-line chemotherapy. Considering the moderate benefit of treatment, an analysis of prognostic and predictive factors is needed and prospective randomized trials are necessary.
No conflict of interest.

2586 POSTER

Dose delivery in a phase III trial (MPACT) of weekly nab-paclitaxel (nab-P) plus gemcitabine (G) vs G alone for patients with metastatic adenocarcinoma of the pancreas

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Background: *nab*-P + G demonstrated superior efficacy to G in the phase III MPACT trial for all endpoints. Here we present data on dose modifications, with an emphasis on their impact on overall treatment delivery.
Methods: 861 previously untreated patients (pts) with metastatic pancreatic cancer (PC) were randomized 1:1 to receive *nab*-P 125 mg/m^2 + G 1000 mg/m^2 days 1, 8, and 15 every 4 weeks or G alone 1000 mg/m^2 weekly for 7 weeks followed by 1 week of rest (cycle 1) and then days 1, 8, and 15 every 4 weeks (cycle $\geqslant$2).
Results: Pts in the *nab*-P + G arm received treatment for a longer duration (median, 3.9 vs 2.7 months), resulting in a higher number of total doses delivered (Table). The median cumulative dose of *nab*-P was 1425 mg/m^2, and the median cumulative doses of G were 11,400 and 9000 mg/m^2 in the *nab*-P + G and G arms, respectively. Furthermore, 71% of *nab*-P doses were delivered at the per-protocol dose of 125 mg/m^2, and the median relative dose intensities of *nab*-P and G in that arm were 81% and 75%, respectively. The overall incidence of treatment-emergent adverse events (AEs) leading to dose reductions (DRs) was higher in the *nab-P* + G (38% and 44%, respectively) vs G arm (31%), and more DRs and dose delays occurred in the *nab*-P + G vs G arm. Associations between DRs and efficacy outcomes will also be examined.

Table. Dose delivery (treated population)

	nab-P + G (n = 421)		G (n = 402)
	nab-P	G	
Total doses administered, n	5770	5888	4769
Per-protocol/total doses, %	71	63	79
Mean percentage of pts receiving per-protocol dose at week 1 by cycle, n/n (%)			
Cycle 3	180/255 (71)	160/258 (62)	144/193 (75)
Cycle 4	134/202 (66)	113/205 (55)	94/136 (69)
Cycle 6	70/131 (53)	57/140 (41)	39/66 (59)
Pts with $\geqslant$1 DR, n (%)	172 (41)	198 (47)	132 (33)
AEs leading to DR[a], n (%)			
Neutropenia	44 (10)	81 (19)	54 (13)
Thrombocytopenia	15 (4)	36 (9)	35 (9)
Peripheral neuropathy	26 (6)	26 (6)	0
Fatigue	18 (4)	19 (5)	9 (2)
Patients with $\geqslant$1 dose delay/omission, n (%)	300 (71)	295 (70)	230 (57)
AEs leading to dose delay/omission[a], n (%)			
Neutropenia	68 (16)	75 (18)	43 (11)
Thrombocytopenia	50 (12)	57 (14)	36 (9)
Peripheral neuropathy	32 (8)	12 (3)	0
Fatigue	34 (8)	33 (8)	15 (4)

[a] Most common treatment-emergent AEs that led to dose modification.

Conclusions: This regimen of *nab*-P + G can be effectively administered to pts with metastatic PC. The *nab*-P + G arm had a longer median treatment duration and higher cumulative dose of G than the G arm.
Conflict of interest: *Ownership: AR: Stock ownership (Celgene). Advisory board: JT, DG, MM, VK, DVH, RR, PH (Celgene). Corporate-sponsored research: JT, DG, MM, VK, DVH, RR (Celgene). Other substantive relationships: AK, AR: Employee of Celgene Corporation*

2587 POSTER

Phase III trial of a 3-weekly vs. 5-weekly schedule of S-1 plus cisplatin (SP) combination chemotherapy for first-line treatment of advanced gastric cancer (AGC): SOS study

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Background: 5-weekly S-1 plus cisplatin (SP5: S-1 80–120 mg/body/day on D1−21, cisplatin 60 mg/m^2 on D8, every 5 weeks) has become a standard first-line chemotherapy for AGC in Japan based on the SPIRITS trial (Lancet Oncol. 2008;9:215). To strengthen the low-dose intensity of cisplatin in this SP5 for greater efficacy, a 3-weekly S-1 plus cisplatin (SP3: S-1 80 mg/m^2/day on D1−14, cisplatin 60 mg/m^2 on D1, every 3 weeks) has been developed in Korea (Cancer Chemother Pharmacol. 2008;61:837).
Methods: This SOS study was a multi-center, randomized, open-label, phase III study to evaluate whether SP3 was non-inferior/superior to SP5 in terms of progression free survival (PFS) determined by a blinded central radiology review according to RECIST v1.1. Patients (pts) with metastatic or recurrent gastric or gastroesophageal junction adenocarcinoma and with

no prior chemotherapy were randomized 1:1 to receive either SP3 or SP5 until disease progression or unacceptable toxicities.
Results: Between February 2009 and January 2012, a total of 625 pts were randomized from 42 sites in Korea and Japan. Median age was 59.6 years. 99% of pts had ECOG performance status 0−1. 16% of pts had prior gastrectomy. 62% of pts had measurable lesions. With a median follow-up of 34.7 months (range, 14.2–48.8) in surviving pts, SP3 was significantly non-inferior and superior to SP5 in PFS (median 5.5 months vs. 4.9 months; HR 0.82, 95% CI 0.68–0.99, p = 0.0418). Overall response rate (ORR) was also better with SP3 than with SP5 (60% vs. 50%, p = 0.029). However, OS of both groups was equivalent (median 14.1 vs. 13.9 months; HR 0.99, 95% CI 0.81–1.21, p = 0.9068). Treatment was well tolerated in both arms, while SP3 was associated with more frequent G3/4 anemia (19% vs. 9%) and neutropenia (39% vs. 9%). Dose intensity was higher in SP3 than in SP5 for both agents (median 331 vs. 317 mg/m^2/week for S-1, p < 0.001; median 18 vs. 12 mg/m^2/week for cisplatin, p < 0.001).
Conclusion: SP3 was non-inferior and superior to SP5 in terms of PFS and ORR. However, considering the small benefit in PFS and no difference in OS, both SP3 and SP5 can be recommended for the first-line treatment of AGC.
Conflict of interest: *Corporate-sponsored research: Taiho pharma, Jeil pharma*

2588 POSTER

Tolerability and quality-of-life (QoL) results from the phase 3 REGARD study: Ramucirumab versus placebo in patients with previously treated gastric or gastroesophageal junction (GEJ) adenocarcinoma

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Background: Ramucirumab (RAM) was associated with significantly longer survival and progression-free survival (PFS) versus placebo (Fuchs et al, GI Cancer Symposium 2013). Here we present assessments of tolerability and QoL from REGARD.
Material and Methods: Patients (pts) with advanced gastric or GEJ adenocarcinoma who had previously been treated were randomized 2:1 to receive RAM 8 mg/kg IV or placebo every 2 weeks; both arms received best supportive care. Pts and investigators were blinded to treatment assignment. Pts were eligible if they had received prior fluoropyrimidine- or platinum-based combination therapy and had ECOG performance status (PS) of 0 or 1. PS was assessed prior to every cycle, at therapy discontinuation, and within 30 days after last dose. Time to PS deterioration was measured from randomization to first change in PS to ⩾2 and evaluated with Kaplan–Meier analysis and log-rank test. Pts completed the EORTC QLQ-C30 (v3) QoL instrument at baseline and on study at Cycles 4, 7, and 10. Scores were classified as improved or worsened if changed by a ⩾10-point difference relative to baseline, otherwise stable. Adverse events (AEs) and supportive therapies were collected while pts were on study.
Results: 355 pts were randomized (238 to RAM, 117 to placebo); 2 pts in each arm did not receive treatment. RAM pts received a median of 4 cycles (interquartile [IQ] range 3−8), while placebo pts received 3 cycles (IQ range 2−4). Treatment discontinuation rates for AEs were 10.5% for RAM and 6.0% for placebo. Time to PS deterioration was longer for RAM (median 5.1 months vs 2.4 months; hazard ratio=0.59 [95% confidence interval: 0.41–0.83], p = 0.002). While on study, QoL completion rates were >86% at all time points. Primarily due to disease progression, <50% of RAM and <25% of placebo pts provided post-baseline QoL data. For the randomized population, rates of improvement were 5−15% for RAM and 3−6% for placebo across the 15 QoL scales at Cycle 4. Rates of stability were 16−37% for RAM and 8−19% for placebo. Rates of worsening were 4−18% for RAM and 1−9% for placebo, with 54% of RAM and 78% of placebo pts providing no data, primarily due to disease progression by 6 weeks. Rates of serious AEs were similar (44.9% RAM, 44.3% placebo). The highest rate of any specific grade ⩾3 AE was <10% in the RAM arm. Select supportive care is summarized in Table 1.

Table 1. Select supportive care for treated pts

	RAM (N = 236)	Placebo (N = 115)
Hospitalizations due to any AE	33.9%	38.3%
Transfusions	11.4%	8.7%
Erythropoietin	2.1%	0.9%
G-CSF	0.8%	0.9%
Anti-hypertensive agents	42.8%	40.0%

Conclusions: In addition to improved survival and PFS for RAM versus placebo, RAM was well tolerated. Rates of serious AEs were similar between arms; for RAM, the incidence of any individual severe toxicity was low and supportive care requirements were modest. For pts who received at least 4 cycles of therapy, more pts maintained their QoL with RAM. Performance status was maintained for a significantly longer time with RAM.
Clinical trial information: NCT00917384
Conflict of interest: *Ownership: Drs Liepa, Hsu, Schwartz and Koshiji own stock in Eli Lilly and Company. Advisory board: Dr Fuchs has served as a consultant or advisor for Amgen, Pfizer, Sanofi, Roche, Genentech, Metamark Genentics, Momenta Pharm, Infinity Pharm, Bayer, and Bristol-Myers Squibb. Dr Zalcberg has served on advisory boards for Bayer, Roche, and Amgen. Dr Tabernero has served as a consultant for Amgen, BI, BMS, Genentech, ImClone, Lilly, Merck KGaA, Millennium, Novartis, Onyx, Pfizer, Roche, Sanofi, and Celgene. Dr Passalacqua has served on boards for Novartis, Roche, and Pfizer. Corporate-sponsored research: Dr Chau's institution has received funding from Lilly for conduct of the current study. Dr Zalcberg's institution has grants from Bayer and Roche. Dr Passalacqua's institution has a grant from Amgen. Dr Passalacqua's institution has received funding from Lilly for conduct of the current study. Other substantive relationships: Drs Liepa and Koshiji are employees of Eli Lilly and Company. Drs Hsu and Schwartz are employees of ImClone Systems LLC, a wholly owned subsidiary of Eli Lilly and Company. Dr Chau has received consulting fees from ImClone, Lilly, Roche, Merck-Serono, Novartis, Sanofi and BMS. Dr Zalcberg has received consulting fees and travel support from ImClone. Dr Passalacqua has served as a consultant for Astellas and Bayer.*

2589 POSTER

'Pazonet': Single-arm multicentric phase II trial of pazopanib in patients with progressive gastroenteropancreatic neuroendocrine tumors (GEPNETs)

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Background: Pazopanib is an oral multitargeted tyrosin kinase inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α/β and c-kit, with antitumoral and antiangiogenic properties. The aim of this study was to evaluate the clinical benefit rate (CBR), [defined as stable disease + response rate], after six months of Pazopanib in patients (pts) with advanced GEPNETs.
Methods: Pts with advanced GEPNETs who had failed chemotherapy, somatostatin analogs (SSAs) or molecular targeted therapies (MTT) received Pazopanib 800 mg qd. Efficacy was evaluated every 8 weeks following RECIST 1.0. A two-stage Simon's design was utilized and positivity defined as CBR>63% of the pts after 6 months on therapy.
Results: Forty-four pts were recruited from Jan 2011 to March 2012, 42 were evaluable. Twenty were women, mean age was 60 years, 44% were pancreatic and 20% had received previous MTT. Median time of Pazopanib treatment was 30 weeks (IQR 16−55). Thirty-six patients (86%) met the primary endpoint (4 partial responses, 32 stable disease). Median progression-free survival (PFS) was 10 months (95% CI 4.3–15.6). CBR

at 6 months was 100% in pts with no previous targeted therapy (9 pts), 80% in pts with previous mTOR inhibitors (8 pts), 87% in pts with previous antiangiogenics (13 pts) and 75% in pts with previous antiangiogenics and mTOR inhibitors (6 pts) respectively. Most frequent grade III−IV toxicities were asthenia (18%), hypertransaminasemia (13.6%) and diarrhea (9%). Concomitant treatment with SSAs ($p = 0.007$), no decrease in serum chromogranin A levels ($p = 0.024$) and pancreatic origin ($p = 0.013$) were associated with longer PFS.
Conclusion: Pazopanib showed remarkable activity in pts with advanced GEPNETs regardless previous MTT treatment. These results raise the hypothesis of non-cross resistance between MTT in this population and could justify the use of sequential targeted therapies. A phase III study of Pazopanib in progressive GEPNETs is planned.
Conflict of interest: *Other substantive relationships: GlaxoSmithKline*

2590 POSTER

Safety, efficacy, and immune analyses of a phase 2, randomized study of GVAX pancreas and CRS-207 immunotherapy in patients with metastatic pancreatic cancer

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Background: GVAX is composed of GM-CSF-secreting allogeneic pancreas cancer cell lines and administered with low-dose cyclophosphamide (CY) to inhibit regulatory T cells. In prior studies, GVAX induced mesothelin-specific T cell responses that correlated with survival. CRS-207 is live-attenuated *Listeria monocytogenes* engineered to express human mesothelin. CRS-207 stimulates potent innate and adaptive immunity and has shown synergy with GVAX in mouse tumor models. Anecdotal survival benefit was observed in the CRS-207 phase 1 study in patients who received prior GVAX.
Material and Methods: Patients were enrolled with metastatic pancreatic ductal adenocarcinoma (PDA) who received or refused $\geqslant 1$ prior chemotherapy, had ECOG 0−1 and adequate organ function. Patients were randomized 2:1 to receive 2 doses of CY/GVAX followed by 4 doses of CRS-207 (Arm A) or 6 doses of CY/GVAX (Arm B) every 3 weeks. Clinically stable patients were offered additional 20-week courses. The primary endpoint was comparison of OS between arms. Secondary endpoints were to evaluate safety, clinical, and immune responses.
Results: 90 patients were treated (Arm A: 61, Arm B: 29). Thirty-four patients completed 1 course (A: 28, B: 6) and 19 patients (A: 17, B: 2) initiated a 2ndcourse. Median age was 63. Median number of prior regimens was 2. No treatment-related serious adverse events (SAEs) or unexpected toxicities were observed. The most frequent Grade (G) 3/4 related toxicities were fever, lymphopenia, hypophosphatemia, elevated liver enzymes, and fatigue after CRS-207 in <5% of subjects. Of 51 patients evaluated post-treatment, 34% had stable disease in Arm A vs. 19% in Arm B. OS for all patients treated was 6 months in Arm A vs. 3.9 months in Arm B (two-sided, $p = 0.0169$). Patients receiving $\geqslant 3$ doses had OS of 8.3 months in Arm A vs. 4.2 months in Arm B ($p = 0.0107$). Immune analyses will be reported.
Conclusions: Combined CY/GVAX pancreas and CRS-207 was generally well-tolerated with no treatment-related SAEs or unexpected G3/4 toxicities. The significant difference in OS between treatment arms met the criteria for early stopping and was confirmed at the primary analysis. This combination immunotherapy resulted in extended survival for metastatic PDA patients and should continue to be developed as an effective therapy.
Conflict of interest: *Other substantive relationships: Elizabeth Jaffee Potential to get royalties. Dirk Brockstedt (ADURO) ownership of stocks and employment*

2591 POSTER

Biweekly irinotecan plus cisplatin (BIRIP) versus irinotecan alone (IRI) after S-1-based chemotherapy failure in patients with advanced gastric cancer (AGC): Final analysis of a randomised phase III trial (TCOG GI-0801/BIRIP trial)

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Background: The optimal second-line chemotherapy for AGC remains uncertain, but favourable results have been obtained with irinotecan. Preclinical and clinical studies have reported that irinotecan acts synergistically with cisplatin. We tested the hypothesis that BIRIP is superior to IRI in terms of progression-free survival (PFS) as second-line chemotherapy in patients with AGC resistant to S-1-based chemotherapy (UMIN Clinical Trial Registration number: UMIN000001028).
Material and Methods: Patients with recurrent or metastatic gastric cancer resistant to S-1-based first-line chemotherapy were randomly assigned to receive irinotecan (60 mg/m^2 on day 1) plus cisplatin (30 mg/m^2 on day 1) every 2 weeks or irinotecan alone (150 mg/m^2 on day 1) every 2 weeks. The statistical design was based on a superiority hypothesis, assuming a median PFS of 110 days with BIRIP and 65 days with IRI (two-sided α=0.05; 1-β=0.8). Planned accrual was 130 patients.
Results: From April 2008 through July 2011, 130 patients were randomized to BIRIP ($n = 64$) or IRI ($n = 66$) at 21 sites in Japan. Patient characteristics were well balanced between the two groups. The primary endpoint was met. PFS with BIRIP was superior to that with IRI (median PFS, 3.8 m [95% CI 3.0−4.7] vs. 2.8 m [95% CI 2.1−3.3], respectively; HR = 0.68 [0.47–0.98], $p = 0.04$). The response rate as secondary endpoint was 21.9% with BIRIP and 15.9% with IRI ($p = 0.50$). The disease control rate with BIRIP was superior that with IRI (75.0% vs. 54.0%, respectively; $p = 0.02$). On exploratory subgroup analyses with a Cox proportional-hazards model, the effect of BIRIP on PFS was greater in patients with target tumors than in those without target tumors and in patients without peritoneal metastasis than in those with peritoneal metastasis. The most common grade 3/4 toxicities in BIRIP/IRI (%) were neutropenia, 39.1/36.4; diarrhoea, 1.6/6.1; and anorexia, 6.3/10.6.
Conclusions: BIRIP as second-line chemotherapy significantly prolongs PFS in patients with AGC resistant to S-1-based first-line chemotherapy.
No conflict of interest.

2592 POSTER

Prognostic factors in locally advanced pancreatic cancer (LAPC) treated with first line chemotherapy

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Background: LAPC is defined as surgically unresectable disease without detectable metastases and is associated with a longer survival than metastatic disease. The natural history of LAPC may differ from metastatic disease and patients may succumb to locoregional tumor complications in the absence of metastatic disease. The aim of this study was to evaluate prognostic factors in LAPC and investigate whether development of metastatic disease conferred a worse overall survival (OS).
Material and Methods: The BC Cancer Agency is a multi-centre institution treating the majority of oncology patients for the province of BC. A total of 244 consecutive patients with LAPC who initiated palliative chemotherapy from 2001 to 2011 were identified using the pharmacy database. Clinicopathologic variables and treatment outcome were retrospectively collected and analyzed. Kaplan–Meier and Cox-regression survival analysis were performed. This study was approved by our Institutional Review Board.
Results: 244 patients (136 males and 108 females) with a median age of 65 years (range 36−88) were included. First-line chemotherapy regimens included single-agent Gemcitabine ($n = 230$), Gemcitabine doublet therapy ($n = 13$), and 5-Fluorouracil, Irinotecan and Oxaliplatin ($n = 1$). 35 (14.4%) patients received locoregional radiation and 128 (52.5%) developed distant metastatic disease. The most frequent sites were liver ($n = 53$), peritoneum/ascites ($n = 52$) and lungs ($n = 18$). Progression-free survival (PFS) and OS were 5.2 months (95% CI, 4.59–5.92) and 11.6 months (95% CI, 10.53–12.65), respectively. On univariate analysis, poor performance status (PS) at diagnosis (ECOG $\geqslant 2$) and high CA19-9 levels ($\geqslant 1000$) were significantly associated with worse OS ($p < 0.001$ and 0.004, respectively). Age, location of the tumor (head or body/tail) and development of metastatic disease were not significantly associated with worse OS. On multivariate analysis,

the only predictors of worse OS were PS (HR 1.67, p = 0.0002) and elevated CA19-9 (HR 1.46, p = 0.009).
Conclusion: On multivariate analysis, performance status and elevated CA 19.9 were the only significant prognostic factors and may be considered as stratification factors among patients enrolled in clinical trials. More than half of LAPC patients died without evidence of metastatic disease, highlighting the importance of locoregional tumor complications.
No conflict of interest.

2593 POSTER

HERBIS-1: A phase II study of tri-weekly S-1 and CDDP with trastuzumab regimen in HER2-positive advanced gastric cancer (updated data)

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Background: S-1 plus cisplatin (SP) is one of the standard regimens as first-line for advanced gastric cancer. In patients with HER2-positive advanced gastric cancer, trastuzumab (T-mab) in combination with capecitabine or fluorouracil and cisplatin improved the overall survival in ToGA study. However, there was no study to evaluate the efficacy and the safety of T-mab in combination with SP regimen. Therefore, we conducted this study to evaluate the efficacy and the safety of the SP plus T-mab combination.
Material and Methods: Main eligibility criteria: gastric or esophagogastric junction adenocarcinoma; HER2-positive (IHC 3+ or IHC 2+ and FISH positive); unresectable or recurrent; measurable lesion; no history of chemotherapy or radiotherapy; age⩽75; ECOG PS of 0−1; and adequate organ function.
S-1 80/100/120 mg/day based on BSA, po, d1−14, q3w plus cisplatin 60 mg/m^2, iv, d1 plus T-mab 8 mg/ kg, iv, d1 (1st course), and 6 mg/ kg, iv, d1 (from 2nd course), was repeated until disease progression.
Primary endpoint was response rate (RR). Secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety.
The threshold RR was defined as 35%, and the expected RR was set at 50% with 80% power and a 1-sided alpha value of 0.1 and the calculated sample size was 50 patients. Trial registration number is UMIN000005739. The primary sponsor is Osaka Gastrointestinal cancer chemotherapy Study Group (OGSG).
Results: A total of 56 patients (median age 66) were enrolled from July 2011 to May 2012. The efficacy and the safety analyses were conducted in the full analysis set of 53 patients. Two patients were excluded for ineligibility and one was for no treatment. The confirmed RR assessed by the independent review committee was 67.9% (95% CI: 53.7–80.1), and the disease control rate was 94.3%. The median PFS was 7.1 months (95% CI: 6.0–10.1). The median OS was not reached at the median follow-up time of 9.2 months. The main grade 3/4 adverse events (⩾5%) were as follows: neutropenia 34%, leucopenia 8%, anorexia 23%, diarrhea 8%, vomiting 6%, and increased creatinine 6%.
Conclusions: This tri-week regimen with SP plus T-mab was tolerable and showed high RR indicating promising results in patients with HER2-positive advanced gastric cancer. We will show the one-year survival rate in the meeting.
Conflict of interest: *Advisory board: Taiho Pharmaceutical Co.,Ltd. and Yakult Honsha Co.,Ltd. Corporate-sponsored research: Taiho Pharmaceutical Co.,Ltd. Other substantive relationships: Taiho Pharmaceutical Co.,Ltd. (Lecture fee)*

2594 POSTER

Final analysis of GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and of its treatment with sorafeNib) in >3000 sorafenib-treated patients: Prognostic value of baseline characteristics and staging systems

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Background: GIDEON (NCT00812175; Bayer), a large, global, prospective, non-interventional study conducted across 5 regions in 39 countries, is now complete. Over 3300 patients with unresectable hepatocellular carcinoma treated with sorafenib were enrolled.
Materials and Methods: Baseline characteristics were recorded at study entry; safety/outcomes data were collected during follow-up. The visit interval for patient evaluation was determined at physicians' discretion. Patient outcomes were evaluated according to baseline characteristics and staging/scoring systems.

	n	Median OS (days)	Median TTP[a] (days)
Baseline characteristics[b]			
ECOG PS[c]			
0	1364	482	147
1	1279	288	154
2	312	143	135
3	56	56	67
Bilirubin, mg/dL; μmol/L[d]			
<2; <34	2601	348	146
2−3; 34−50	309	176	105
>3; >50	176	102	140
Albumin, g/dL; g/L[d]			
3.5; >35	1731	408	148
2.8−3.5; 28−35	1014	233	141
<2.8; <28	245	121	108
AFP, ng/mL[c]			
<400	1745	440	175
⩾400	1164	203	100
Staging system[b]			
Child-Pugh[e]			
A	1975	415	142
B	669	158	134
C	73	78	110
BCLC[e]			
A	226	791	273
B	632	475	192
C	1673	277	120
D	173	120	86
MELD[c]			
<10	1500	406	139
10–<20	779	248	140
20–<30	37	187	248
30–<40	10	260	202
CLIP[e]			
0	233	667	223
1	689	593	196
2	629	297	125
3	454	211	106
4−6	349	100	76
TNM[e]			
I	154	652	253
II	388	578	175
IIIA	789	289	162
IIIB	97	279	196
IIIC	255	327	150
IV	1126	276	106

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; ECOG PS, Eastern Cooperative Oncology Group performance status; MELD, model for end-stage liver disease; TNM, tumor node metastasis.
[a]TTP defined as time (days) from start of sorafenib treatment to date of first documented disease progression (PD). Only radiologically documented PD of tumor considered as PD.
[b]At study entry; [c]ECOG PS 4 (n = 7); AFP other (n = 303); MELD ⩾40 (n = 2) not shown; [d]Patients with unknown status not shown; [e]Non-evaluable patients not shown.

Results: Prognostic values of baseline characteristics and various staging systems for median overall survival (OS) and time to progression (TTP) in the intent-to-treat population (n = 3213) are shown in the table.
The safety profile in the final analysis was consistent with that reported in the first and second interim analyses of GIDEON and in Phase III studies.
Conclusions: Consistent with previously reported studies, final data indicate that baseline characteristics and scoring/staging systems, including ECOG PS, Child-Pugh status, BCLC stage, and CLIP and MELD scores, appear to be useful prognostic factors for OS. However, BCLC also appears to be predictive of TTP. Further analyses will be presented.
Conflict of interest: *Ownership: Nakajima (stock), Bayer HealthCare. Advisory board: Bronowicki, Bayer HealthCare Kudo, Bayer HealthCare Papandreou, Bayer HealthCare Marrero, Bayer HealthCare and Onyx. Corporate-sponsored research: Bronowick, Bayer HealthCare Venook, Genentech, Roche, GSK, Bayer HealthCare and Onyx Marrero, Bayer HealthCare. Other substantive relationships: Lencioni (lecture fees), Bayer HealthCare Nakajima (employment), Bayer HealthCare*

2595 POSTER

Efficacy and safety of Gemcitabine plus S-1 treatment in locally advanced and metastatic pancreatic cancer: A pooled analysis of three randomized trials using updated individual patient data

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Background: S-1 is an oral fluoropyrimidine derivative shown efficacy for advanced and resected pancreatic cancer (PC). Three randomized studies (Phase III: GEST, randomized phase II: JACCRO PC-01 and GEMSAP) were conducted to evaluate the efficacy of gemcitabine plus S-1 (GS) treatment compared with gemcitabine alone (GEM) for advanced PC in Japan. In this pooled analysis, the efficacy and safety of GS was evaluated according to the extent of disease (locally advanced or metastatic) and all population using individual patient data of these trials.
Material and Methods: Additional follow up was conducted and we used updated survival data in these three trials. On these updated individual patient data, Cox's proportional hazards model and log-rank test for overall survival (OS) and progression-free survival (PFS) were used to compare GS group to GEM group. Combined safety data was also evaluated. The sponsor for this pooled analysis is Taiho Pharmaceutical Co., Ltd.
Results: 770 patients (pts) were included in this pooled analysis (GEM: 389 pts, GS: 381 pts) and 738 events for OS were observed (95.8%). In patients with locally advanced disease, median survival time was 11.8 months in GEM group and 16.4 months in GS group (HR = 0.708, 95% CI: 0.527–0.951, p = 0.0220). GS also improved OS in all patients but not in patients with metastatic disease. Other results (HR of OS and PFS in locally, metastatic and all population) were shown in the table. Grade 3/4 toxicities (%) in GEM group and GS group were neutropenia 37.2/57.1, thrombocytopenia 8.9/15.1, vomiting 0.5/3.2, and diarrhea 0.8/4.0.
Conclusions: GS significantly improved OS in all patients and patients with locally advanced disease compared with GEM. The OS benefit from adding S-1 to GEM was more pronounced in patients with locally advanced disease. Toxicity of GS was higher than GEM but considered to be tolerable.

	n (FAS)	OS: HR (95% CI)	p	PFS: HR (95% CI)	p
Local	193	0.708 (0.527–0.951)	0.0220	0.597 (0.441–0.808)	0.0008
Meta	577	0.872 (0.738–1.032)	0.1102	0.668 (0.564–0.790)	<0.0001
ALL	770	0.823 (0.712–0.952)	0.0085	0.655 (0.566–0.758)	<0.0001

Conflict of interest: *Corporate-sponsored research: Taiho Pharmaceutical Co., Ltd. Other substantive relationships: Taiho Pharmaceutical Co., Ltd.(honoraria)*

2596 POSTER

Trastuzumab in combination with different first-line chemotherapies for treatment of HER2-positive metastatic gastric or gastro-oesophageal junction cancer: Findings from the German non-interventional observational study HerMES

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Background: The international phase III study ToGA has shown that trastuzumab (Herceptin®) is effective in prolonging survival in HER2-positive metastatic gastric or gastro-oesophageal junction cancer (MGC). However, few data are available for trastuzumab as part of routine clinical practice.
Methods: This non-interventional observational study (NCT01220934) was conducted to evaluate the efficacy, safety and feasibility of trastuzumab in previously untreated pts with HER2-positive MGC.
Results: Between April 2010 and February 2013, data from 270 pts were collected. All pts were evaluable for safety. Baseline pt characteristics were as follows: median age 65 yrs (range 29–88); gender (male 74%; female 26%); ECOG PS (0: 28%; 1: 48%; 2: 13%; 3: 3%); distant mets (90%): liver (53%), lymph node (37%), peritoneal carcinomatosis (23%), lung (16%). The mean duration of trastuzumab treatment was 6.2 months. According to the schedule of chemotherapy trastuzumab was administered every 2–3 weeks in a median dose of 4–6 mg/kg BW with accordant loading doses. Only 27% of pts received trastuzumab according to the label in combination with cisplatin and 5-FU or capecitabine (see table). Most pts (52%) did not receive cisplatin-based therapy. 39 pts (14%) received trastuzumab for more than 12 months.

Trastuzumab containing regimen	n	(%)
+ 5-FU + cisplatin	55	(20)
+ 5-FU + cisplatin + leucovorin	41	(15)
+ 5-FU + oxaliplatin (+ leucovorin)	32	(12)
+ 5-FU + oxaliplatin + docetaxel	25	(9)
+ capecitabine + cisplatin	18	(7)
+ capecitabine	17	(6)
other combinations	71	(26)
trastuzumab monotherapy	11	(4)

Preliminary median progression-free survival was 6.8 months, thus comparable to the ToGA data. Most common AEs (all grades) were diarrhoea (7%), nausea (6%), vomiting (5%) and fatigue (4%). Most common grade 3/4 AEs were general physical health deterioration (2%), vomiting (2%), acute renal failure (1%) and fatigue (1%). Health-related quality of life as assessed by EORTC QLQ-C30 and QLQ-STO22 remained stable during observation time. An updated analysis of over 300 pts will be presented at the meeting.
Conclusions: Trastuzumab combined with diverse chemotherapies, including less toxic cisplatin-free schedules, is safe and effective in the routine treatment of MGC. Overall, the results are in line with those from the ToGA trial. Trastuzumab is the standard of care for pts with HER2-positive MGC.
Conflict of interest: *Advisory board: Roche*

2597 POSTER

Quality-of-life (QoL) assessments in patients (pts) with pancreatic neuroendocrine tumors (pNET) enrolled in the open-label, phase 3b, multicenter, expanded access study of everolimus in pts with advanced NET

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Background: Everolimus (EVE) improved median progression-free survival by 6.4 months in pts with advanced pNET (HR. 35, 95% CI. 27-.45, $P<0.001$) compared with placebo in the double-blind, placebo-controlled, phase 3 RADIANT-3 study. QoL was not measured. An expanded access protocol was launched to gather additional safety data, to provide access to EVE for pts with advanced NET while awaiting regulatory approval (EudraCT No: 2010–023032−17), and to incorporate pt-reported outcomes to understand the impact of EVE on QoL. Here we present an analysis of QoL in pts with pNET enrolled in this study.

Methods: Pts aged ⩾18 years with biopsy-proven NET, WHO performance status 0−2, and adequate bone, hepatic, and renal function were enrolled. Main exclusion criteria were poorly differentiated NET and cytotoxic therapy within 4 wks of enrollment. EVE (10 mg/d) was administered until disease progression, unacceptable toxicity, discontinuation, death, commercial availability of EVE, or until May 30, 2012. Pts were enrolled from April 21, 2011, to April 20, 2012. The primary objective was safety of EVE. Secondary objectives included health-related QoL values assessed by the EORTC QLQ-C30 and the EORTC QLQ-GINET21 at baseline; cycles 1, 2, and 3; and then every 3 cycles until end of treatment. The QLQ-C30 has 30 items in 15 subscales, including global health status. The QLQ-GINET21 is used with the QLQ-C30 and includes NET-specific symptom and treatment-related questions not covered in the QLQ-C30 along with social and emotional well-being assessment. The EQ-5D was also administered.

Results: The full analysis set included 246 pts; 126 had pNET. Safety was similar to that reported for RADIANT-3. Throughout the treatment period, QLQ-C30 global health status remained stable (change from baseline at end of treatment = −3.9 points, n = 86). At end of treatment, the functional cognitive, emotional, physical, role, and social functioning scales were similar to baseline. Fatigue had the greatest change in symptom score (change from baseline to end of treatment, 8.9 points, n = 86), which was not considered clinically meaningful (defined as change >10 points). Similarly, the NET-specific QLQ-GINET21 symptom and functional assessment changes from baseline to end of treatment were <9 points on all scores.

Conclusions: Throughout the treatment period, as reported by pts and assessed by by QLQ-C30 and QLQ-GINET21, EVE maintained QoL in pts with pNET.

Support: Novartis Pharmaceuticals Corp

Conflict of interest: *Advisory board: Novartis, Ipsen, Pfizer. Other substantive relationships: Honoraria from Novartis, Ipsen, Pfizer. Employee of Novartis.*

2598 POSTER

A phase 1b study of gemcitabine plus PEGPH20 (pegylated recombinant human hyaluronidase) in patients with stage IV previously untreated pancreatic cancer

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Background: PEGPH20 is a PEGylated version of human recombinant hyaluronidase. In preclinical studies, PEGPH20 depleted pancreatic cancers of their high hyaluronan (HA) content. In a genetically engineered murine model of PDA, PEGPH20 + gemcitabine (Gem) significantly prolonged survival compared to Gem alone. In Phase 1 PEGPH20 monotherapy studies, the MTD was 3 μg/kg. The most common AEs were musculoskeletal events.

Materials and Methods: This was a dose-escalation study to find the recommended Phase 2 dose (RP2D) of PEGPH20 in combination with Gem in patients (pts) with Stage IV previously untreated pancreatic cancer. Pts received PEGPH20 at 1, 1.6, or 3 μg/kg IV twice a week for Wks 1−4, weekly for Wks 5−7, then 1 wk rest. Dose escalation was based on safety. Gem was given at 1000 mg/m^2 IV once a week for Wks 1−7, then 1 wk rest. Thereafter, PEGPH20 + Gem were given once a week for 3 wks in 4-wk cycles. Dexamethasone was given pre and post PEGPH20 doses.

Results: Of the 28 pts enrolled, the majority had a Karnofsky performance status ⩾80%. Median age was 59 yrs. Metastatic sites were liver (89% pts), visceral (36%), lung (21%), and lymph nodes (21%). Median CA19-9 was 1139 U/mL. Four pts received PEGPH20 at 1 μg/kg, 4 at 1.6 μg/kg, and 20 at 3 μg/kg. The RP2D was 3 μg/kg. Median PEGPH20 treatment was 68 days (1–271 days); 4 pts remain on study. Three pts had 1 PEGPH20 dose reduction (3 to 1.6 μg/kg). The majority of PEGPH20-related AEs were Grade 1/2. The most common related AEs were muscle spasm (43%), myalgia (32%), arthralgia (25%), and fatigue (25%). Objective response was assessed by an independent central radiologist using RECIST 1.1. Partial response (PR) was seen in 10/24 pts (1.6 and 3 μg/kg) for an overall response rate of 42% (22−61%, 95% CI), and 8 pts had stable disease (41–189 days). Tumor biopsies from 17 pts (1.6 and 3 μg/kg) were evaluated for HA staining. PR occurred in 7/11 pts (64%) with high HA staining and in 2/6 pts (33%) with low HA staining. HA data were not available for the last PR pt. CA19-9 reductions ⩾70% occurred in 6/14 pts with elevated baseline levels (1.6 and 3 μg/kg). CA19-9 reductions were generally associated with response. PK results showed dose-dependent exposure consistent with PEGPH20 monotherapy studies.

Conclusions: PEGPH20 in combination with Gem is generally well tolerated in advanced pancreatic cancer and shows promising efficacy, especially in pts with high intratumoral HA content.

Conflict of interest: *Ownership: Halozyme Therapeutics, San Diego, CA (Joy Zhu − stock ownership). Other substantive relationships: Halozyme Therapeutics, San Diego, CA (Joy Zhu − employee)*

2599 POSTER

Randomized phase III trial of irinotecan plus cisplatin versus irinotecan in patients with metastatic gastric cancer resistant to S-1 monotherapy: Survival analysis

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Background: The standard second-line regimen for the treatment of metastatic gastric cancer remains to be established. We have implemented a phase III trial comparing combination therapy with irinotecan (CPT-11) and cisplatin (CDDP) to monotherapy with CPT-11 (TRICS trial). The results of the safety analysis have already been reported (Hasegawa et al. ESMO 2012). Here we report the results of the survival analysis.
Methods: Patients with metastatic gastric cancer resistant to S-1 monotherapy were randomly allocated to the CPT-11/CDDP arm (CPT-11−60 mg/m^2, CDDP 30 mg/m^2, Day 1, q2w) or the CPT-11 arm (150 mg/m^2, Day 1, q2w). The main eligibility criteria included disease progression after receiving S-1 monotherapy or recurrence within 6 months after or during S-1 adjuvant chemotherapy (discontinuation due to adverse events was not included). The primary endpoint was to compare overall survival (OS). The planned sample size was 200, including ineligibility or dropout.
Results: Between 2007 and 2011, 168 patients were randomly assigned to the CPT-11/CDDP or CPT-11 arm, respectively. The median follow-up was 59.0 months (M). Median OS was 13.9 M in the CPT-11/CDDP arm and 12.7 M in the CPT-11 arm (hazard ratio [HR] 0.834, 95% CI 0.596–1.167, p = 0.288). There were no significant differences in the secondary endpoints: progression free survival (4.6 M vs. 4.1 M, HR 0.860, p = 0.376), response rate (16.9% vs. 15.4%, p = 0.812) and time to treatment failure (3.3 M vs. 3.5 M, HR 1.009, p = 0.96). The incidence of grade 3−4 neutropenia (35.4% vs 27.2%, p = 0.259), anemia (15.9% vs 3.7%, p = 0.009) and LDH (5% vs. 0%, p = 0.04) was greater in the CPT-11/CDDP arm than in the CPT-11 arm. An exploratory subgroup analysis revealed that the CPT-11/CDDP arm was significantly more effective in intestinal type gastric adenocarcinoma (median OS 17.3 M vs. 14.0 M, HR 0.561, p = 0.021).
Conclusions: CPT-11/CDDP combination therapy was not statistically superior to CPT-11 monotherapy for the OS. But the combination regimen may be particularly effective for intestinal type tumors.
No conflict of interest.

2600 POSTER

No improvement in median survival for patients with metastatic gastric cancer despite increased use of chemotherapy

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Background: Gastric cancer often presents late in an irresectable or metastasized stage. We conducted a population-based study to evaluate trends in systemic treatment and survival of metastatic non-cardia gastric cancer.
Method: All patients with non-cardia adenocarcinoma of the stomach, diagnosed between 1990 and 2011 in the Eindhoven Cancer Registry area in the Netherlands were included (N = 4797). We conducted multivariable logistic regression analysis to evaluate trends in administration of palliative chemotherapy and multivariable proportional hazards regression analyses to evaluate trends in crude overall survival.
Results: The proportion of patients presenting with metastatic gastric cancer, defined as stage IV according to the TNM classification in the respective period, increased from 25% in 1990 to 44% in 2011 (p < 0.0001). The use of palliative chemotherapy increased, from 5% in 1990 to 36% in 2011, with a strong increase in particular after 2006 (p < 0.0001). Younger patients aged <50 yrs (46%, (adjusted odds ratio (OR_{adj}) 4.3, p < 0.001) or between 50−59 yrs (23%, OR_{adj} 1.7, p = 0.02) and patients with a high socioeconomic status (25%, OR_{adj} 1.5, p = 0.02) more often received chemotherapy. In contrast, older patients aged between 70−79 yrs (10%, OR_{adj} 0.28, p < 0.001) or 80+ yrs (1%, OR_{adj} 0.02, p < 0.001), patients with comorbidity (17%, OR_{adj} 0.6, p = 0.02), linitis plastica (19%, OR_{adj} 0.6, p = 0.04) or multiple distant metastases (18%, OR_{adj} 0.5, p = 0.007) were less often treated with chemotherapy. A large hospital variation was observed in the administration of palliative chemotherapy (9−27%). Median overall survival remained constant between 16 (95% CI 12.3–18.6) and 18 (95% CI 15.4–21.1) weeks (p = 0.10). In addition, female sex (HR 0.8, p = 0.001), poor or undifferentiated tumor grade (HR 1.2, p = 0.001), liver metastases (HR 1.6, p < 0.001), multiple distant metastases (HR 1.5, p < 0.001) and administration of chemotherapy (HR 0.6, p < 0.001) had an independent effect on survival.
Conclusion: The increased administration of chemotherapy in patients with metastatic gastric cancer did not lead to an increase in population-based overall survival. Identification of the subgroup of patients which benefits from palliative chemotherapy is of utmost importance to avoid unnecessary treatment.
No conflict of interest.

2601 POSTER

Subgroup analysis of prognostic factors for overall survival in the SHELTER trial evaluating resminostat in advanced hepatocellular carcinoma (HCC) − the SHELTER Study Group

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Background: Previously published results of the phase I/II SHELTER study demonstrated efficacy and safety of the oral pan-HDAC inhibitor resminostat in second-line treatment of HCC patients, who had progressed under first-line sorafenib therapy. An analysis of the influence of patient baseline characteristics on overall survival (OS) was performed.
Methods: Patients with advanced-stage HCC and centrally confirmed radiologic progression under first-line sorafenib therapy were included in a multi-center, two-arm trial where resminostat was administered either alone or in combination with sorafenib. A Cox proportional-hazards model was used to evaluate the interaction between baseline characteristics and OS in both treatment groups.
Results: In the combination group, pts with Child-Pugh-A, ECOG 0 or absence of vascular invasion had a statistically significant lower risk of death compared to pts with Child-Pugh-B (HR 0.19, 95% CI 0.06–0.55), ECOG 1 (HR 0.15, 95% CI 0.05–0.44), or vascular invasion (HR 0.37, 95% CI 0.15–0.93), respectively. For pts with BCLC-B there was a strong trend, although not statistically significant, for a lower risk of death when compared to pts with BCLC-C (HR 0.43, 95% CI 0.13–1.49). Etiology, prior TACE therapy, extrahepatic spread and interval between first- and second-line treatment had no impact on overall survival in this study. Comparing the impact of these baseline characteristics in the combination and resminostat monotherapy, no statistically significant different influence on OS between both treatment groups was observed.
Conclusions: Resminostat in combination with sorafenib showed a substantial median OS of 8.1 months in second-line treatment of advanced HCC patients who had developed progressive disease under first-line sorafenib therapy. Subgroup analysis of patient baseline characteristics revealed a significant influence of Child-Pugh index, ECOG classification, and vascular invasion on overall survival, whereas e.g. the interval between first- and second-line treatment had no impact.
Conflict of interest: *Other substantive relationships: 4SC AG*

2602 POSTER

Safety of two different doses of pertuzumab (P) in combination with trastuzumab (T) and chemotherapy (CTx) in patients (pts) with HER2-positive advanced gastric cancer (aGC)

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Background: HER2 is overexpressed in 15−20% of aGC. Phase III results demonstrated that T + CTx significantly improved overall survival compared with CTx alone in pts with HER2-positive aGC and/or gastro-oesophageal junction (GEJ) cancer (Bang Lancet 2010). The most frequent grade 3/4

adverse events (AEs) reported in that trial in pts receiving T + CTx were neutropenia, anaemia, diarrhoea, nausea, anorexia and vomiting. The combination of P with T + docetaxel significantly improved progression-free survival (Baselga NEJM 2012) and overall survival (Swain SABCS 2012) compared with T + docetaxel in HER2-positive first-line (1L) metastatic breast cancer. P + T + CTx has the potential to improve survival outcomes in HER2-positive aGC. We therefore conducted a Phase IIa study to investigate the pharmacokinetics (PK) and safety of P in combination with T + CTx in HER2-positive inoperable locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or GEJ (JOSHUA, NCT01461057).

Materials and Methods: JOSHUA was a randomised, open-label, multicentre study evaluating two different doses of P in 1L treatment of pts with HER2-positive aGC or GEJ cancer. Pts received P 840 mg for Cycle 1 and 420 mg q3w for Cycles 2−6 (Arm A) or P 840 mg q3w for all 6 cycles (Arm B). Six cycles of T, cisplatin and capecitabine were also given, followed by T q3w until disease progression or unmanageable toxicity. Primary endpoints were P trough concentrations (C_{min}) at Day 43 (to identify the P dose giving a steady-state C_{min} of $\geqslant$20 μg/mL in $\geqslant$90% of pts), safety and tolerability.

Results: 15 pts were randomised into each arm and both arms were well balanced in terms of tumour stage and race. However, there were more males (93 vs. 67%), older pts (median age 67 vs. 59 years) and more pts with ECOG performance status 0 (67 vs. 40%) in Arm A than in Arm B. The mean C_{min} at Day 43 in Arms A and B was 40.0 μg/mL (CV 43.2%) and 57.9 μg/mL (CV 56.5%), respectively, and the estimated proportion of pts achieving the target C_{min} was 91.6% (95% CI 78.3–99.2) in Arm A and 98.3% (95% CI 91.4–99.97) in Arm B. At this interim safety assessment, treatment was well tolerated and there was no difference in AE profile between arms. The most common grade $\geqslant$3 AEs ($\geqslant$4 pts overall) were diarrhoea, neutropenia, anaemia, decreased appetite, fatigue, febrile neutropenia, hyponatraemia and stomatitis. Diarrhoea was the most frequent AE in both arms and occurred early during study treatment. Updated safety data and preliminary efficacy data will also be presented.

Conclusions: The safety profile was similar between arms, with diarrhoea being the most common AE. Based on the PK and safety data, the higher dose of P (840 mg q3w) has been selected for a Phase III study comparing the safety and efficacy of P + T + CTx vs. placebo + T + CTx in 1L HER2-positive metastatic gastric or GEJ cancer (JACOB, NCT01774786).

Trial status: Fully recruited

Trial sponsor: Roche

Conflict of interest: *Ownership: RY and AG hold shares in Roche. Advisory board: YKK and YJB have participated in advisory boards for Roche. Corporate-sponsored research: JB is an investigator in clinical trials sponsored by Roche, Novartis and Taiho and AstraZeneca.YJB is an investigator in clinical trials sponsored by Roche. Other substantive relationships: YJB has received honoraria in the past from Roche.RY, TS and AG are employees of Genentech*

2603 POSTER

Comparison of aggressive gastric B-cell lymphoma patients according to HIV infection status in the era of combination antiretroviral therapy

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Background: Human immunodeficiency virus (HIV)-associated non-Hodgkin lymphoma is the most common HIV-associated malignancy despite the advent of combination antiretroviral therapy (cART). The gastrointestinal (GI) tract is one of the most common extranodal sites, and the stomach is the most common site. This study investigated the clinical characteristics and survival outcomes of gastric lymphoma patients according to HIV infection status.

Material and Methods: We retrospectively analyzed the medical records of patients diagnosed with GI lymphoma and HIV-associated lymphoma at Osaka National Hospital from April 2000 to March 2013.

Results: Of 2,314 HIV-positive patients, 16 were diagnosed with GI lymphoma. The stomach was the most common site of GI involvement (n = 10, 63%), followed by the duodenum (n = 5, 31%). One patient was diagnosed upon autopsy with gastric diffuse large B-cell lymphoma (DLBCL). Of the 9 HIV-positive gastric lymphoma patients, 6 (67%) had Burkitt lymphoma and 3 (33%) had DLBCL according the WHO classification. One patient (11%) had stage I disease, 2 (22%) had stage II disease, and 6 (67%) had stage IV disease according to the Ann Arbor classification. At the time of diagnosis, the median CD4 lymphocyte count was 239/mm^3, and the HIV RNA viral load was 52,000 copies/mm^3. One patient (11%) had a prior AIDS-defining illness, and 2 (22%) had been previously treated with cART. Seven patients (78%) received systemic chemotherapy, and 1 (11%) received chemotherapy followed by locoregional radiotherapy. Five (56%) of the 9 patients have died within 6 months. Of the 49 HIV-negative gastric lymphoma patients evaluated, 24 (49%) were diagnosed with DLBCL. In total, 9 HIV-positive and 24 HIV-negative patients with aggressive gastric B-cell lymphoma were evaluated. Age at diagnosis was lower and LDH levels were higher in HIV-positive patients than in HIV-negative patients. After a median follow-up of 22 months (range, 0–138 months), the 2-year survival rates of patients with and without HIV infection were 44% and 72%, respectively. The overall survival rate differed significantly between HIV-positive and HIV-negative patients ($P = 0.049$).

Conclusions: Gastric aggressive B-cell lymphoma patients infected with HIV continue to experience higher mortality rates than those not infected with HIV, even in the era of cART. Better management and therapeutic approaches are needed to improve survival in HIV-infected patients who develop gastric lymphoma.

No conflict of interest.

2604 POSTER

Multivariate prognostic factor analysis in patients (pts) with advanced biliary tract cancer (aBTC) treated with second-line chemotherapy (CT)

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Background: We retrospectively evaluated the impact of different clinico-pathologic factors on the survival of aBTC pts treated with second-line CT.

Material and Methods: Consecutive aBTC pts who received second-line CT at 8 Italian Institutions since 2004 were identified. The association between different clinico-pathological factors and progression-free survival (PFS) and overall survival (OS) was investigated by log-rank test and Cox model setting statistical significance at $P<0.05$. A prognostic score was calculated by assigning 1 point to each factor found significant at multivariate analysis.

Table 1.

Variable	PFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
ECOG PS				
0	1		1	
1−2	1.550 (1.095–2.193)	0.013	2.675 (1.629–4.394)	<0.001
PFS after first-line				
$\geqslant$6 months	1		1	
<6 months	1.418 (1.047–1.919)	0.024	1.760 (1.099–2.819)	0.019
Leucocyte count				
$\geqslant$10000/μL	1		1	
<10000/μL	0.549 (0.355–0.851)	0.007	0.556 (0.321–0.964)	0.036
CA19.9 level				
$\geqslant$120 U/mL	1		1	
<120 U/mL	0.677 (0.501–0.914)	0.011	0.456 (0.292–0.711)	0.001
Lung metastases				
Yes	1		NS	
No	0.720 (0.524–0.989)	0.043		

NS: not significant

Results: 247 patients were identified: male, 45%; median age, 65 years (range 28−85); ECOG performance status 0/1−2, 64%/36%; disease site, intrahepatic 52%/extrahepatic 22%/ gallbladder 18%/ampullary 8%; previous surgery, 57%; previous adjuvant CT, 24%; first-line gemcitabine plus platinum, 61%; the majority of patients had metastatic disease; sites of metastases 1/>1, 46%/54%; second-line monotherapy/combination, 30%/70%. At a median follow up of 23 months, response rate with second-line CT is 5% (stable disease: 31%), while median PFS and OS are 3.3 months (95% CI: 2.9−3.7) and 8.2 months (95% CI: 6.8−9.6), respectively. The factors associated with PFS and OS at multivariate analysis are listed in the Table. By combining these factors, 204 pts with complete data were categorized into three risk groups: low (0 points), intermediate (1 to 2 points), and high (3 or more points). As regards PFS, median survival time for low, intermediate and high risk groups is 6.8, 3.5 and 2.4 respectively ($P<0.0001$). As regards OS, median survival time for low, intermediate, and high risk groups is 17.4, 8.0 and 3.1 respectively ($P<0.0001$).

Conclusions: aBTC is a heterogeneous disease for which no standard second-line CT has been established yet: easily available clinico-pathologic factors may help identifying aBTC pts with different prognosis, thus helping second-line treatment decision in each case.
No conflict of interest.

2605 POSTER

Comparison of three different docetaxel and cisplatin plus fluorouracil (DCF) as first-line therapy for advanced gastric cancer: A retrospective analysis of the two institution

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Background: We performed a retrospective analysis of the efficacy and side effects of three different docetaxel and cisplatin plus fluorouracil (DCF) in the advanced gastric cancer with first-line chemotherapy treated patients.
Patients and Methods: We retrospectively reviewed 202 locally advanced or metastatic gastric cancer patients. The standard DCF group was administered 75 mg/ m^2 docetaxel and cisplatin on day 1 and 750 mg/ m^2/day 5-fluorouracil infusion for 5 days, repeated every 3 weeks. The mDCF group received 60 mg/ m^2 docetaxel and cisplatin on day 1 and 600 mg/m^2 5-fluorouracil continuous infusion per day on days 1−5, every 3 weeks. The de Gramont regimen group consisted of 60 mg/ m^2 docetaxel and 50 mg/m^2 cisplatin on day 1 and bolus fluorouracil (400 mg/ m^2) on day 1, and continuous infusion of fluorouracil (2400 mg/ m^2) on two days, repeated every two weeks.
Result: The standard DCF arm 87 (M: 57, F: 30), The mDCF group arm 26 (M: 15, F: 11), de Gramont regimen arm 89 (M: 67, F: 22) are patients. Patients with the de Gramont regimen had a higher dose reduction ($p = 0.001$). Between treatment groups, gender, age, the number of cycles, histology, stage, second-line chemotherapy did not have a statistically difference (p >0.05). PFS and OS were more favorable in the de Gramont regimen in present study, while the differences were not statistically significant (p>0.05). The rate of response did not have a difference statistically. In spite of the fact that treatment efficacy were similar in between groups, grade III−IV neutropenia, febrile neutropenia, thrombocytopenia, anaemia, nausea and vomiting were higher in the standard DCF(table).

Table: Efficiency of the treatment and survival

Response	Group A (%)	Group B (%)	Group C (%)	*p*
Complete response	10.0	5.3	3.4	>0.05
Partial response	35.7	36.8	24.7	>0.05
Stable disease	32.9	36.8	39.3	>0.05
Progressive disease	21.4	21.1	32.6	>0.05
OS (months)	10.0 (6.9–13.0)	9.0 (7.4–10.6)	11.6 (10.7–12.4)	>0.05
PFS (months)	6.0 (4.7−7.2)	6.0 (3.0−8.9)	7.9 (6.8−8.9)	0.08

Conclusion: The response rate, median PFS and OS are similar in different DCF regimen, while the mDCF and de Gramont-based DCF regimens are more favourable than the DCF regimen for toxicity profile. mDCF and de Gramont-based DCF regimens may provide an alternative regimen to the standard DCF.
No conflict of interest.

2606 POSTER

Present status of screening of hepatitis B virus infection in patients who undergo chemotherapy in Japan

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Background: Reactivation of hepatitis B virus (HBV) has been often reported as a fatal complication, such as acute hepatitis, during or following chemotherapy. The Japanese HBV guideline for the prevention of HBV reactivation caused by immunosuppressive therapy or chemotherapy was published in 2009 by the research team of Ministry of Health, Labour and Welfare. This guideline recommends that the high risk patient group should be identified by measuring HBsAg, anti-HBc and anti-HBs before the commencement of chemotherapy. The aim of this study was to investigate the present status of screening of HBV in patients who underwent chemotherapy for malignancy.
Methods: This study was conducted through utilising the Claims Database which Japan Medical Data Center possesses. The study subjects abstracted from it were 1,995 patients who had been newly undergone chemotherapy for malignancy. They are abstracted from 28,087 patients with solid tumours and haematological malignancy among 1,154,774 insured people (individuals and families) who were member of multiple Health Insurance Association from Jan 2008 through Dec 2012. The proportion of patients who measured HBsAg (P-HBs) and HBsAg negative patients who measured anti-HBc or anti-HBs (P-HBc/HBs) before chemotherapy were investigated.
Results: Comparison P-HBs with P-HBc/HBs in all 1,995 patients were 64.2% and 15.7%, respectively. P-HBs and P-HBc/HBs in patients with solid tumours and haematological malignancy were 64.0% and 65.3% ($p = 0.89$), and 8.6% and 67.1% ($p < 0.0001$), respectively. P-HBs and P-HBc/HBs in patients on cancer center and non-cancer center were 64.6% and 63.3% ($p = 0.80$), and 21.2% and 8.7% ($p < 0.0001$), respectively. P-HBs and P-HBc/HBs in patients before and after the announcement of the Japanese guideline and haematological malignancy were 49.2% and 65.7% (p=24), and 6.7% and 16.5% ($p = 0.005$), respectively.
Conclusions: P-HBc was higher in patients with haematological malignancy and on cancer center, and this finding demonstrated that the oncologists charged in these patients were highly aware of HBV reactivation. However, the proportion was not sufficient, and the enlightenment for 'HBV reactivation by chemotherapy' was warranted.
No conflict of interest.

2607 POSTER

UK audit of sorafenib for advanced hepatocellular cancer

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Background: Based on two randomised controlled trials, sorafenib is the current standard of care for patients with advanced hepatocellular carcinoma (HCC) and well compensated liver disease. In the SHARP trial, conducted in the western population including the UK, median survival was increased from 7.9 to 10.7 months (mo). Patients in SHARP had Child-Pugh (CP) score A (95%), and 54% had an ECOG performance status (PS) of 0. They received a mean daily dose of 710 mg/day for a median duration of 5.3 mo. We performed a retrospective national audit of patients treated with sorafenib in the UK to determine the outcome for patients treated outside a clinical trial.
Method: All UK centres that treat HCC were invited to participate. Patients with HCC who had received sorafenib between 1st Jan 2009 and 1st Jan 2013 were identified via the Cancer Drugs Fund records. Clinical, pathological and treatment data were collected from medical and pharmacy records. The primary outcome measure was overall survival which was estimated according to the Kaplan–Meier method.
Results: Data was received for 379 patients from 11 UK hospitals. Median age was 68 (range 17−89) and 78% were male. Background liver disease was known for 83% and was: alcohol 28%; none 23%; hepatitis C 16%; hepatitis B 12%; NASH 10%; other 16%. At baseline, ECOG PS was recorded for 84% of which: PS0 30%; PS1 47%; PS2 23%, and (CP) score was recorded for 83% of which: CPA 84% and CPB 16%. BCLC stage at baseline was reported for 85% of which: BCLC B 28% and BCLC C 71%. Previous loco-regional therapy had been given to 38%, and 38% had extra-hepatic metastases. At the time of analysis, 73% had completed treatment, with a median time on treatment of 3.2 mo, and an average daily dose of 585 mg. Dose was reduced in 43% of patients and 26% had a treatment interruption. The main reasons for stopping sorafenib treatment were toxicity (26%), radiological progression (24%) or clinical progression/death (41%). Median overall survival for 374 evaluable patients and 219 events was 8.5 mo (95% CI 7.4−9.7).
Conclusion: Clinical outcomes were compatible with those reported in other European audits. Overall, compared with the SHARP trial, patients had worse PS and background liver function, but also received a lower average dose and had a shorter time on treatment.
No conflict of interest.

2608 POSTER

Phase II open-label single-arm trial of combining the epitope peptide derived from Vascular Endothelial Growth Factor Receptor-2 with gemcitabine for patients with unresectable biliary tract cancer OTS102 Study202

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Background: Gemcitabine (GEM) is considered one of the standard therapies for advanced biliary tract cancer; however, due to still poor prognosis further improvement was needed. Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2/Flk-1/KDR) is an essential target for tumor angiogenesis, which expression is also correlates to the progression of the biliary tract cancer. VEGFR2 peptide (OTS102, Elpamotide) specifically targets the cells expressing VEGFR-2/ KDR. Based on promising Phase I trial results on solid tumors, we conducted an open-label Phase II study to evaluate the efficacy and safety of the combination with OTS102 and gemcitabine.
Methods: This is a multi-center, single-arm, open-label, phase II study with the main eligibility criteria as unresectable and recurrent biliary tract cancer, with the status of human leukocyte antigen A*24:02, PS: 0−1, radiotherapy or chemotherapy naive. Patients received combination OTS102+GEM therapy by subcutaneous OTS102 injection on day 1, 8, 15 and 22 of each 28-day treatment cycles and GEM at a fixed dose of 1000 mg/m^2 on day 1, 8 and 15. Therapy was repeated for 18 months or termination criteria had been met. The primary endpoint was overall survival. Assuming 1-year survival as 15−30%, the increase of 1-year survival by OTS102 by 15%, one-sided significance level of 10%, and power of 80%, the sample size necessary was estimated as 50 patients. Kaplan–Meier method was used to draw survival curve, and 1-year survival and 95% CI of both sides were estimated. Historical data (GEM Historical) selected for the analysis of this report was a phase II single-agent GEM study (Okusaka et al. Cancer Chemother Pharmacol. 2006).
Results: From July 2009 to June 2011, 55 pts were registered from 14 facilities all over the Japan, and 54 were treated. For full analysis set of 54 pts, mean pt age was 62.9 years. Types of cancer pts had were: extrahepatic bile duct cancer, 13 pts; intrahepatic bile duct cancer, 20 pts; gallbladder cancer, 18 pts; and ampulla of Vater cancer, 3 pts. Mean survival time was 10.05 months (95% CI: 7.95–13.96) in OTS102+GEM group, whereas it was 7.6 months in GEM alone group (log-rank test, p = 0.043). 1-year survival rate, 44.4% vs 25.0%, respectively.
Conclusion: OTS102 added to GEM suggested to prolong OS compared to GEM alone. Further analysis with multiple historical data with adjustment to match the study population of this trial has been currently ongoing.
Conflict of interest: *Ownership: Tsunoda T: OncoTherapy Science,Inc*

2609 POSTER

Overall survival of specific HCC patient subgroups in prospective, non-interventional INSIGHT study treated with sorafenib

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Background: INSIGHT is a prospective, non-interventional study, conducted in pts with hepatocellular carcinoma at ~170 sites in Germany and Austria. The objectives of this study are the evaluation of safety and efficacy in daily clinical practice. Enrollment into INSIGHT is not restricted to a particular tumor stage.
Methods: Data are collected at the start of sorafenib treatment, then at intervals of approximately every 2−4 months. The time from start of sorafenib therapy until evidence of disease progression or unacceptable toxicities are defined as observation period. Documentation of tumor status evaluation, adverse events, changes of concomitant medication/treatments, and patient status is performed at each follow-up visit sorafenib therapy. In addition to baseline data the performance status, tumor status (clinical and/or radiological), and overall survival time are documented. This interim analysis (data cut-off 11 DEC 2012) evaluated overall survival and safety data in clinically relevant subgroups. Documentation of adverse events comprises relationship with drug, seriousness, grade (CTCAE version 3.0), and outcome.
Results: Until the data cut-off 781 pts have been enrolled; 778 of which were evaluated regarding efficacy and safety. The table summarises major baseline characteristics together with median overall survival (mOS) data for relevant subpopulations.

Table 1. Patient characteristics

	n	(%)
Patients recruited	778	
Male	667	(86)
ECOG PS		
0	243	(31)
1	403	(52)
2	123	(16)
BCLC stage		
A	100	(13)
B	192	(25)
C	389	(50)
D	14	(2)
Missing	83	(11)
Child Pugh stage		
A	322	(41)
B (7−9)	128	(17)
C (>9)	18	(2)
Missing	310	(40)

Table 2. Overall survival

Population	Overall survival (months)
mOS total population (Events n = 219)	15.8
mOS according to BCLC	
A	29.1
B	25.1
C	14.4
D	3.1
mOS according to age	(p = 0.4166)
<65 years	19.7
⩾65 years	15.6
mOS according to NASH at baseline	(p = 0.2610)
no/missing (n = 690)	15.8
yes (n = 88)	14.5
mOS according to diabetes at baseline	(p = 0.3302)
no/missing (n = 422)	18.6
yes (n = 356)	14.5

Conclusions: The efficacy of sorafenib therapy for HCC patients in German and Austrian hospitals and private practices under everyday clinical conditions is comparable with that reported in prospective, randomized clinical trials. The data suggest that the survival of elderly and HCC patients with risk factors (e.g. NASH and diabetes) is similar to the general study population.
Conflict of interest: *Ownership: No. Advisory board: Bayer, MSD, Novartis. Board of directors: No. Corporate-sponsored research: Bayer, Novartis. Other substantive relationships: Presentation fee from Bayer, Abbott, AstraZeneca, Falk Foundation*

2610 POSTER

Does timing of adjuvant chemotherapy for gastric cancer influence outcome?

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Background: According to recent large phase III trials, adjuvant chemotherapy is currently established as standard treatment in patients with stage II, III gastric cancer. However, to the authors' knowledge, the effect of the interval between surgery and the start of chemotherapy on outcome has not been investigated.
Methods: A retrospective review was conducted of 716 patients who underwent adjuvant chemotherapy for stage IB−IIIC (AJCC 7th edition) gastric cancer after radical surgery with D2 dissection between 1994 and 2004 at the Ajou University Hospital. Overall survival (OS) was compared among patients grouped by time from surgery to start of adjuvant chemotherapy.
Results: In terms of chemotherapy regimens, 5-FU/mitomycin-C-based (61.3%) was the most commonly used regimen, followed by 5-FU/doxorubicin-based one (16.9%), oral fluoropyrimidines (10.3%) and others (11.4%). The median time from surgery to chemotherapy was 20 days (range: 4–105 days), while 114 patients (15.9%) began adjuvant chemotherapy >4 weeks after surgery. The median follow-up duration was 152 months (range: 97–222 months) for the survivors. There was no significant difference in 10 year-OS between patients starting chemotherapy ⩽20 days after surgery and those initiating later (51.2% vs. 48.5%, p = 0.896). Commencing chemotherapy 4 weeks, 6 weeks and 8 weeks after surgery was not associated with inferior OS, compared with earlier initiation at each time interval (p = 0.183, 0.739, 0.434, respectively). Even very early initiation of chemotherapy (⩽2 weeks after surgery) did not correlate with better outcome (p = 0.579).
Conclusion: This study did not demonstrate any significant survival benefit from early initiation of adjuvant chemotherapy after surgery.
No conflict of interest.

2611 POSTER

Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID): Results of long-term radiological follow-up

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Background: Octreotide LAR compared to placebo significantly lengthens the time to tumor progression (TTP) in patients with metastatic midgut neuroendocrine tumors (Rinke et al. 2009). The antiproliferative effect was pronounced in patients with low (⩽10%) hepatic tumor load (HL). Aim of this follow-up trial was to analyze the prognostic significance of HL on overall survival (OS) and to assess long term development of HL.
Patients and Methods: Between July 2001 and January 2008 42 and 43 treatment naive patients were randomly assigned to receive octreotide LAR and placebo, respectively. Post-study treatment was at the discretion of the local investigator. However, >90% of patients in the placebo group received octreotide LAR after progression. Up to January, 2013 HL was determined in CT or MRI scans by central review. HL was assessed semiquantitatively (HL groups: 0%, >0%- ⩽10%; >10%-⩽25%; >25%-⩽50%; >50%). OS was analyzed using the Kaplan–Meier method for patients with HL ⩽10% at study entry (low HL) vs those with HL >10% (high HL) and compared using the log-rank test.
Results: 26 of 64 patients (40.6%) (10 in the octreotide LAR vs 16 in the placebo arm) died in the low HL at baseline subgroup and 15 of 21 patients (71.4%) (9 in the octreotide LAR vs 6 in the placebo arm) in the high HL (p = 0.002, HR = 2.7). Cause of death was tumor-related in 33 of 41 cases. In 53 of 85 patients follow up scans for central review were available. 4 patients randomized to octreotide LAR were without progression at the last evaluation (50, 71, 100 and 107 months after randomization).
Patients in the octreotide LAR treatment group with low HL at baseline more often remained in this HL group up to the last evaluation than patients in the placebo group (octreotide LAR: 16/32; placebo: 8/32).
At the last evaluation a lower HL as compared to the baseline evaluation was rarely found (3/53 patients) and resulted from chemoembolization (n = 2) and resection (n = 1).
Most patients with available scans who died during follow up had an HL>10% at the last evaluation (16/19), 9 of them had HL >50%. In 2 of the 3 remaining patients death was not tumor-related. The only patient with low HL at last evaluation and tumor-related death developed progressive extrahepatic disease.
Conclusion: In patients with well differentiated midgut tumors low HL is predictive for better response to early octreotide LAR treatment. High HL is associated with a shorter overall survival.
Conflict of interest: *Ownership: Novartis Pharma GmbH. Advisory board: A. Rinke was a member of the advisory board last year. Other substantive relationships: R.Arnold and A. Rinke received honaria for presentations.*

2612 POSTER

Chemotherapy of metastatic or recurrent, locally advanced squamous cell carcinoma (SCC) of the anal canal: A multicenter study by the Association of Gastroenterologists Oncologists (AGEO) in 116 patients (pts)

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Background: We sought to define the chemotherapy (CT) regimens used and their effectiveness in the treatment of recurrent or metastatic anal SCC in a retrospective multicenter study.
Material and Methods: Were eligible pts with histologically proven anal SCC and local recurrence after initial treatment or with metastases treated by CT between January 1991 and April 2012. Primary and secondary endpoints were progression-free survival (PFS) and overall survival (OS), respectively.
Results: We enrolled 116 consecutive pts (women, 84; median age, 57 years; range, 23−84; local recurrence, 16; and metastases with or without local recurrence, 100) in five french centers. Metastases were synchronous in 18 of 100 pts (18%). Previous treatment was radiochemotherapy (RCT) (n = 74), radiotherapy (RT) (n = 17) or surgery alone (n = 2). A salvage surgery after RT/RCT was performed in 43 pts including 37 abdomino-perineal resections. The median PFS was 5.1 months. It was 4.6 months with platinum-based CT vs 7.6 months with platinum-free CT (n = 22) (p = 0.62). The median OS was 15.5 months. It was 15.1 months with platinum-based CT vs 19.3 months with platinum-free CT (p = 0.99). The median PFS and OS were respectively 4.7 and 15.0 months for pts with metachronous metastases or local recurrence vs 12.7 and 46.2 months in pts with synchronous metastases (n = 18) (p = 0.039 and p = 0.0057, respectively). Among 116 pts, 81 (69%) received second-line CT, mostly platinum-based (n = 21).
Conclusions: In this retrospective multicenter study (the largest reported to date), there was no statistically significant difference in OS or PFS according to the type of CT(with or without platinum). Pts with synchronous metastases had median OS and PFS significantly higher than pts with metachronous metastases or local recurrence, suggesting a development of resistance to CT. The majority of pts received second-line CT.
No conflict of interest.

2613 POSTER

A retrospective analysis comparing the treatment outcomes of gemcitabine and S-1 combination therapy to gemcitabine and cisplatin combination therapy in patients with advanced biliary tract cancer

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Background: Gemcitabine and cisplatin (GC) combination therapy became the standard of care for the treatment of advanced biliary tract cancer. In Japan, gemcitabine and S-1 (GS) combination therapy also showed good tumour efficacy in phase II setting, and a large phase III study comparing GS combination therapy to GC combination therapy are now planned. Before starting a prospective study, we conducted a retrospective analysis to compare the treatment outcomes of these two treatments.
Material and Methods: Advanced biliary tract cancer patients with performance status of 0 or 1 who were treated with GS combination

therapy or GC combination therapy were enrolled in this analysis. Treatment outcomes were compared between these two groups. Predictive factor for overall survival was also assessed using Cox proportional hazard model.
Results: One hundred eighteen patients were treated with GS combination therapy and thirty-nine patients were treated with GC combination therapy. Patient characteristics (age, sex, performance status, biliary site, disease status) were well balanced except age (median age; 68 for GS combination therapy, 73 for GC combination therapy; $p = 0.02$). Response rate of GS combination therapy was significantly higher than that of GC combination therapy (29% vs 8%; $p < 0.01$). Median time-to-progressions of GS and GC combination therapy were 5.7 months and 7.6 months, respectively ($p = 0.33$). Median overall survival of GS and GC combination therapy were 13.1 months and 9.7 months, respectively ($p = 0.13$). Based on the multivariate analysis, only performance status of one and gallbladder cancer were extracted as poor predictive factors of overall survival.
Conclusion: GS combination therapy showed better tumour shrinkage than GC combination therapy. Overall survival and time-to-progression were not statistically different between GS combination therapy and GC combination therapy. As previously reported, poor performance status and gallbladder cancer were extracted as poor predictive factors of prognosis.
No conflict of interest.

2614 POSTER

Multicentre randomized phase II trial of adjuvant imatinib for 6 versus 12 months in patients with intermediate or high risk GIST: Interim analysis results

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Background: Although the Z9001 study demonstrated that adjuvant imatinib for 1 year improved recurrence free survival (RFS) in GIST ($\geqslant$3 cm) patients and the SSGXVIII study showed that 3 years adjuvant imatinib improved RFS and overall survival (OS) for high risk GIST patients compared to 1 year adjuvant imatinib, there was no study to evaluate non-inferiority of shorter period of adjuvant imatinib than 1 year. We conducted a randomized phase II study to compare 6 months with 12 months adjuvant imatinib for intermediate or high risk GIST patients.
Material and Methods: Study design was an open-label randomized phase II trial conducted in 37 institutes in Japan. Eligibility criteria included ECOG-PS of 0 or 1, age between 20 and 79 years and histologically proven primary KIT-positive GIST with intermediate or high risk according to the Fletcher's risk classification. Patients were randomly assigned to the 6 or 12 months administration of imatinib 400 mg/day within 12 weeks after complete gross resection of a primary GIST, stratified by risk classification and primary site. The primary endpoint was RFS. We assessed non-inferiority of 6 months adjuvant imatinib compared with 12 months with a margin of hazard ratio 1.67, 1-sided alpha 0.2 and power 0.8.
Results: Ninety-two patients were randomly allocated into the 6 months group ($n = 45$) or the 12 months group ($n = 47$) between Dec 2007 and Aug 2011, which was well balanced for baseline characteristics. One patient was ineligible due to non-GIST (desmoid) tumor at a central review. The proportions of patients completed their assigned adjuvant treatment were 80% in the 6 months group and 70% in the 12 moths group. The first interim analysis was conducted at Sep 2012 with the median surveillance period of 33 months. Adjuvant imatinib was relatively tolerated, with one patient of Grade 4 rash and no treatment-related death. The 1- and 2-year RFS were 82% and 65% in the 6 months group and 96% and 86% in the 12 months group, respectively. Hazard ratio of recurrence was 1.81 (95% CI: 0.84–3.91), and the 2-sided log-rank p value was 0.12. A subset analysis according to the Fletcher's risk classification of primary GIST showed that Hazard ratio of recurrence in the 6 months group with intermediate and high risk was 1.15 (95% CI: 0.072–18.2) and 2.15 (95% CI: 0.96–4.81), respectively. Because of the lower efficacy of the 6 months adjuvant imatinib, the Data and Safety Monitoring Committee recommended the early release of first interim results.
Conclusions: Adjuvant imatinib for shorter period is not recommended at least for high risk GIST patients.
No conflict of interest.

2615 POSTER

Safety profile of erlotinib in a Japanese post-marketing surveillance study of pancreatic cancer patients (pts): Interim analysis of the first 313 pts of 855 pts enrolled

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Background: First-line erlotinib combined with gemcitabine is approved in Japan for the treatment of unresectable pancreatic cancer (PC). A surveillance study has been implemented to investigate erlotinib safety and efficacy in Japanese pts, focusing on the incidence of interstitial lung disease (ILD), highlighted in a Japanese Phase II study with an ILD incidence of 8.5% as an adverse drug reaction (ADR) of particular concern in this population.
Methods: Enrolment was from July 2011 to Aug 2012; observation period was 28 weeks. ADRs were defined as adverse events where erlotinib could not be ruled out as the cause. All events resembling ILD, excluding pts who did not have images available for analysis, were assessed by an independent committee. These interim safety analysis data are for pts enrolled prior to 28 Dec 2011.
Results: Of the 855 total enrolled pts, data from 313 pts with case report forms were obtained by 13 Apr 2013 for analysis. All pts were eligible for treatment of unresectable PC. Baseline characteristics included: male 56.2%; median age 65 yrs; any smoking history 41.8%; lung metastasis 18.0%; adenocarcinoma 97.9%; ECOG PS 0 69.7%. ADRs were reported in 82.7% of pts and the most common were skin disorders (64.5%), including rash (32.6%), and gastrointestinal disorders (31.6%), including diarrhoea (16.9%). 'ILD-like' events were experienced by 19 pts and ILD was confirmed by the independent ILD review committee in 18 pts (5.8% of the population), with a mortality rate of 0.64% (2 pts). 'ILD-like' events occurred throughout the observation period with an incidence of 21.1% within 4 weeks, 26.3% from 4−8 weeks, 31.6% from 8−12 weeks, and 21.1% >12 weeks from the start of therapy. This is in contrast to the highest ILD incidence occurring during the first 4 weeks (58.9%) in a Japanese post-marketing surveillance study (PMS) in non-small cell lung cancer (NSCLC) pts with a mortality rate of 1.54%. Data collection and analysis for this PC surveillance study are ongoing and further results for the 313 pts who have been registered as the interim safety evaluation population will be presented.
Conclusions: The interim safety profile of this surveillance study of erlotinib plus gemcitabine in Japanese PC pts was similar to previous clinical studies. In contrast to the PMS in NSCLC, ILD developed at various times during the observation period and showed a low mortality rate. This analysis provides the treatment profile of this population.
Conflict of interest: *Ownership: Stocks in Kissei Pharmaceutical Co Ltd (A Seki). Advisory board: Chugai Pharmaceutical Co Ltd (T Okusaka, J Furuse, A Gemma, T Hatori, W Ichikawa). Board of directors: N/A. Corporate-sponsored research: N/A. Other substantive relationships: A Seki is an employee of Chugai Pharmaceutical Ltd*

2616 POSTER

Intensified weekly paclitaxel, epirubicin, and cisplatin combination in neoadjuvant chemotherapy for resectable gastroesophageal cancer: A multicenter phase II trial (IPEC study)

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Background: Perioperative chemotherapy improves overall survival among patients with resectable, gastric and gastroesophageal adenocarcinoma

(GEA). However, more than 40% of the patients are not healthy enough to complete their post-operative chemotherapy.
Docetaxel demonstrated significant overall survival benefit in addition to cisplatin and 5FU in advanced GEA. The potential interest of taxanes in perioperative setting was recently suggested by two studies, providing an opportunity to optimize pre-operative chemotherapy in GEA. Then, we conducted a phase II trial to assess the feasibility of a dose-dense chemotherapy combining paclitaxel, epirubicin, and cisplatin as neoadjuvant treatment for resectable GEA (Trial registration: NCT01830270).
Material and Methods: GEA patients with>T1N0M0 disease were treated with eight preoperative cycles of intensified chemotherapy including paclitaxel 90 mg/m^2 Day 1, epirubicin 50 mg/m^2 Day 1, and cisplatin 30 mg/m^2 Day 1, every week. Primary prophylaxis by G-CSF was administered on day 3 to 5. Surgery was performed 4 to 6 weeks following the last cycle of chemotherapy. A complete resection rate higher than 79% was the primary endpoint. Secondary endpoints were safety, response rate, histological response rate (Becker score), PFS, and OS.
Results: 25 patients were analysed until the planned intermediate analysis. Median age was 64 (range, 43−83) and 6 patients (24%) presented signet-cell histology. Sixteen patients (64%) completed all 8 cycles and 80% received 7 or more cycles. Twelve patients (48%) experienced grade 3/4 neutropenia but only 1 patient had febrile neutropenia. Other grade 3/4 toxicities were rare. Twenty-three patients underwent surgery and a pathological complete response was observed for two of them, with nearly complete responses (Becker score 1b) for three other patients. A complete resection (R0 resection rate) was achieved for 82 % of the patients. PFS at 6 and 12 months were 94% and 74% respectively. 4 patients are died so far, including 2 disease-progression, a toxic death after surgery (pulmonary infection) and an angiocholitis-related sepsis diagnosed 4 months post-surgery.
Conclusions: Neoadjuvant, dose-dense, weekly paclitaxel-epirubicin-cisplatin regimen is feasible in resectable GEA and it met pre-planned criteria for intermediate analysis.
No conflict of interest.

2617 POSTER

A phase I/II study of biweekly docetaxel (D) combined with cisplatin and fluorouracil (CF) in patients (pts) with distant metastatic esophageal cancer (MEC)(JCOG0807)

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Background: Though a triplet chemotherapy of D plus CF (DCF) has shown superiority to CF in overall survival (OS), a high incidence of adverse events (AEs) especially in febrile neutropenia (FN) has been observed in previous trials (TAX324, 325). To reduce the incidence of AEs without reduction of efficacy, we conducted a multicenter open-label phase I/II study of a biweekly regimen of D plus CF for MEC and reported at ASCO2013 (S Hironaka et al). We herein report the results with subgroup analyses in OS.
Material and Methods: The main inclusion criteria included histologically proven MEC with measurable, metastatic or recurrent disease, age 20 to 75, and performance status (PS) 0 to 1. Patients (pts) received D (dose level (DL) 1: 30 mg/m^2, DL 2: 40 mg/m^2, on days 1, 15) combined with CF (cisplatin 80 mg/m^2 on day 1, fluorouracil 800 mg/m^2 on days 1−5) repeated every 4 weeks. The primary endpoint was dose limiting toxicity (DLT) in phase I part (P-I) and confirmed response rate (RR) defined by central peer review in phase II part (P-II). Based on a SWOG two stage design (p0=35%, p1=50%; one-sided α=0.1, β=0.2) at least 22 responders among 50 eligible pts should be observed to satisfy the primary endpoint. Subgroup analyses of OS were conducted with variables (recurrent, prior adjuvant chemotherapy (AC), number of baseline metastatic sites (No. of MS), only distant lymph node metastasis (DLN)).
Results: Between Feb 2009 and Jun 2011, 62 pts were enrolled in this study. In P-I, 10 pts were enrolled with DLT of 0/3 in DL1 and 2/7 in DL2. Considering DLT and treatment compliance, the recommended dose for P-II was determined as DL1. Then, 3 pts in P-I and 52 pts in P-II were analyzed: 53 for efficacy (excluding 2 ineligible) and 55 for safety. Pts characteristics were as follows: male/female 49/6, age median 61 (range 44−75), PS 0/1 39/16. The RR was 62% (95% confidence interval, 48−75%, p < 0.0001). Median OS and PFS were 11.1 and 5.8 months. No grade 3/4 FN was observed. Treatment related death occurred in one patient due to pneumonitis. In exploratory analyses, median OS was 11.5/9.2 months (metastatic/recurrent, p = 0.91), 9.2/11.5 months (AC +/−, p = 0.86), 14.0/9.3 months (No. of MS $\leqslant$1/2$\leqslant$, p = 0.010) and 13.3/10.5 months (DLN only/others, p = 0.14).
Conclusions: Biweekly D combined with CF showed promising efficacy and tolerability. A phase III study comparing DCF with CF is now planned and will also provide important information on these prognostic factors for MEC.
No conflict of interest.

2618 POSTER

Temozolomide plus capecitabine as salvage treatment for patients with advanced neuroendocrine tumors (NETs) in the community setting

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Background: Chemotherapy schemes based on streptozotocin and doxorubicin have been use widely in the past for the treatment of advanced NETs. Unfortunately, balance between efficacy and toxicity is clearly improvable. Novel combinations of cytotoxic agents like temozolomide and capecitabine, have shown promising antitumoral activity in retrospective series. We aimed to evaluate the efficacy and safety of this combination in patients with advanced NETs derived from the daily clinical practice.
Methods: We analyzed the clinical outcome of the 37 patients (pts) consecutively treated with temozolomide (150 mg/m^2 qo, days 10−14) plus capecitabine (1.000 mg/m^2 bid, days 1−14) every 28 days, between June-2008 and April-2013 in six referenced centers in Spain for the treatment of NETs under compassionate use.
Results: 24 pts (65%), were pancreatic primary NETs (pNETs). 10 pts (27%) were treated as first-line. 28 pts (77.7%) had ECOG 0 or 1 and 8 (22.3%) had ECOG 2. 1 pt (2.7%), 21 (56.8%), and 11 (29.7%) pts had low (G1), intermediate (G2) or high-grade (G3) respectively. Grade was not available in 4 pts (10.8%). Median administered cycles were 8 (range 1−26). At the time of the data cut-off (April-2013) 7 pts (18.9%) were still on treatment after a median follow up of 10.9 months. Fourteen of the 37 pts (37.8%) had partial response (PR) and 12 (32.4%) stable disease (SD) according to RECIST 1.1 criteria. Estimated median time to progression (TTP) was 9.4 months IC95% (5.3−13.6) in the intention to treat population. Thrombocytopenia was the most frequent toxicity found in grade 3 or more (8%). Other grade 3 toxicities according to CTCAE v4.0 were observed in less than 5% of pts. There were no toxicity-related deaths.
Conclusion: These encouraging results show a promising activity and a favorable safety profile of the combination of temozolomide and capecitabine in patients with advanced NETs of the daily clinical practice and deserves for further clinical research in the future.
No conflict of interest.

2619 POSTER

Sunitinib (S) and everolimus (E) in pancreatic neuroendocrine tumours (pNETs): A retrospective UKINETS study

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Background: Two randomised phase III trials in patients (pts) with progressive metastatic well-differentiated pNETS reported benefit in progression free survival (PFS) with S (median 11.4 months, HR 0.42,

Raymond NEJM 2011) or E (median 11.0 months, HR 0.35, Yao NEJM 2011), over placebo. S and E were funded in the UK through the Cancer Drugs Fund (CDF) in Dec 2010 and Sept 2011, respectively. Use of these agents through the CDF will inform on benefit out with trials, in real-world clinical practice.
Methods: Pts diagnosed with pNET and treated with either S or E were identified through the CDF register at individual NET centres between Dec 2010 − Dec 2012. Data was collected on pts demographics, clinical characteristics and PFS.
Results: A total of 82 patients (51 (62%) males, median age 58) were treated with 88 courses of therapy (6 pts received sequential S then E). Tumour grade was well-differentiated in 72, poorly-differentiated in 3 and unknown in 7 pts. Median time from diagnosis was 3.5 years; median follow-up was 7 months. Treatment history and clinical outcome by agent is shown (table). Univariate analysis showed that age, sex, previous surgery, previous or current somatostatin treatment and time from diagnosis were not significant for outcome.

Characteristic	S (n = 57)	E (N = 25)
No prior treatment	5 (9%)	4 (16%)
Prior treatment	52(91%)	21(84%)
Surgery (curative)	19 (33%)	7 (28%)
Surgery (palliative)	11 (19%)	8 (32%)
Somatostatin analogue current	14 (25%)	8 (32%)
previous	7 (12%)	1 (4%)
Liver directed therapy (TACE/RFA)	5 (9%)	3 (12%)
Radionuclide therapy	8 (14%)	4 (16%)
Chemotherapy/immunotherapy	32 (56%)	14 (56%)
S /sorafenib (on trial)	0 (0%)	7 (28%)
E (on trial)	1 (2%)	0 (0%)
Median duration of treatment (months)	5	3
Reason for cessation Disease Progression	30 (53%)	4 (16%)
Toxicity	7 (12%)	10 (40%)
Median PFS (months)*	8.8	8.9
Median PFS all patients (months)*	8.8	

*Excluding patients with poorly-differentiated tumours (n = 3).

Conclusions: Real-world efficacy of S or E in more heavily pre-treated, non-study pNET pts is lower but approaching published data with either agent. Longer follow-up will determine the long term benefit and assess the effect of cross-over between S and E.
Conflict of interest: *Advisory board: Novartis (Valle),Pfizer (Waters, Valle). Corporate-sponsored research: novartis(Valle). Other substantive relationships: sponsorship for esmo conference attendence-novartis (Waters, Wadesley)*

2620 POSTER

A multicenter phase II study of gemcitabine plus S-1 chemotherapy for advanced biliary tract cancer

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Background: Gemcitabine (GEM) plus cisplatin (CDDP) chemotherapy has been used worldwide as the first-line standard treatment for advanced biliary tract cancer (BTC). A previous phase II trial also suggested promising activity of *GEM plus S-1 chemotherapy* against advanced BTC.
The aim of this study was to evaluate efficacy and safety of GEM plus S-1 chemotherapy in patients with advanced BTC.
Methods: The eligibility criteria were as follows: histologically proven BTC, unresectable or recurrent disease, ECOG performance status (PS) of 0−1 regardless of pretreatment. Gemcitabine was administered intravenously at the dose of 1,000 mg/m^2 over 30 min on days 1 and 8, and S-1 was administered orally at the dose of 60/80/100 mg/day based on the BSA, from day 1 to day 14, every 3 weeks.
The primary endpoint was the response rate according to RESIST, ver. 1.1, and the secondary endpoints were the toxicity, progression-free survival (PFS) and overall survival (OS).
Results: A total of 38 patients were enrolled between August 2008 and November 2011. There were 19 men and 19 women, with a median age of 66 years (range, 44−81 years). Seven patients had a previous history of first-line or adjuvant chemotherapy after surgery. The PS was 0 and 1 in 30 and 7 patients, respectively. There were 6 cases with confirmed partial response (15.8%) and 18 patients (47.4%) with stable disease. The median PFS and OS were 5.8 and 15.9 months, respectively. The toxicity was generally mild, and the most common grade 3/4 toxicities were leukopenia (31.6%), neutropenia (36.8%), nausea and vomiting (2.6%) and diarrhea (2.6%). There was one treatment-related death due to interstitial pneumonia.
Conclusion: Gemcitabine plus S-1 chemotherapy was well-tolerated and exhibited favorable antitumor activity in patients with advanced BTC.
No conflict of interest.

2621 POSTER

Multicenter phase 2 study of TAS-102 monotherapy in patients with pretreated advanced gastric cancer

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Background: TAS-102 is a novel oral nucleoside antitumor agent, which showed promising activity in a randomized phase 2 trial for pretreated colorectal cancer. Although a previous study of TAS102 for gastric cancer showed disappointing results (only one SD in 18 patients), the evaluated dose was lower than that recommended on Japanese phase 1 trial and used in phase 2 trial for colorectal cancer. Therefore, we investigated efficacy and safety of TAS-102 for gastric cancer patients with the same dose schedule as that for colorectal cancer.
Patients and Methods: We conducted a multicenter phase 2 study of TAS-102 monotherapy in patients with pretreated advanced gastric cancer. All the patients had a treatment history of fluoropyrimidine and platinum and a treatment history of taxane or irinotecan. TAS-102 of 35 mg/m^2 was orally administered twice a day in a 28-day cycle (2-week cycle of 5 days of treatment, followed by a 2-day rest period and then a 14-day rest period). The primary objective of this study was to evaluate the disease control (CR, PR, and SD) rate (DCR) at 8 weeks as the null hypothesis of 30%. The response rate (RR), PFS, OS, safety, and pharmacokinetic parameters were also evaluated as secondary objectives.
Results: A total of 29 patients (median age, 64 years; performance status 0/1 = 20/9) were assessable. One patient achieved PR, and other 18 patients had SD. DCR and RR was 67.9% (95% CI, 47.6% to 84.1%) and 3.6% (95% CI, 0.1% to 18.3%), respectively. Median PFS was 2.9 months (95% CI, 1.1 to 5.3 months). Common grade 3 or 4 adverse events included neutropenia, leukopenia, anemia, and anorexia, which were profiles similar to those of TAS-102 in patients with colorectal cancer. Only one case of febrile neutropenia was observed, and no treatment-related deaths occurred.
Conclusions: TAS-102 monotherapy resulted in a promising DCR and acceptable toxicity profile in patients with pretreated advanced gastric cancer. A higher dose of TAS-102 may have a positive effect on patients with advanced gastric cancer, and further confirmatory trials are required.
No conflict of interest.

2622 POSTER

Lack of association between ERCC1 expression in biliary tract malignancy and response to chemotherapy

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High tumor expression of the excision cross-complementing gene-1 (ERCC1) has been associated with resistance to platinum-based regimens in many solid tumors such as lung and colorectal cancer. The predictive and/or prognostic value of this biomarker in biliary tract malignancy (BTC) is unknown.
We retrospectively evaluated all consecutive patients (pts) with advanced/metastatic BTC who received first line gemcitabine and cisplatin (GC) at the Instituto do Cancer do Estado de São Paulo, Brazil, in a 3 year-period. Pts had their paraffin-embedded tumor tissues tested for ERCC1 immunohistochemistry (IHC) expression. Such expression was scored

based on its extension and its intensity of staining. Extension was scored from 0 to 4 (0: negative, 1: 0−25%, 2: 25−50%, 3: 50−75% and 4: 75–100%) and intensity, from 1 to 3 (1: weak, 2: moderate and 3: strong); the final score was the product of each result. Tumor response was measured by RECIST 1.1. The predictive value of ERCC1 was evaluated through comparison of the proportion of pts who responded to treatment with high/ positive ERCC1 expression vs low/negative, using the Chi-2 test. The prognostic effect of ERCC1 was explored by a Cox regression model, considering the ERCC1 expression as a continuous variable.
From June 2009 to June 2011, 75 pts received GC of whom 44 had their pathology material evaluable. Median age was 59 years [range: 32−80], and 59% were female. Nearly half (55%) of pts experienced clinical benefit (complete response [CR], partial response [PR] and stable disease [SD]) from GC treatment. 48% had positive ERCC1 IHC expression (score $\geqslant$2). ERCC1 expression was not associated with either clinical benefit or tumor response. The mean score of IHC expression was 2.65 for those who had PD and 4.0 for pts with clinical benefit (p = 0.28, OR 1.09 [IC − 95%: 0.93–1.26]). When comparing pts with PD and SD vs CR/ PR, the mean ERCC1 expression was also not different: 3.0 vs. 4.6 (p = 0.25, OR 1.1 [IC − 95%: 0.94–1.29]. ERCC1 expression did not influence pts survival (p = 0.349 HR 0.96 [IC − 95%: 0.88–1.05]).
Our results suggest that ERCC1 IHC expression in advanced BTC patients is neither a prognostic nor a predictive factor for the efficacy of CG regimen.
No conflict of interest.

2623 POSTER

A randomized phase II study of S-1 monotherapy or S-1 plus leucovorin as 2nd line chemotherapy in patients with advanced pancreatic cancer

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Background: Gemcitabine-based chemotherapy has been the standard treatment as 1st line for advanced pancreatic cancer. So far, the role of 2nd treatment after gemcitabine-based chemotherapy failure is unclear. S-1, as an oral fluoropyrimidine has shown comparable efficacy as compared with gemcitabine in 1st line setting, suggesting probable role of S-1 as a salvage therapy after gemcitabine failure. We conducted this randomized phase II study to verify the hypothesis the efficacy of the S-1 plus leucovorin (SL regimen) is superior to S-1 monotherapy as 2nd line therapy in patients with advanced pancreatic cancer.
Methods: Eligible patients had histologically or cytologically confirmed advanced pancreatic cancer, PS 0−2, previous gemicitabine-based regimen 1st line treatment failure, with adequate hematologic, hepatic and renal function. S-1 was administrated 40 mg/m ^{2} BSA twice a day on days 1−14 (Arm A) or plus LV 25 mg twice a day on days 1−14 (Arm B), followed by 7 days interval. The primary endpoint was overall survival (OS). Secondary endopints were progression-free survival(PFS), response rate(ORR), disease control rate (DCR), clinical benefit rate (CBR), safety, and quality of life (QoL).
Results: Eighty-one patients from 5 hospitals were enrolled between May 2010 and November 2012. Median OS and PFS were 5.7 and 3.1 months in Arm A and 7.1 and 3.8 months in Arm B (p = 0.571, HR 0.856 for OS, p = 0.884, HR 1.040 for PFS). ORR, DCR, and CBR were 5.3%, 55.2%, and 27.6% in Arm A and 6.1%, 66.7%, and 27.3% in Arm B (p = 0.638 for ORR, p = 0.211 for DCR, p = 0.978 for CBR). 7.1% patients in Arm A and 15.4% in Arm B discontinued treatment due to drug toxicities. All grade toxicities were 97.6% in Arm A and 100% in Arm B (p = 0.338). The major adverse events (AEs) were anorexia, stomatitis, fatigue, nausea, diarrhea, and neutropenia. Arm B had more grade 3/4 AEs than Arm A (30.9% vs 53.9%, p = 0.035). Biomarker research data was avaliable in 79 patients.
Conclusions: S-1 monotherapy or SL regimen is effective and tolerable as 2nd line therapy in patients with advanced pancreatic cancer. The addition of LV to S-1 resulted in a modest OS prolongation, but no significant difference(P = 0.571, HR 0.856). This study is still ongoing, and the biomarker research data will be presented also.
No conflict of interest.

2624 POSTER

A phase 1/2 study of S-1 with sorafenib in advanced hepatocellular carcinoma

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Background: Sorafenib was only drug, which was approved as effective systemic chemotherapy for patients with advanced hepatocellular carcinoma (HCC). But, the prognosis of advanced HCC patients is still poor. Development of more effective treatment is necessary for them. So, we conducted a phase 1/2 study of S-1with sorafenib in advanced HCC.
Method: S-1 was administered twice daily each day for day 1−14 and sorafenib was administered every day. This was repeated every 21 days. In part 1, we determined the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs). Dose of each drug was planned as follows: cohort 1: 48 mg/m^2/day/400 mg qd,2a: 48 mg/m^2/day/400 mg bid,2b: 64 mg/m^2/day/400 mg qd,3: 64 mg/m^2/day/400 mg bid,4: 80 mg/m^2/day/400 mg bid (S-1/sorafenib). In part 2, patients are being treated at the MTD to evaluate safety and efficacy.
Results: In part 1, 19 patients were enrolled. 1 in 6 patients at cohort 1 experienced DLT (increased transaminase). 0 in 3 patients at cohort 2a experienced DLT. 1 in 6 patients at cohort3 experienced DLT (bleeding). 3 in 3 patients at cohort 4 experienced DLT (2 hand foot skin reaction and 1 infection). So, cohort 3 was considered MTD. In part 2, 26 patients were enrolled. Most common grade 3/4 toxicities were aspartate aminotranspherase increased (38.5%), thrombocytopenia (23.1%), neutropenia (19.2%), blood bilirubin increased (15.4%), alanine aminotranspherase increased (15.4%), hyponatremia (11.5%), rash (11.5%) and hypophosphatemia (11.5%). Sudden death was occurred in one patient (3.8%). One (3.8%) was considered as PR, 15(57.7%) as SD and 10(38.5%) as PD. The median TTP and OS were 2.4 and 10.5 months, respectively.
Conclusion: The MTD of S-1 and sorafenib in patients with advanced HCC was 64 mg/m^2 /day and 400 mg bid, respectively. But, its toxicities were slightly severe and its effect does not seem to be improved than sorafenib alone.
Conflict of interest: *Other substantive relationships: O. Yokosuka: Research grants: Bayer*

2625 POSTER

A multicentre retrospective analysis of single agent nab-paclitaxel (nab-P) in heavily pretreated pancreatic cancer (aPDAC) patients (pts)

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Background: No standard treatment exists in pretreated aPDAC pts, who have already received available active drugs. *nab*-P has shown to improve survival in combination with GEM in first line and to be active in GEM-resistant aPDAC pts.
Material and Methods: aPDAC pts who received off-label single agent *nab*-P (125 or 100 mg/m^2 over 30 minutes on days 1, 8, and 15 of a 28-day cycle) as 2nd or further line of treatment for metastatic disease in three Italian centers were retrospectively reviewed.
Results: 29 pts were identified (M/F: 16/13; median age: 66 yrs, range: 39−83); >50% of pts had an ECOG PS 2; median number of previous treatment lines: 2 (range 1−5); 7 pts had received Folfirinox as first line. *nab*-P starting dose was 125 mg/m^2 in 5 pts and 100 mg/m^2 in the others. A median of 2 cycles (range 1−10) were administered. Two partial responses (44 and 46-wk duration) were observed; 4 pts had stable disease SD (9, 16, 23, 28-wk duration, respectively); 5 pt are presently not evaluable. Median and mean progression free survival (PFS) were 8 (95% CI: 5−11) and 13 (95% CI: 7−18) wks, respectively; median and mean overall survival (OS) were 13 (95% CI: 9−17) and 25 (95% CI: 15−35) wks, respectively. Three- and 6-month PFS rates were 33% and 15%, respectively; 6- and 12-month OS rates were 36% and 22%, respectively. Toxicity was mild with G4 neutropenia in 1 pt and G3 neuropathy in 1 pts. With at least 10 out of 29 pts free from progression at 3 months (3-month PFS rate: 35%), our results satisfy the following post-hoc statistical hypothesis: p0: 15%, p1: 35%, a: 5%, 1-b: 80%, according to A'Hern exact single stage phase II design.

Conclusions: *nab*-P is well tolerated and moderately active, even in heavily pretreated aPDAC pts. Further analyses are warranted, especially to identify the small proportion of pts who derive exceptionally prolonged benefit from *nab*-P monotherapy.
No conflict of interest.

2626 POSTER

An open, multi-center, phase II clinical trial to evaluate efficacy and safety of S-1 plus split cisplatin in patients with advanced gastric cancer (AGC) − HGCSG0702 preliminary report

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Background: From the results of SPIRITS trial, S-1 plus cisplatin has been regarded as standard first-line chemotherapy for patients with AGC in Japan (Koizumi W, et al. Lancet Oncol, 2008). However, conventional S-1 plus cisplatin regimen requires hospitalization for hydration. Therefore, in Hokkaido Gastrointestinal Cancer Study Group (HGCSG), to investigate the safety and efficacy, we conducted a multicenter phase II clinical trials of S-1 plus split cisplatin as a therapeutic strategy that can be administered in the outpatient clinic.
Methods: Eligibility criteria included pathologically confirmed AGC; no prior chemotherapy; Age 20 to 75, ECOG performance status (PS) of 0 to 1; adequate organ function; and written informed consent. S-1 (40−60 mg depending on patients' body surface area) was given orally, twice daily for 3 consecutive weeks, and 30 mg/m^2 cisplatin was given intravenously on day 1 and 15, followed by 2-week rest period, within a 5-week cycle. Primary endpoint was the response rate (RR), and secondary endpoints were progression-free survival, overall survival, safety profile, and duration of hospitalization.
Results: Between Mar 2008 and Mar 2012, 40 pts were enrolled. Patients characteristics were as follows: median age 63 years (range 41−75), Male: female 30:10, PS 0:1 33:7, diffuse: intestinal 23:17, initially unresectable: recurrent 31:9. Median no. of cycles was 3. The most common non-hematological adverse events (AE) were anorexia (70%), nausea (60%), fatigue (60%) and diarrhea (47.5%) and hematological AE were anemia (87.5%), neutropenia (82.5%), leukocytopenia (67.5%) and thrombocytopenia (60%). The main grade 3−4 AE were neutropenia (40%), anemia (30%), anorexia (30%) and fatigue (15%). These toxicities were safely managed. The median relative dose intensity of S-1 was 0.782, and cisplatin was 0.824. No treatment-related death was observed. Response rate was 57.5% (95% CI 42.2–72.8%) and disease control rate was 90.0%. Median progression-free survival was 6.1 months (95%C.I. 3.0−9.1 months).
Conclusions: We conclude that this S-1 plus split cisplatin regimen was highly active and tolerated in the treatment of AGC, and most patients could be administered in the outpatient clinic. Based on those result, we are planning the further study.
Conflict of interest: *Advisory board: Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Yakult Honsha Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Merck Serono Co., Ltd., Bristol-Myers Squibb Co., Pfizer Japan Inc., Novartis Pharma K.K., Sawai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd. Corporate-sponsored research: Taiho Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Novartis Pharma K.K., Yakult Honsha Co., Ltd., Daiichi Sankyo Co., Ltd., Merck Serono Co., Ltd., Takeda Pharmaceutical Co., Ltd., Kureha Corporation. Other substantive relationships: Synergy International, Inc.*

2627 POSTER

Safety and pharmacology of gemcitabine and capecitabine in patients with advanced pancreatico-biliary cancer and hepatic dysfunction

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Background: The study prospectively assessed the impact of hepatic dysfunction (HD) on the safety and pharmacology of gemcitabine and capecitabine in advanced pancreatico-biliary cancer, a condition that is of substantial clinical relevance (EKSG 08–087).
Materials and Methods: We included 12 patients with advanced pancreatico-biliary cancer receiving 3-weekly gemcitabine 1,000 mg/m^2/30min on day 1 and 8, and oral capecitabine 650 mg/m^2 b.i.d. over 2 weeks until disease progression or dose-limiting toxicity (DLT). Patients were included into one cohort with normal liver function (cohort 1, total bilirubin (TB) $\leqslant$15 μmol/L) and 3 cohorts with increasing HD, i.e. cohort 2 with a TB of 16−39 μmol/L, cohort 3 with a TB of 40−80 μmol/L and cohort 4 with a TB >80 μmol/L. Gemcitabine and dFdU were sampled at 15, 30, 60 and 90 minutes after the start of infusion on day 1 and 8. Intracellular gemcitabine triphosphates (dFdCTP) were measured in peripheral blood mononuclear cells 30 minutes after gemcitabine. Capecitabine (CAP), 5′-deoxy-5-fluorocytidine (DFCR), 5′-deoxy-5-fluorouridine (DFUR) and 5-fluorouracil (5FU) were sampled at 0.5, 1, 2, 3 and 4 hours after oral intake, as well as at steady-state on day 8. All compounds were analyzed using validated (HP)LC-MS/MS methodology, and submitted to population pharmacokinetic analysis using the NONMEM software version VII.
Results:: The reason for HD was intrahepatic cholestasis in 4 out of 8 patients (50%) and extrahepatic cholestasis in another 4 patients (50%). DLT was a further increase of TB (n = 2) and severe neutropenia (n = 2), but DLT resulting in dose reduction of any of the two drugs was not associcated with HD (Table). There was no significant increase of severe hematological or non-hematological toxicity with HD (Table). Gemcitabine clearance (CL) significantly decreased with increasing HD, but capecitabine CL did not (Table). Intracellular dFdCTP concentrations decreased with more severe HD (p = 0.001). One out of 3 patients with CCL<60 ml/min experienced DLT.
Conclusions: Gemcitabine/capecitabine can be given in patients with severe HD, but gemcitabine's activity is potentially limited due to poor intracellular activation. In patients with severe HD, initial monotherapy with capecitabine may be an option, followed by the addition of gemcitabine in case of improving hyperbilirubinemia.
No conflict of interest.

	Cohort 1 (n = 4)	Cohort 2 (n = 2)	Cohort 3 (n = 3)	Cohort 4 (n = 3)	p-value (ANOVA)
Severe myelosuppression	3	0	2	1	0.3
Severe non-hematological toxicity	0	1	1	3	0.07
Any dose reduction	1	0	1	2	0.55
CL gemcitabine (L/h)	235	227	185	105	0.02
CL capecitabine (L/h)	340	243	169	163	0.41

2628 POSTER

Implementation of a nurse-driven educational program improves management of sorafenib's toxicities in hepatocellular carcinoma

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Background: Sorafenib is the standard of care for advanced hepatocellular Carcinoma (HCC). This drug is orally-given and associated with substantial toxicity, emphasizing the need for proper supportive care. We aimed to improve usual care by adding an educational program (EP) driven by trained nurses.
Material and Methods: Since January 2011, after deciding treatment with sorafenib, gastrointestinal oncologists referred patients to the EP. Patients were seen by the clinical nurses before the first administration in a one-hour visit. The nurses also communicate with the general practitioner. Patients were followed with weekly phone calls and with a 30-minutes

interview before every oncologist visit. In this study, we retrospectively compared safety data from patients treated with sorafenib for HCC in 3 contexts: followed with the EP, with usual care (UC), or in clinical trials (CT). Comparisons were made by a Pearson's Chi-2 test.
Results: Since 2008, 129 patients were treated at our institution with sorafenib for HCC, 31 (24%) in the EP, 22 (17%) in CT and 76 (59%) with UC. Patients treated in the EP and in CT were more frequently treated for hypertension (19% and 23% respectively vs 0% for UC, $p < 0.001$ for both). Moreover, 71% of patients in the EP had toxicities identified during the phone call, which prompted symptomatic measures in 65% of patients and leaded to sorafenib dosing modification before the planned on-site visit in 29% of patients. Patients followed with the EP required less dose reductions (39% vs 61% for UC, $p = 0.04$). The median time to first dose reduction was shorter with EP than with UC (25 vs 45 days, $p = 0.04$). There was also a trend toward less treatment delay (19% vs 34%, $p = 0.13$) and toward less treatment discontinuation for toxicity (26% vs 36%, $p = 0.33$). These trends do not appear in patients in CT (dose reduction 46%, $p = 0.21$, treatment delay 36%, $p = 0.85$, cessation for toxicity 32%, $p = 0.75$). However, there was no difference in the incidence of severe toxicities (48% for EP vs 50% for CT vs 42% for UC, $p = 0.73$) or hospitalization for toxicity (7% for EP vs 18% for CT vs 11% for UC, $p = 0.40$).
Conclusion: Albeit retrospective, this study provides evidence for a clinical benefit of the EP, with a better management of toxicities leading to a quicker reaction and less dose reductions. These results represent meaningful improvement of patient tolerability of the treatment. However, this did not translate in decrease of major toxicities.
No conflict of interest.

2629 POSTER

Correlative study of mTOR inhibition with temsirolimus and tumour stathmin expression for unresectable hepatocellular carcinoma (HCC)

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Background: HCC is a common cause of cancer morbidity and mortality. The oncogenic PI3K/Akt/mTOR pathway is frequently activated in HCC. Preliminary studies on mTOR inhibitors such as temsirolimus show promising results but there is limited data on potential biomarker to predict clinical benefit of temsirolimus in HCC patients. It has been observed loss of PTEN, the negative regulator of PI3K, results in robust activation of this pathway. Stathmin, encoded by the signature gene STMN1, has been suggested to be an accurate IHC marker of the PTEN signature with a potential role as a prognosticator. Thus, evaluation of stathmin may be an effective way to quantitatively measure PI3K pathway. The objective of this study is to evaluate if stathmin overexpression is correlated with therapeutic efficacy of temsirolimus.
Materials and Methods: We have conducted a phase I/II study to examine temsirolimus in advanced HCC. Major eligibility criteria included histologically confirmed HCC that is not amenable to curative treatment. Pre-treatment tumour biopsies were collected. Phase I portion identified 25 mg weekly every 3 weeks to be the maximum tolerated dose. Phase II adopts a single arm design, the clinical endpoints were response rate, disease stabilization (PR/CR/SD $\geqslant$12 weeks), PFS and OS. Reassessment CT scans were done every 6 weeks. OS and PFS were calculated using the Kaplan–Meier method.
Results: A total of 36 patients were enrolled. The median follow-up was 17.0 months. 52.8% received $\geqslant$1 line of prior systemic therapies All had Child's A cirrhosis. 34 patients had pre-treatment HCC biopsies available for marker analysis. The PR and SD rates were 2.8% (1/35) and 57.1% (20/35) respectively. Disease stabilization rate was 38.9%. The median PFS and OS were 2.83 and 8.88 months respectively. Biomarker analysis for stathmin revealed that disease stabilization rates in tumors having high and low stathmin histoscores were 33.3% and 53.8%%, respectively ($p = 0.2376$). There was no difference in PFS and OS among pts with/without stathmin overexpression.
Conclusions: In this patient population, stathmin overexpression did not correlate with clinical outcomes. Further studies to identify patient subgroup that will benefit from this agent are warranted.
Sponsor: Pfizer Corporation Inc.
Conflict of interest: *Corporate-sponsored research: The study was sponsored by Pfizer Corporation Inc.*

2630 POSTER

Phase II study of salvage mFOLFOX (5-fluorouracil, leucovorin, oxaliplatin) in patients with unresectable biliary tract cancer who had failed gemcitabine

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Background: We conducted a phase II trial of 5-fluorouracil and oxaliplatin combination chemotherapy as a second-line treatment in unresectable biliary tract cancer (BTC) patients who had failed gemcitabine-based chemotherapy.
Material and Methods: Patients treated with gemcitabine-based palliative treatment were enrolled in this study. Patients received oxaliplatin 85 mg/m^2 (2-hour intravenous infusion, Day 1) and leucovorin 30 mg intravenous (Day 1, 2) followed by 5-fluorouracil 1,500 mg/m^2 (23-h continuous infusion, Day 1, 2) every 2 weeks.
Results: Between March 2010 and June 2012, a total of 30 patients were enrolled in this study. Twenty-nine patients were evaluable for treatment response. One achieved complete response and no partial response was observed. By the intent-to-treat analysis, the overall response rate (ORR) was 3.3% (95% confidence interval [CI]: 0.08–17.2%). Stable disease was observed in 12 patients (40%), and 15 patients (50%) had progressive disease. The median follow-up duration was 4.2 months (range: 0.8–11.3 months). The median progression free survival (PFS) was 1.6 months (95% CI: 1.5−1.7 months), and the median overall survival (OS) time was 4.4 months (95% CI: 2.6−6.2 months). Grade 3/4 hematologic toxicities included neutropenia (20%), thrombocytopenia (10%) and anemia (3.3%) per patient. Grade 3 non-hematologic toxicities included hyperbilirubinemia (13.3%), increase of alkaline phosphatase (3.3%), diarrhea (6.6%), fatigue (3.3%) and vomiting (3.3%) per patient, respectively. One treatment-related death due to neutropenic infection was occurred.
Conclusions: Despite the first phase II study of salvage chemotherapy for patients with Gemcitabine refractory BTC, the results in terms of ORR, PFS, and OS were lower than expected. Together, we do not recommend further evaluation of this regimen as salvage treatment for patients with unresectable BTC who had failed gemcitabine.
No conflict of interest.

2631 POSTER

Extra- and Intra-hepatic biliary tract adenocarcinoma: Surgery alone versus surgery plus postoperative therapy

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Background: Complete surgical resection provides the only possibility of cure in extra- and intrahepatic biliary tract adenocarcinoma. However, even in patients undergoing curative resection, the prognosis has remained poor. Given these poor outcomes, adjuvant therapy should be considered for these patients. However, the benefits of adjuvant therapy for those patients have remained unclear. The aim of this retrospective review was to evaluate the effect of adjuvant therapy versus surgery alone in patients with resectable biliary tract adenocarcinoma.
Material and Methods: The study involved 97 patients with biliary tract adenocarcinoma (BTA) undergoing curative resection between March 2010 and December 2012. The patients with BTA were included gall bladder cancer, intrahepatic bile duct cancer, perihilar bile duct cancer, distal bile duct cancer, and ampull of Vater cancer. Of the 97 patients, 49 received adjuvant chemoradiotherapy (CRT), chemotherapy, or radiotherapy (adjuvant therapy group) and 48 did not (surgery alone group). Recurrence-free survival (RFS) and overall survival (OS) was analyzed according to the presence of adjuvant therapy. Subgroup analyses were performed according to primary tumor sites.
Results: Baseline clinicopathologic characteristics were comparable between two groups, except age. The patients aged $\leqslant$65 years were more likely to have received adjuvant therapy than >65 years old ($p = 0.001$).

In adjuvant therapy group, CRT was 29 patients (59.1%), chemotherapy only was 19 patients (38.8%) and radiotherapy only was 2 patients (4.1%). With a median follow-up duration of 14 months for all patients, recurrence was developed in 21 patients (42.9%) of adjuvant therapy group, and in 25 patients (52.1%) of surgery alone group. For all patients, 1-year RFS and OS were 39.5% and 60.9%, respectively. The median RFS was 1-year survival rate were 14.5 months and 62.3% in adjuvant therapy group and 13.6 months and 57.4% in surgery alone group, respectively (p=o.623, $p = 0.279$). In subgroup analysis, the patients with distal bile duct cancer who received adjuvant therapy group tended to be higher 1-year RFS (57.7% versus 30.3%, $p = 0.06$) and OS (82.5% versus 61.4%, $p = 0.058$) than those who underwent surgery alone.
Conclusions: Adjuvant therapy might not be useful in patients with biliary tract adenocarcinoma after surgery. However, for those patients with distal bile duct cancer, adjuvant therapy deserves to consider after surgery.
No conflict of interest.

2632 POSTER

Capecitabine/5-fluorouracil and oxaliplatin (XELOX/FOLFOX): Suitable treatments for progressing G1-G2 neuroendocrine tumors

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Background: Beyond the usual regimens based on streptozocin and doxorubicin or 5-fluorouracil, no second-line therapy for metastatic neuroendocrine tumor (NET) has gained wide acceptance. Oxaliplatin plus 5-Fluorouracil (FOLFOX) or oral capecitabine (XELOX) have been evaluated in limited phase II studies in NET. We evaluate our experience in metastatic well differentiated G1 G2 NET patients (pt) treated with these chemotherapy regimens.
Materials and Methods: From October 2005 to February 2013, eighteen consecutive NET pt with progressive disease after failure of somatostatin analog (SSA) therapy and/or chemotherapy, targeted therapy, Peptide Receptor Radionuclide Therapy were treated with FOLFOX or XELOX. The primary tumor site was pancreas in 5 pt, gastrointestinal tract in 7 pt, lung in 3 pt, and unknown in 3 pt. Pt received oxaliplatin e.v. 130 mg/mq i.v. g1 and capecitabine 1000 mg/mq/die os gg1−14 (XELOX) or oxaliplatin e.v. 85 mg/mq i.v. g1 5-fluorouracil 2800 mg/mq ev 48 h gg1−3 q21 (FOLFOX). Patients were followed for evidence of toxicity, response assessed using RECIST criteria, and survival.
Results: Four (22.2%) out of 18 pt had a partial response, 9 pt (50%) showed stable disease, and 5 (27.8%) pt showed progressive disease; median progression-free survival was 8.23 months, 1 patient is still in treatment.
Median number of cycles was 5 (2−10). At a median follow-up of 46 months, median OS is 24 months (10 patient are still alive). G1-G2 toxicities were diarrhea, nausea, asthenia, neutropenia, neurotoxicity; main G3-G4 toxicities was neurotoxicity (5%) and diarrhea (11%).
Conclusions: XELOX or FOLFOX showed interesting activity and efficacy in pretreated patients with progressive NET, also after many previous treatments, with acceptable toxicity.
No conflict of interest.

2633 POSTER

Serum alpha-fetoprotein (AFP) level is a prognostic factor for advanced gastric cancer

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Backgrounds Gastric cancer is one of the most common AFP-producing cancers, reported having highly metastatic potent and a poor prognosis. Tissue AFP staining is not always evaluated in daily practice, and gastric cancer tissue has various degrees of heterogeneity. It is not clarified that the correlation between the serum AFP level and clinical outcome in advanced stage.
Objective: To explore the prognostic value of serum AFP in advanced gastric cancer.
Patients and Methods: Patients included that with histologically proven unresectable or recurrent gastric cancer, administered chemotherapy from January 2001 to Jan 2012 in Hokkaido University Hospital, and was obtained serum AFP level before treatment. The serum level of AFP was measured by using commercial kits with cut-off values of 10 ng/ml.
Survival analyses were performed with Kaplan–Meier method, log-rank test and Cox proportional hazards model.
Results: Of 153 pts were able to evaluate for this analysis. Patient's characteristics were as follows: male/female 114/39, median age 64 (range 24−85), ECOG PS (0 /1/ 2-) 93/39/21. Thirty-four patients were above normal upper limit of serum AFP. Elevated AFP group showed shorter survival time (MST 10.5 vs. 13.9 months, p = 0.03) than AFP normal group, but in Cox multivariate analysis, AFP elevation did not show independent prognostic impact (relative hazard: 1.36, 95% CI: 0.87–2.14, p = 0.18).
Conclusion: AFP elevation before treatment was not correlated to the poor prognosis for the patients with advanced gastric cancer in this analysis.
Conflict of interest: *Advisory board: Yakult Honsha, Taiho Pharmaceutical, Chugai Pharma, Merck Serono, Pfizer, Novartis, Sawai, Ono Pharmaceutical, Daiichi Sankyo, Takeda. Corporate-sponsored research: Yakult Honsha, Taiho Pharmaceutical, Lily, Novartis, Daiichi Sankyo, Takeda, Merck Serono, Kureha*

2634 POSTER

Gemcitabine after failure of cisplatin plus pemetrexed in patients with malignant peritoneal mesothelioma: A single-center experience

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Background: Malignant peritoneal mesothelioma (MPeM) is an extremely rare cancer. No established standard treatment exists for this disease, and it is treated in the same way as malignant pleural mesothelioma (MPlM). For MPlM patients, cisplatin plus pemetrexed (CP) combination chemotherapy is the standard first-line chemotherapy, and gemcitabine (GEM) has been recommended by the National Comprehensive Cancer Network Guideline as a post-treatment option. However, as far as we know, there have been no reports of the use of GEM in MPeM. Here, we evaluated the efficacy and safety of GEM in MPeM patients who had failed CP therapy.
Materials and Methods: MPeM patients who had received GEM at our hospital after failure of CP therapy were reviewed retrospectively. GEM was given 1000 mg/m^2 weekly for 3 out of every 4 weeks until progressive or unacceptable toxicity occurred. Tumor response and adverse events were evaluated with RECIST ver. 1.1 and CTCAE ver. 4.0, respectively. Progression-free survival (PFS) and overall survival (OS) were estimated by using Kaplan–Meier methods.
Results: Between February 2007 and January 2013, 24 patients received CP as a first-line treatment. Seven of these 24 patients received GEM after failure of CP. The characteristics of these 7 patients were as follows: median age, 59 years (range 43−65 years); performance status, 0/1/2 = 2/4/1; pathologic diagnosis: epithelial/sarcomatoid/unknown = 4/2/1; and second-line/third-line treatment = 4/3. The response rate was 14% (partial response/stable disease/progressive disease = 1/3/3) and the disease-control rate was 57%. The median number of doses of GEM was 2 (range 2 to 106); all patients discontinued GEM because of progressive disease. Median PFS was 3.2 months (95% CI: 0.0−8.1 months) and median OS was 6.4 months (95% CI: 2.2–10.6 months). Grade 3 or more adverse events were observed in only 1 patient (Grade 3 anorexia).
Conclusion: GEM appears to have activity with mild toxicity in MPeM patients who fail CP therapy.
No conflict of interest.

2635 POSTER

JASPAC 02: A phase II study of gemcitabine and oxaliplatin (GEMOX) for gemcitabine-refractory advanced biliary tract cancer

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Background: Gemcitabine (GEM) -based chemotherapy has been widely used in the first-line treatment for advanced biliary tract cancer (BTC). However, no standard second-line regimen after disease progression has been established and prognosis for such patients remains very poor with reported median survival times of 5.6−7.5 months. This study evaluated the

efficacy and safety of GEMOX, with a fixed dose rate of GEM combined with oxaliplatin (OX), for GEM-refractory BTC (UMIN000003650).
Patients and Methods: Patients with GEM-refractory BTC (gallbladder [GB], intrahepatic biliary duct [IHBD], extrahepatic biliary duct [EHBD], ampulla of Vater [AV]), an ECOG PS of 0−1, and adequate organ function, were eligible. Patients received GEM (1,000 mg/m^2 [10 mg/m^2/min]) followed by OX (100 mg/m^2) intravenously every 2 weeks until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) by RECIST v1.1. Planned sample size of 40 provided 80% power to reject the ORR of 5% under the expectation of 15% with one-sided alpha of 0.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and toxicity (CTCAE v3.0).
Results: From July 2010 to December 2011, 41 patients were enrolled from eight centers. Two patients received no study treatment. Of 39 evaluable for analysis, the median age was 67 years (range, 53−79); 20/19 males/females; 25/14 with PS 0/1; 12/15/7/5 with GB/IHBD/EHBD/AV. First-line GEM-based regimens consisted of GEM alone (22 patients), GEM+cisplatin (8 patients), GEM+S-1 (5 patients), and others (4 patients). The median treatment cycle was 5 (range, 2−18) and the median relative dose intensity of GEM/OX was 88%/86%. CR/PR/SD was confirmed in 0/4/15 patients with an ORR of 10.3% (95% CI, 2.9–24.2%, 80%CI corresponding to one-sided alpha of 0.1, 4.6–19.5%) and a disease control rate of 48.7% (95% CI, 32.4–65.2%). The median PFS and OS were 2.7 and 7.1 months, respectively. The most common grade 3 or 4 adverse events were leukopenia (10%), neutropenia (8%), hemoglobin decrease (8%), sensory neuropathy (8%), thrombocytopenia (5%), anorexia (5%), and hyponatremia (5%).
Conclusions: GEMOX regimen showed a promising anti-tumor activity with acceptable toxicity for GEM-refractory advanced BTC. Further considerations are warranted.
Conflict of interest: *Advisory board: Yakult Honsha Co., Ltd, Eli Lilly Japan K.K. Other substantive relationships: Yakult Honsha Co., Ltd., Eli Lilly Japan K.K.*

2636 POSTER

The effects of variability of mean erythrocyte corpuscular volume (MCV) in patients with advanced stage gastrointestinal stromal tumor (GIST) using imatinib on progression free survival

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Background: There is need for predictive factors to determine the reponses of patients with locally advanced and/or metastatic GIST to treatment. Imatinib increases in red blood cell size as measured by MCV and MCH via the KIT signaling pathway in bone marrow.

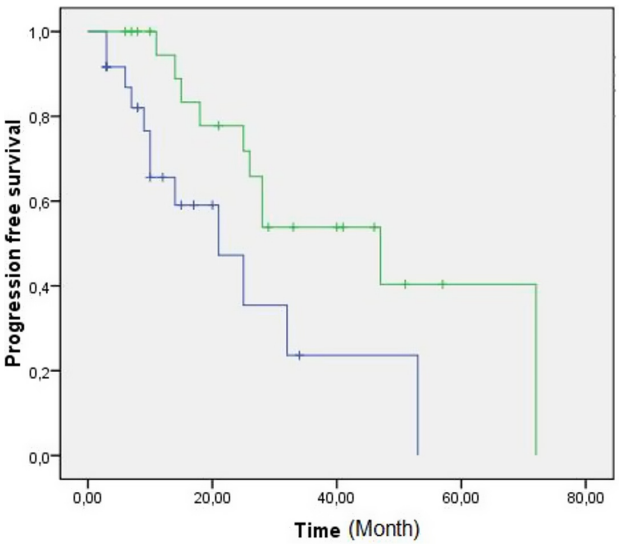

Figure 1. PFS according to the change that has occurred in MCV values.

Material and Method: In this study, we evaluated the relationship between MCV and MCH variability with progression free survival (PFS) three months after the start of the imatinib treatment. Patients with inoperable or metastatic GIST who were dignosed between the years 2000 and 2012 from five centers were included in the study. Blood parameters were evaluated before the start of imatinib treatment and three months after the treatment for the patients' MCV and MCH variability percentage change (?%: MCV 3 months after- MCV before treatment/ MCVX100 before treatment). Kaplan–Meier analysis was used for PFS and log rank was used for comparisons.
Results: A total of 49 patients, 19 female (% 38.8) and 30 male (% 61.2), were evaluated for analysis. Median age was 55 (24−80). Primary tumor locations were found to be stomach in 16 patients, small intestine 17 patients and sites of metastasis were liver in 26 patients. PFS exhibited a significant prolongation in patients with 5 % or more increase in MCV three months after the treatment (47 months versus 21 months respectively, p = 0.022). A PFS prolongation which was not statistically significant was observed in patients (11/49) who had 10 % or more increase in MCH values (28 months versus 26 months respectively, p = 0.968).
Conclusions: Changes in simple laboratory values of patients with locally advanced or metastatic GIST occur as a result of Imatinib pharmacokinetics and can be used in predicting clinical responses.
No conflict of interest.

2637 POSTER

Impact of prior chemotherapy (CT) and somatostatin analogues (SSAs) on clinical outcome in well differentiated pancreatic neuroendocrine tumors (pWDNETs) before treatment with Everolimus (EV)

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Background: EV has been investigated in advanced pWDNETs patients (pts) whitin a large Phase III trial (RADIANT-3), showing a significant improvement of progression-free survival (PFS) of 6.4 months compared with placebo. This effect was long lasting (35% stable at 18 months) but tumor remissions were rare (5%). The most frequent adverse events included stomatitis (64%), rash (49%), diarrhea (34%), fatigue (31%), infections (23%) and pulmonary infiltrates (17%). Based on such results, EV was approved for the treatment of advanced pWDNETs by both FDA and EMA. The ESMO Clinical Practice Guidelines 2012, for diagnosis, treatment and follow up, recommended the use of EV in advanced pWDNETs G1/G2 pts. Aim of this study was to evaluate the disease control rate (DCR) at first radiologic assessment (12 week) defined as the proportion of the best radiological response achieved in pts with complete response (CR), partial response (PR) or stable disease (SD), as a measure of antitumor effect of EV on either pWDNETs naive pts or pts progressing after CT and/or SSAs.
Patients and Methods: We retrospectively analyzed 32 pWDNETs pts treated with EV, between 2010 to April 2013 at our institution.
Results: Median age was 55.5 years, male/female = 22/10. Overall, 22/32 pts received prior SSAs or CT (group A), and 10/32 were treatment naive (group B) before commencing EV. DCR was documented in both groups 12 weeks after EV treatment as follows: 90% (group A) and 70% (group B) respectively. Four out of 32 pts (2 pts in group A and 3 pts in group B) showed disease progression at first evaluation.
Although 13 pts are still on EV treatment, overall SD was achieved in 80% of pts, with a median duration of response of 10 and 13 mos for pretreated and naive patient respectively.
Conclusions: Despite median SD of EV is better in responder naive pts, the overall DCR at 12 weeks is worse when compared to pretreated pts. RADIANT III showed the benefit of EV in terms of PFS, but the therapeutic sequencing for advanced pWDNET remains still unclear. A comparative study is warranted to assess the best sequence strategy for EV in order to evaluate its role up front or following SSAs+/−CT in pWDNETs.
No conflict of interest.

2638 POSTER

Effects of single nucleotide polymorphisms on treatment outcomes and toxicity in patients treated with sunitinib for biliary tract and gastric cancers

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Background: We analyzed the efficacy and toxicity profile of sunitinib according to single nucleotide polymorphisms (SNPs) of *VEGFA* and *KDR* among the patients with gastric or biliary tract cancer.
Methods: We examined 8 known SNPs of *VEGFA* and 5 SNPs of *KDR* among patients with gastric or biliary tract cancer who were treated with sunitinib in our two previous phase II studies. We assessed time to treatment failure (TTF), overall survival (OS), and toxicity and their relationships to these SNPs.
Results: A total of 63 patients were evaluable. Among candidate SNPs, rs2010963, rs833068, and rs1870377 were associated with poor TTF (P =. 009,. 002, and. 029, respectively), while rs1870377 and rs7692791 were associated with poor OS (P =. 001 and 0.03, respectively). Multivariate analysis showed that only rs1870377 had significant effects on both TTF and OS. Toxicity evaluation indicated that rs1531289 was associated with grade 3−4 anemia. (P =. 021).
Conclusions: Certain SNPs of *KDR* may affect treatment outcome and toxicity of patients treated with sunitinib.
No conflict of interest.

2639 POSTER

Five-year outcomes of a phase II study of adjuvant chemotherapy with docetaxel, capecitabine, and cisplatin in stage IIIB-IV(M0) gastric cancer patients

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Background: Postoperative adjuvant chemotherapy with S-1 or capecitabine/oxaliplatin combination is standard after D2 gastrectomy in patients with stage II−III (by AJCC 6th edition) gastric cancer. However, in patients with stage IIIB-IV(M0), despite apparently curative resection, more than 70% of patients have recurrence and die within 5 years. Therefore, we investigated the effect of more intensive adjuvant chemotherapy with triplet of docetaxel, capecitabine, and ciaplatin (DXP) for these patients.
Materials and Methods: This prospective, open label, single center phase II study was conducted for patients with histologically confirmed stage IIIB-IV(M0) gastric cancer who underwent D2 gastrectomy. Patients received adjuvant chemotherapy of six 3-week cycles of intravenous docetaxel (60 mg/m^2 on day 1), oral capecitabine (1,875 mg/m^2/day on days 1 to 14), and intravenous cisplatin (60 mg/m^2 on day 1). The primary end point was recurrence-free survival (RFS). The secondary end points were safety profiles, and overall survival (OS).
Results: From January 2007 to August 2008, a total of 46 patients (stage IIIB: 14, IV: 32) were included in this study. The median age was 53 years (29−70), and ratio of males to females was 0.44. Treatment was completed as planned in 40 (87%) patients. After a median follow-up of 56.1 months (range, 52.2–64.1), 28 patients had recurrence. The median RFS was 26.9 months (95% C.I. 7.5–46.4) and 5 year RFS rate was 39.1%. The median OS was 43.9 months (95% C.I. 29.2–58.7) and 5 year OS rate was 41.3%. Grade 3 or 4 toxicities included anemia (6.5%), leukopenia (23.9%), neutropenia (39.1%), thrombocytopenia (4.3%), febrile neutropenia (15.2%), fatigue (10.9%), anorexia (21.7%), nausea (10.9%), vomiting (4.3%), stomatitis (4.3%), diarrhea (4.3%), and myalgia (2.2%). There was no treatment-related mortality. Median relative dose intensity for docetaxel, capecitabine, and cisplatin were 87%, 75%, and 94%, respectively.
Conclusions: These results suggest that intensive adjuvant chemotherapy with triplet DXP combination is feasible and may be effective for patients with stage IIIB, IV (M0) gastric cancer.
Conflict of interest: *Advisory board: Sanofi, Roche. Corporate-sponsored research: Sanofi, Roche*

2640 POSTER

Somatostatin analogs (SSA) treatment in G1-G2 gastroenteropancreatic neuroendocrine tumors (GEP-NET): A single centre experience

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Background: In a recent study, 85 patients with advanced midgut neuroendocrine tumors (NETs) and predominantly low-volume disease were randomly assigned to receive treatment with octreotide long-acting release or placebo. Patients randomly assigned to the octreotide arm had a significantly longer median time to progression than patients assigned to the placebo arm (14.3 *v* 6 months, respectively; $P < 0.01$) at a planned interim analysis, leading to early termination of the study, giving the evidence of antitumor activity associated with SSA. In this study we analyze our experience with Octreotide LAR in metastatic G1-G2 GEP-NET.
Method: A retrospective analysis was conducted on 103 patients (pt) with advanced GEP-NETs treated upfront with Octreotide LAR (30 mg 1 fl every 28 days) or Lanreotide LAR (120 mg 1 fl every 28 days) until disease progression: 66 gastrointestinal (GI) NET pt (45 treated with Octreotide LAR, 21 with Lanreotide LAR), 37 pancreatic (P) NET pt (29 treated with Octreotide LAR, 8 with Lanreotide LAR).
Results: In 45 GI NET pt group treated with Octreotide LAR mPFS was 22.9 months: in this group, mPFS was 42.23 months in pt with a single metastatic organ and 19.67 months in pt with >1 metastatic organs.
In 21 GI NET pt group treated with Lanreotide LAR mPFS was 18.61 months: in this group, mPFS was 75.25 months in pt with a single metastatic organ and 16.08 months in pt with >1 metastatic organs.
In 29 P NET pt group treated with Octreotide LAR mPFS was 24.97 months: in this group, mPFS was 28.67 months in pt with a single metastatic organ and 21.78 months in pt with >1 metastatic organs.
In 8 P NET pt group treated with Lanreotide LAR mPFS was 25.10 months: in this group, mPFS was 22.28 months in pt with a single metastatic organ and 22.40 months in pt with >1 metastatic organs.

NET	Treatment	Patient number	mPFS (months)	mPFS in patients with 1 metastatic organ	mPFS in patients with >1 metastatic organs
GI	Octreotide LAR	45	22.9	42.23	19.67
	Lanreotide LAR	21	18.61	75.25	16.08
P	Octreotide LAR	29	24.97	28.67	21.78
	Lanreotide LAR	8	25.1	22.28	22.4

Conclusion: Octreotide LAR and Lanreotide LAR showed comparable efficacy in terms of PFS in both PNET and GI NET, especially in pt with limited metastatic involvement.
No conflict of interest.

2641 POSTER

Salvage chemotherapy of fixed dose rate gemcitabine and S-1 combination therapy (FGS) for gemcitabine-refractory advanced pancreatic cancer

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Background: No standard salvage chemotherapy regimen has been established for patients with advanced pancreatic cancer after failure of gemcitabine-based treatment. Although a phase I/II study of FGS was conducted in patients with gemcitabine-refractory advanced pancreatic cancer, the number of patients enrolled was small and efficacy and safety of FGS is still not well known.
Materials and Methods: We retrospectively reviewed 59 patients who received FGS as salvage chemotherapy at our institution from March 2009 to March 2013. The selection criteria in this study were progressive disease under gemcitabine-based chemotherapy, ECOG performance status 2 as a 120-min infusion on day 1 and S-1 was administered orally twice a day at a dose of 40 mg/m^2 on day 1 to 7. Cycles were repeated every 14 days.
Results: Fifty-eight patients were selected for the analysis. Fifteen patients of them had received second-line treatment before FGS. The overall response rate was 13.8% and the disease control rate was 50.0%. The median progression-free survival time was 2.7 months and the median overall survival time was 7.4 months. The common grade 3/4 toxicities were leukopenia (12%), neutropenia (16%), diarrhea (3%), anorexia (2%) and fatigue (2%). Univariate analysis showed that performance status of >0, presence of ascites, serum carcinoembryonic antigen level of >10 ng/ml, serum albumin level of 500 IU/L and serum C-reactive protein level of

>1.0 mg/dl were significantly associated with a poor prognosis. Multivariate analysis identified a performance status of >0 and serum C-reactive protein level of >1.0 mg/dl as factors independently associated with a poor prognosis.
Conclusion: FGS as salvage chemotherapy for patients with gemcitabine-refractory advanced pancreatic cancer is marginally effective and well tolerated in a practical setting. These results could be useful as reference data for optimizing treatment strategies and planning future clinical trials in patients with advanced pancreatic cancer after failure of the first-line treatment.
No conflict of interest.

2642 POSTER

Evaluation of polymorphisms as markers of pazopanib efficacy and toxicity in metastatic/advanced neuroendocrine tumors

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Introduction: Pazopanib is an anti-angiogenic tyrosine kinase inhibitor (TKI) that targets VEGFR-1, 2, and 3; PDGFR-α and β; and c-KIT. The PAZONET is a phase II clinical trial that aimed to determine the efficacy and safety and to identify predictive biomarkers of pazopanib in metastatic/advanced neuroendocrine tumor (NET) patients refractory to other systemic approaches. Within this study, here we evaluated the impact of single-nucleotide polymorphisms (SNPs), previously proposed as predictors of sunitinib outcome, on pazopanib response and toxicity.
Methods: Forty four NET patients were included, in the PAZONET trial. A blood sample for genomic DNA isolation was obtained from 29 of these patients. *VEGFR3* rs307821 (R1324L), *VEGFR3* rs307826 (T494A) and *CYP3A5* rs776747 (splicing defect) were genotyped using standard techniques. Cox regression was used to study genotype associations with progression free survival (PFS) and overall survival (OS), and logistic regression was used to study response and toxicity.
Results: The two *VEGFR3* missense polymorphisms were associated with reduced PFS in gastrointestinal NET (HR = 12.3, P = 0.042 for rs307821; HR = 6.9, P = 0.055 for rs307826). We did not find an association between *CYP3A5* rs776746 and pazopanib toxicity or response.
Conclusion: Polymorphisms in *VEGFR3* may define a subset of patients with decreased pazopanib response in gastrointestinal NET. These results confirm prior observations in kidney cancer, thus these SNPs could determine TKI resistance regardless of the tumor type.
Conflict of interest: *Other substantive relationships: GlaxoSmithKline*

2643 POSTER

The prognostic value of a trio of the EMT (tumour-mesenchymal transition) markers for patients with gastric cancer

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Background: Gastric cancer is one of the leading cancers in the Far East and commonly seen in most part of the world. Despite the progress in the diagnosis and treatment options, it remains one of the tumour types with the highest mortality. The most frequently used methods in assessing the prognosis of the patients are the combined clinical and pathological information of the patients. EMT, Tumour-Mesenchymal Transition, is defined by a number of cellular function changes and characterised by a panel of specific biomarkers. EMT is a cellular process in cancer that is highly involved in the development and progression of cancer and cancer cells. In the present study, we have examined the expression of some of the key EMT molecules in gastric cancer and their value in assessing patients prognosis.
Materials and Methods: A cohort of 189 patients with gastric cancer who received gastrectomy entered the study. Tumour and normal gastric tissues were immediately obtained immediately after surgery. The paired samples were processed for histological and genetic based analyses. The gene transcript levels of a panel of recognised EMT markers were quantified in the paired tumour and normal tissues. The clinical and prognostic value of the expression of the EMT markers and the combined power of the markers were analysed against the clinical, histological, pathological and clinical outcome of the patients.
Results: Expression of Slug, Twist and cadherin-1 (CDH-1) were found to be aberrant in gastric cancer tissues when compared with normal tissues of the stomach. For examples, CDH1 was found to be markedly reduced in tumour compared with normal tissues ($p < 0.001$). Likewise, expression of Twist and Slug were also significantly different between tumour and normal tissues in that tumour had a markedly high level ($p < 0.0001$ and $p = 0.015$ respectively). Other EMT markers were found to be less aberrant in gastric cancers. The markers individually did not appear to be significantly correlated with the histological type nor the location of the tumour. However, the trio of the markers, namely, CDH1, Slug and Twist were significantly correlated with the incidence free survival ($p = 0.005$) and overall survival ($p = 0.008$), based on the Kaplan–Meier survival model. Likewise, patients with the Trio EMT marker abnormalities had a lower five-year survival rate.
Conclusions: A selective trio of the tumour-mesenchymal transition markers is an important indicator in the disease progression of gastric cancer and have prognostic value in predicting patients clinical outcome.
No conflict of interest.

2644 POSTER

Study of the expression of connective tissue growth factor (CTGF) and hypoxia-inducible-factor (HIF) in hepatocellular carcinoma (HCC)

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Background: CTGF is a matricellular protein involved in inflammation, tumour growth and angiogenesis. A hypoxic (HIF related) CTGF expression, independent of TGFβ, with implications in fibrosis and metastatic potential was described in renal cancer. The aim of this study is to clarify if this data could match in HCC.
Material and Methods: Patients (pts) diagnosed with HCC, with paraffin-embedded biopsy tissue and relapse and survival data available were eligible. A tissue microarray (TMA) was constructed from $\geqslant$70% tumoural sections and non-necrotic areas of the tumour foci. The expressions of CTGF, HIF1α and HIF2α were analysed by immunohistochemistry (IHC). The primary end point was relapse rate. Secondary end points were disease-free survival (DFS) and overall survival (OS). Univariate and multivariate analysis were performed.
Results: Fifty-three pts were analysed; 39 pts were eligible for this retrospective analysis. The median age at diagnosis was 66.9 years (range 36−82). 76.9% were men and 51.3% had hepatitis C related cirrhosis. Stage at diagnosis was as follows n(%): 10(25.6%) I, 14(35.9%) II, 6(15.4%) III, 2(5.1%) IV and 7(17.9%) unknown. Most of the pts were treated with surgery alone (84.6%) or combined with other treatment (10.3%). 5 pts (12.8%) died during the surgery or during the postoperative period. The median follow-up was 36.1 months (range 0–98.8). At the end of the follow up, 23(59%) pts relapsed [11(28.2%) locally, 4(10.3%) multicentric liver relapse and 3(7.7%) distant metastases)] and 27(69.2%) died; 8(20.5%) were alive and free of disease while 4(10.3%) were alive on treatment for HCC. Estimated median DFS was 23.4 months (95% CI 7.18–39.66) and median OS 38.6 months (95% CI 30.7–46.6). Expression of CTGF was: negative 9(23.1%), focal 19(48.7%) and diffuse 9(23.1%). Expression of HIF1α was positive 14(35.9%) and negative 16(41%) while expression of HIF2α was positive 11(28.2%) and negative 21(53.8%). 2 CTGF, 9 HIF1α and 7 HIF2α IHC were not evaluable. Non statistical significant relationship between expression of CTGF and HIF was shown (p0.93(HIF1α); p0.932(HIF2α)). CTGF expression was related to longer DFS (p0.028) and OS (p0.005) while expression of HIF2α was predictable of relapse (p0.034). Other prognosis factors were type of relapse ($p < 0.001$) and hepatic baseline disease (p0.022) for DFS and stage at diagnosis (p0.006) and type of relapse ($p < 0.001$) for OS. In the multivariable analysis, type of relapse (p0.09; HR 1.65; 95% CI 1.13–2.39) and CTGF expression (p0.016; HR 2.46; 95% CI 1.18–5.15) were independent factors related to OS.
Conclusions: Our results support that expression of CTGF is an independent factor related with OS in HCC. It would be worth performing further analysis of CTGF expression in larger series of HCC as prognostic biomarker and druggable target.
Conflict of interest: *Corporate-sponsored research: Jorge Barriuso participates in clinical trials sponsored by Roche, Novartis, Taiho, AstraZeneca and Pfizer. Other substantive relationships: Angela Lamarca is actually supported by ESMO Fellowship program. Jorge Barriuso is partly funded by Asociación Española Contra el Cancer (AECC).*

2645 POSTER

Correlation between VEGF and VEGF-R polymorphisms, toxicity and clinical outcome in HCC patients receiving sorafenib

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Background: The introduction of sorafenib for the treatment of advanced HCC radically changed patients' clinical outcome. However response to treatment as well as toxicity are still largely unpredictable in the single patient. We previously reported that VEGF and VEGFR polymorphisms may have a predictive and prognostic role in this setting, but little is known about the possible correlation with toxicity.
The aim of our study was to evaluate whether VEGF and VEGFR genotyping was able to correlate with toxicity in HCC patients receiving sorafenib.
Methods: 73 histological samples of HCC patients receiving sorafenib were tested for VEGF-A, VEGF-C and VEGFR-1,2,3 single nucleotide polymorphisms (SNPs). Patients time to progression (TTP), overall survival (OS) and toxicities were analysed.
Results: VEGF-A rs833061 T>C, rs699947 C>A and rs2010963 C>G polymorphisms were statistically significant associated with any grade global (respectively: $p = 0.031$; $p = 0.018$; $p = 0.003$) and cutaneous toxicities (respectively: $p = 0.043$; $p = 0.019$; $p = 0.025$). Furthermore patients with any grade global and cutaneous toxicities showed a better progression free survival and overall survival (global toxicity PFS: 7.0 vs 5.0 months, $p = 0.016$; OS: 26.8 vs 13.0 months, $p = 0.023$) (cutaneous toxicity PFS: 7.6 vs 5.1 months, $p = 0.033$; OS: 22.7 vs 13.3 months, $p = 0.014$).
Conclusions: In our analysis patients with polymorphism T at rs833061, C at rs699947 and C at rs2010963 showed a higher rate of toxicities and, accordingly to our previous report, this correlates with a better PFS and OS. Analysis of VEGF and its receptor genes polymorphisms represents a clinical tool to identify patients with favourable response to sorafenib presumably related to a more efficient control of tumour growth. The occurrence of toxicity could be an interesting clinical surrogate during sorafenib treatment and may help clinicians in a more cautious and aware management of HCC patients.
No conflict of interest.

2646 POSTER

Prognostic impact of c-MET status on overall survival of patients with advanced gastric cancer treated with standard chemotherapy: A Japanese multicenter collaborative retrospective study

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Background: c-MET overexpression has been reported in 18−82% of gastric cancer with immunohistochemistry (IHC) and was correlated with poor prognosis. However, the prognostic impact of c-MET status on overall survival (OS) of patients with advanced gastric cancer (AGC) treated with standard chemotherapy remains unclear. We investigated whether c-MET status is an independent prognostic factor for AGC patients.
Materials and Methods: Formalin-fixed paraffin-embedded tumor samples from 293 eligible patients were examined for c-MET by IHC. IHC staining was performed automatically with Ventana BenchMark® ULTRA using primary antibodies against rabbit anti-c-MET polyclonal antibody (SP44; Ventana). We used three separate IHC evaluation criteria to define c-MET+: (A) IHC 2+ or 3+ according to the DAKO HercepTest guideline; (B) $\geqslant$25% of tumor cells with any membrane staining intensity; and (C) a majority ($\geqslant$50%) of tumor cells with IHC 2+ or 3+ membrane staining intensity. Eligibility criteria included: 1) histology confirmed gastric or gastroesophageal junction adenocarcinoma, 2) unresectable or recurrent cancer, 3) treated with S-1 plus cisplatin as first-line chemotherapy, 4) age: $\geqslant$20, 5) ECOG performance status score: 0−2 and 6) with archived tumor sample.
Results: Of 293 patients, 142 (48.5%) were c-MET+ using criteria (A), 158 (53.9%) using (B), and 120 (40.9%) using (C). Under criteria (C), baseline patient characteristics between c-MET+ and c-MET− patients were significantly different by histology (intestinal/diffuse, 51.7%/48.3% vs. 36.4%/63.6%; $p = 0.012$), liver metastasis (41.7% vs. 29.5%; $p = 0.034$), and HER2 status (20.0% vs. 11.0%; $p = 0.043$). After median follow-up time of 48.9 months with 270 (92%) death events, there was significant difference in OS between c-MET+ and c-MET− patients using criteria (C) (median, 11.9 vs. 14.2 months; hazard ratio [HR] 1.282, 95% CI 1.004–1.636; log rank $p = 0.046$); whereas OS among c-MET+ and c-MET− groups selected by criteria (A) or (B) did not vary significantly. A multivariate Cox model with backward selection found c-MET+ using (C) was a marginal prognostic factor for OS (HR 1.283; 95% CI: 0.996–1.652; $p = 0.054$).
Conclusions: The present study suggested that c-MET+ AGC patients with $\geqslant$50% tumor cells with IHC 2+ or 3+ had a poor prognosis than those with c-Met−.
Conflict of interest: *Other substantive relationships: Taiho Pharmaceutical, Daiichi-Sankyo,Chugai-Roche, Takeda Pharmaceutical*

2647 POSTER

Prognostic impact of epidermal growth factor receptor status on overall survival of advanced gastric cancer patients treated with standard chemotherapy: A Japanese multicenter collaborative retrospective study

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Background: Epidermal growth factor receptor (EGFR) overexpression, observed in 27−44% of gastric cancer patients, has been generally reported to be a poor prognostic factor in patients who underwent resection. The prognostic impact of EGFR status on overall survival (OS) of advanced gastric cancer (AGC) patients treated with standard chemotherapy remains unclear. We investigated whether EGFR status is an independent prognostic factor for AGC patients.
Patients and Methods: Formalin-fixed paraffin-embedded tumor samples from 293 eligible patients were examined for EGFR by immunohistochemistry (IHC). IHC staining was performed automatically with Ventana BenchMark® ULTRA using primary antibodies against EGFR (CONFIRM EGFR 3C6). An EGFR-positive sample was defined as IHC 2+ or 3+ according to the DAKO HercepTest guideline. Eligibility criteria included: 1) histology confirmed gastric or gastroesophageal junction adenocarcinoma, 2) unresectable or recurrent cancer, 3) treated with S-1 plus cisplatin as first-line chemotherapy between January, 2006 and March, 2010, 4) age: $\geqslant$20, 5) Eastern Cooperative Oncology Group performance status score: 0−2 and 6) with archived tumor sample.
Results: Of 293 patients, 79 (27.0%) were EGFR-positive. Baseline patient characteristics between EGFR-positive and -negative patients were significant different by disease status (unresectable/recurrent 91%/9% vs. 79%/21%; $p = 0.016$). After a median follow-up time of 48.9 months with 270 (92%) death events, there was no significant difference in OS between EGFR-positive and EGFR-negative patients (median, 11.9 vs. 14.2 months; hazard ratio 1.065, 95% CI 0.811–1.397; log rank $p = 0.650$). After adjusting other prognostic factors with Cox hazard model, EGFR status was still not prognostic factor for OS.
Conclusions: EGFR status has no significant prognostic impact on OS of AGC patients treated with S-1 plus cisplatin as a first-line treatment.
Conflict of interest: *Other substantive relationships: Taiho Pharmaceutical, Daiichi-Sankyo, Chugai-Roche*

2648 POSTER

Plasma sVEGFR2 as predictor of efficacy of Pazopanib in patients with progressive neuroendocrine tumors: PAZONET biological Substudy

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Background: The objective of this study is to evaluate the predictive role of plasma VEGF-A and sVEGFR2 in patients with progressive neuroendocrine tumors (NETs) treated with Pazopanib in the PAZONET clinical trial. As the trial allowed pre-treatment of patients with previous targeted therapies, the predictive value of these molecules was studied depending on pre-treatment.
Methods: Patients with advanced NETs progressing to prior chemotherapy, somatostatin analogs (SA) or targeted therapies (mTOR inhibitors or antiangiogenic drugs) were treated with Pazopanib 800 mg/day until progression or unacceptable toxicity in the PAZONET clinical trial (Grande et al, ESMO 2012; Grande et al, ASCO 2013). Blood samples were retrieved at baseline and after 12 weeks of treatment and plasma VEGF-A and sVEGFR2 were determined by ELISA. Disease was evaluated bimonthly with CT scans (RECIST1.0).
Results: Neither baseline VEGF-A (n = 39, median 108 pg/ml) vs on-treatment VEGF-A (n = 30, median 132 pg/ml), nor individual increase or decrease on VEGF-A levels demonstrated predictive value. Nevertheless plasma levels of sVEGFR2, demonstrated a significant decrease on treatment (baseline n = 41 median 8520 pg/ml; on-treatment n = 27, median 6561 pg/ml, $p < 0.0001$). Furthermore, the amplitude of sVEGFR2 decrease was associated with longer treatment duration ($p = 0.0046$), with −20% decrease in sVEGFR2 corresponding to 50 weeks of treatment.
PFS was longer for patients with greater decreases of sVEGFR2, with a median of 12.6 versus 9.1 for patients with decreases above or below the median, respectively ($p = 0.067$). This association was statistically significant among patients that had not received prior antiangiogenic therapy (n = 13, PFS of 20.1 versus 9.1 months respectively, $p = 0.028$), but not in the subset of patients with previous antiangiogenic therapy (n = 14, $p = 0.93$). As transient changes in pro-angiogenic factors have been described (Teulé & Casanovas 2012; Lieu et al. 2012), we subdivided patients according to time since previous antiangiogenic therapy and found sVEGFR2 to be predictive of PFS in past/older pre-treated patients compared to recent ones (median cutoff of 30 days since pre-treatment, n = 19 $p = 0.036$).
Conclusions: Pazopanib treatment is associated with a decrease in plasma levels of sVEGFR2. Stronger decrease of VEGFR2 is associated with improved PFS, especially in patients without prior antiangiogenic therapy and in those with a longer time elapsed since previous antiangiogenic therapy.
Conflict of interest: *Corporate-sponsored research: Research Grant from GSK*

2649 POSTER

MutaGIST study: a prospective assessment of prognostic significance of the mutational status of KIT, PDGFRA, BRAF and expression of IGF-1, IGF-2, and S6k-phosphorylated in localized gastrointestinal stromal tumors (GIST). A molecular and clinicopathologic GIST study − preliminary results

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Background: There is a well-known correlation between tumor genotyping and clinical outcome of patients with metastatic GIST treated with imatinib. However, limited experience is available related to the role that GIST molecular subtype could play in the adjuvant setting. We aimed to prospectively assess the impact that mutational status could have in terms of time to relapse of patients with resected GIST and to obtain a better knowledge of early stage GIST.
Methods: A multicenter, prospective, observational study to establish the mutational status of KIT, PDGFRA and BRAF genes by sequencing exons and the expression level of the IGF1, IGF2 and pS6K proteins by immunohistochemistry in localized and resected GIST tumor samples at diagnosis. Patients will be followed for 24 months after inclusion and the same molecular analysis will be performed at relapse.
Results: 83 patients (pts) were included from 2011 to 2012. Median age was 66 yrs., 46 females and 35 males. The Stomach was the more frequent location, Median tumor size was 6 cm and median mitotic index was 5%. According to Miettinen criteria: 8.2% had very low risk, 26% low risk, 16.4% intermediate risk and 42.5% high risk. 48 pts received adjuvant therapy. 41 pts had spindle cell histology. Mutational showed that 21 (25.3%) exon 11 mutation (mut); 11 (13.2%) pts had KIT exon 9 mut; 2 (2.4%) pts exon 13 mut; and 2 (2.4%) exon 17 mut. PDGFRA mutational analysis showed that 13 (15.6%) pts had exon 18 mut (11 D842V). 46 pts were analyzed for BRAF and 1 (2.1%) patient had exon 15 mut. After a median follow-up of 16 months only 2 relapses have been identified.
Conclusions: This preliminary shows that there is a significant variations between the proportion of mutations in KIT, PDGFR, and BRAF genes in localized compared to advanced GIST samples. Exon 18 mutations were very frequent in primary GIST compared with metastatic GIST. A longer follow up will be needed to correlate the tumor genotyping with the benefit to imatinib in the adjuvant setting.
No conflict of interest.

2650 POSTER

Phase I study of vorinostat combined with capecitabine plus cisplatin as first-line chemotherapy in patients with advanced gastric cancer: The results of pharmacodynamic analysis

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Background: Vorinostat is an oral histone deacetylase (HDAC) inhibitor. The purpose of this trial was to determine recommended phase II dose of vorinostat in combination with capecitabine plus cisplatin in patients with advanced gastric cancer. The results of dose-finding portion of study were previously presented (J Clin Oncol 30:2012; suppl 34; abstr 73). Here, we report the results of pharmacodynamic analysis in this patient cohort (NCT01045538).
Materials and Methods: Peripheral blood mononuclear cells (PBMCs) were obtained before the study treatment and 2 hours after ingestion of vorinostat capsules at post-treatment day 8 of cycle 1. HDAC2 expression and histone H3 acetylation were measured by Western blot analysis, and normalized to histone H3 expression. The correlations between the change of acetyl-H3 after treatment and covariates were analyzed by linear regression.
Results: Among 30 patients enrolled in this study, pre- and post- vorinostat PBMC samples were available in 29 patients. The vorinostat-induced change of histone acetyl-H3 was median 9.1% (95% confidence interval [CI], −10.3–224.1) over baseline ($p = 0.09$). Acetyl-H3 was significantly increased in patients who received vorinostat 400 mg/day (median 24.2%, $p = 0.02$), while not in those with 300 mg/day (4.0%, $p = 0.33$). The change of acetyl-H3 in PBMC was correlated with baseline acetyl-H3 ($p < 0.001$), but not with baseline HDAC2 expression ($p = 0.38$). Multivariate analysis was performed with inclusion of baseline HDAC2, baseline acety-H3, and vorinostat dose. In this analysis, baseline acetyl-H3 (beta = −0.71, $p < 0.001$) and vorinostat dose (300 vs 400 mg/day; beta=0.33, $p = 0.03$) were significantly correlated with the change of acetyl-H3 after study treatment.
Conclusions: In patients who received this combination regimen, baseline expression of histone acetyl-H3 was inversely correlated with the change in acetyl-H3 after treatment. Our finding suggests that baseline acetyl-H3 in PBMCs is a potential biomarker of vorinostat.
Conflict of interest: *Corporate-sponsored research: YK Kang received a research grant from Merck & Co., Inc., and honoraria for a lecture and a research grant from Roche.*

2651 POSTER

Gene expression characterization of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and their correlation with clinical factors and tumor behavior: initial molecular profile

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Background: Although distinctive biological features of GEP-NETs, such as somatostatin receptor expression, high vascularization and altered signal transduction activation, are currently being used as therapeutic tools, the development of specific therapies targeting GEP-NETs is impaired by their inherent heterogeneity, lack of a characteristic molecular profile and absence of adequate cellular or animal models.
Methods: A national multicenter study was initiated to characterize in GEP-NETs the molecular profile of 36 genes by quantitative real-time-PCR including somatostatin and dopamine receptors, VEGF pathway components, mTOR pathway components, and a number of tyrosine kinase receptors and adhesion molecules. Molecular information will be correlated with clinical factors such as localization of primary tumors, ploidy, Ki-67 index, stage of disease, and tumor functionality. 40 fresh-frozen tumor samples from patients with well differentiated gastrointestinal and pancreatic NETs (GI-NETs and pNETs) have been included.
Results: Initial analyses focused on somatostatin (sst1, sst2, sst3, sst5) and dopamine receptor expression (D2RT: total D2R isoform and D2RL: D2R long isoform). The first 15 patients analyzed (10 male, mean age 55 years) included 7 GEP-NETs of pancreatic origin (pNETs) and 8 GEP-NETs which originated in the bowel (GI-NETs). Of the 7 pNETs (G1, n = 3; G2, n = 4), 3 presented Stage IV at diagnosis and 1 was a secreting tumor. Of the 8 GI-NETs [foregut (G1, n = 1; G2, n = 2), midgut (G1, n = 2; G2, n = 1), hindgut (G2, n = 2)] 6 had Stage IV at diagnosis and 2 had secreting tumors.
Molecular data show that the sst1 mRNA transcript is the dominant sst isoform in pNET samples (1260±264 copies), followed by lower levels of sst2 (833±164 copies) and sst5 (713±277 copies) and negligible expression of sst3 (<100 copies). In GI-NET samples, sst1 (579±210 copies), sst2 (772±427 copies) and sst5 (455±197 copies) transcripts were expressed at similar levels; sst3 expression in GI-NETs was also very low (<100 copies). Sst1 transcript expression in GEP-NETs was significantly higher in non-functioning tumors compared with functioning tumors (1129±226 copies vs 312±199 copies, $p < 0.05$). Stage IV tumors had significantly lower sst1 transcript expression levels than earlier stages of disease (509±83 copies vs 1386±565 copies, $p < 0.02$). There were no significant differences of D2RT and D2RL isoforms between pNET and GI-NET samples, with limited mRNA expression levels in all samples (<50 copies).
Conclusion: Somatostatin receptor subtype transcriptional profile in GEP-NETs may substantially differ according to primary tumor type, functionality or stage of disease. Further analysis detailing the molecular phenotype of these tumors may help identify molecular targets of prognostic, diagnostic and/or therapeutic value, and shall ultimately improve stratification, diagnosis and management of patients with different types of GEP-NETs.
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2652 POSTER

Personalized treatment of advanced pancreatic cancer based on a combined biomarker analysis: A feasibility targeted therapy study

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Background: Treatment options for patients (pts) with pancreatic cancer (PC) have increased in the last years, but there are no validated molecular markers in PC to select which agents are better to treat an individual case. The aim of this study was to determine the feasibility of implementing a molecular biomarker panel (MoBP) to guide treatment selection in PC.
Material and Methods: PC tumor samples were analyzed with a predefined set of 7 molecular targets, including: *KRAS* mutations, *EGFR* amplification (FISH), and thymidylate synthase (TS), thymidine phosphorylase (TP), ERCC-1, topoisomerase I (Topo I), and SPARC expression by IHC. Clinical characteristics and response to chemotherapy were registered. To establish the utility of this panel, we selected 3 groups of pts with completed clinical data: pts with MoBP determination that prospectively selected treatment (Group A), pts with MoBP determination but inconsistent treatment (Group B) and pts without MoBP and treated based on clinical guidelines (Group C).
Results: A total of 67 pts were studied. 63 pts were analyzed for overall survival. We determined MoBP in 35 (56%) Only 6 % required a repeated biopsy to obtain sufficient tumor for molecular analysis. In 47 % of pts was feasible to study 5/7 targets. There were 14/21 pts (67%) with *KRAS* mutant PC. TS was positive in 15/28 cases (54%), TP in 6/19 (32%), ERCC-1 in 7/28 (25%), Topo I in 7/15 (47%). SPARC was negative in tumoral and positive in stromal cells in 15/21 (71%). None of 20 pts had EGFR amplification. Clinical flow up was available in 67 pts (38 males, median age 66, 95% ECOG 0−1). 67, 47 and 16 pts received 1st, 2nd or 3rd line of chemotherapy respectively. Only TS and TP predicts response to treatment based on fluoropirimidines or capecitabine: PFS (months) in fluorpirimidine-treated group 6.9 (TS negative) vs. 2.2 (TS positive) $p = 0.015$; PFS (months) in Capecitabine-treated group 10.7 (TS negative and TP positive) vs 2.0 (TS positive or TP negative) $p = 0.036$. We selected 63 pts for overall survival, 23 pts in Group A, 12 in Group B and 28 in Group C. OS (months) in Group A (12) differs significantly from Group B (8.5) or Group C (7.6) $p = 0.013$. No significant differences between Group B and Group C were detected.
Conclusions: This MoPB is feasible to implement and should be explore to predict treatment response to PC.
No conflict of interest.

2653 POSTER

Clinical significance of CD151 expression in patients with advanced gastric cancer

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Background: Tetraspanin CD151 is known to be involved in cancer invasion and metastasis, and its overexpression appears to be associated with a poor prognosis in various types of cancers. CD151 is also implicated in the formation of signaling complexes between c-erbB2 and c-Met, modulating cancer cell motility and morphogenesis elicited by the activation of these molecules. However, the expression status of CD151 and its prognostic impact in gastric cancers has not been elucidated yet.
Methods: We investigated the expression of CD151, c-erbB2, and c-Met by immunohistochemistry in 160 cases of advanced gastric cancers. Clinicopathological and prognostic significance of these biomarkers was evaluated.
Results: Overexpression of CD151 was observed in a subset of advanced gastric adenocarcinomas (25.6%), while c-erbB2 and c-Met were overexpressed in 15% and 16.9% of our cohort, respectively. The expression of CD151 was not correlated with the expression of c-erbB2 and c-Met ($P = 0.666$ and $P = 0.969$). CD151 overexpression was more frequently observed in tumors from younger patients ($P = 0.028$). Interestingly, the expression rate of CD151 seemed to be gradually increased according to the depth of invasion (T stage) (x2 test for trend; $P = 0.082$), N stage ($P = 0.233$), and pathologic stage ($P = 0.133$), although they were not statistically significant. However, CD151 overexpression was closely associated with patients overall survival (OS; $P < 0.001$) and progression-free survival (PFS; $P < 0.001$). In multivariate analysis, CD151 overexpression was an independent prognostic factor for predicting worse

OS (P = 0.004) and PFS (P = 0.009) along with T stage and N stage. The expression status of c-erbB2 and c-Met did not exhibited a meaningful correlation with OS and PFS, respectively.
Conclusions: CD151 is a good tissue marker that has a powerful prognostic significance in advanced gastric cancers, and may become a new promising therapeutic target.
No conflict of interest.

2654 POSTER

A survey of MET overexpression and amplification in 287 patients with hepatocellular carcinoma

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Background: c-MET is a new potential drug target for treatment of hepatocellular carcinoma (HCC) patients, and a recent study of c-MET inhibitor in HCC patients has shown promising results. In the present study, we investigated the incidence of c-MET overexpression and its prognostic impact.
Methods: Tumor tissue microarrays were used to detect the expression of c-MET in samples from 287 HCC patients who underwent surgical resection at Samsung Medical Center. We explored the relationships between c-MET overexpression and clinicopathologic features of HCC and investigated recurrence-free survival (RFS) and HCC-specific survival according to the level of c-MET expression. Additionally, we explored the correlation between c-MET protein overexpression, MET mRNA expression and MET copy number variation.
Results: Most patients in this study were male (n = 297, 82.6%), with Child-Pugh class A liver function (n = 286, 99.7%) and hepatitis B viral infection (n = 217, 75.6%). c-MET overexpression was observed in 80 patients (27.9%), and it was not associated with Edmondson grade, tumor size, microvascular invasion, major portal vein invasion or AJCC stage. In addition, c-Met expression level did not affect RFS or HCC-specific survival. c-MET expression was weakly correlated with MET copy number variation (r = 0.255, $P<0.001$), but over half of patients with c-MET^{high} expression showed neutral copy number. c-MET IHC expression showed a very weakly but significantly positive correlation with its mRNA expression (r = 0.199, $P = 0.002$).
Conclusion: c-MET overexpression did not show a prognostic impact on recurrence or survival in HCC patients with surgical resection. However, 27.9% of HCC patients who had c-MET overexpression are candidates for treatment with c-MET inhibitor.
No conflict of interest.

2655 POSTER

ERCC1 codon 118 polymorphism as a predictive factor for pathologic complete response to S1/oxaliplatin combination chemoradiotherapy in patients with esophageal cancer

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Background: DNA repair gene excision repair cross-complementing group 1 (ERCC1) polymorphism is known to be a predictive marker for response to the platinum-based chemotherapy. We aimed to investigate whether the single-nucleotide polymorphisms of ERCC1 at codon 118 affected clinical outcomes in patients with resectable esophageal cancer who underwent preoperative chemoradiotherapy with S1/oxaliplatin combination chemotherapy (Yoon DH et al., J Clin Oncol 30, 2012 suppl; abstr 4093).
Methods: A total 62 patients among those 97 patients who were enrolled in the clinical trial to evaluate the efficacy and safety of preoperative chemoradiotherapy with S1 and oxaliplatin doublets with or without induction chemotherapy with the same regimen underwent genotyping of ERCC1 with peripheral blood lymphocytes by the SNaPshot assay.
Results: Thirty five (56%) were homozygous for AAC codon (C/C genotype), 3 (5%) were homozygous for AAT codon (T/T genotype) and 24 (39%) were heterozygous (C/T genotype). Genotypes were not significantly different between the treatment arms (p = 0.725). Among those 45 patients who underwent esophagectomy after preoperative chemoradiotherapy, the pathologic complete response (pCR) rate was significantly lower in the C/C genotype compared with the C/T or the C/C genotype groups (34.6% vs. 68.4%, p = 0.025). With a median follow-up period of 31.0 mo (range, 17.8–47.8 mo) among surviving patients, 2-year progression-free survival (PFS) rate was 45.4% in the C/C genotype group and 70.8% in the C/T or the C/C genotype groups, respectively (p = 0.065). Two-year overall survival (OS) rate was 51.4% and 72.5%, respectively (p = 0.142). In the multivariate model with the treatment group (with or without induction chemotherapy), ERCC1 genotypes (C/C vs. C/T or T/T) were marginally correlated with PFS (HR = 2.2, p = 0.055) and OS (HR = 1.8, p = 0.169). Among those who underwent esophagectomy, 2-year PFS rate was significantly lower in the C//C genotype group (57.4% vs. 88.4%, p = 0.025).
Conclusions: pCR rate was significantly lower in the patients with ERCC1 118 C/C genotype treated by oxaliplatin-based chemoradiotherapy.
No conflict of interest.

2656 POSTER

NY-ESO-1 protein vaccine complexed with cholesteryl pullulan (CHP-NY-ESO-1) provides dose-dependent effects on immune responses and survival benefits for recurrent esophageal cancer patients

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Background: Cancer vaccines using tumor-antigen proteins are expected to efficiently induce immune responses to multiple T cell epitopes. Cholesteryl pullulan (CHP) is a novel antigen-delivery system for cancer vaccines. NY-ESO-1 antigen is a cancer-testis antigen that is exclusively expressed in tumor tissues, except in testis and placenta. This antigen is considered an ideal target for cancer immunotherapy. We evaluated the safety and immune responses to the NY-ESO-1 antigen over the vaccination period, and explored the clinical impact on esophageal cancer patients with a poor prognosis.
Patients and Methods: Patients with advanced/metastatic esophageal cancer were enrolled and subcutaneously vaccinated with either 100 μg or 200 μg of CHP-NY-ESO-1. The primary endpoints were the toxicity and humoral immune responses, and the secondary endpoint was clinical efficacy.
Results: 25 patients were enrolled. Twelve and thirteen patients were repeatedly vaccinated with 100 μg or 200 μg of CHP-NY-ESO-1 with a median of 8 or 9.5 doses, respectively. No serious adverse events related to the vaccine were observed. In the 100-μg cohort, an antibody response was observed in 5 out of 10 pre-antibody-negatives patients, and the antibody levels were augmented in 2 pre-antibody-positive patients. In the 200-μg cohort, all 5 pre-antibody-negative patients became seropositive, and the antibody level was amplified in all 7 pre-antibody-positive patients. No tumor shrinkage was observed. No difference of time-to-progression was seen between 100-μg and 200-μg cohort. The patients who received 200 μg survived longer than patients receiving 100 μg, even those who exhibited unresponsiveness to previous therapies or had higher tumor burdens.
Conclusions: The safety and immunogenicity of CHP-NY-ESO-1 were confirmed. The 200-μg dose more efficiently induced immune responses and provided better survival benefits.
Conflict of interest: *Ownership: H Shiku is a stockholder of ImmunoFrontier, Inc., which provided CHP-NY-ESO-1 protein vaccine.*

	100 μg (n = 13)	200 μg (n = 12)	
Immune responses			
Sero-conversion	5/10	5/5	
Augmentation	2/3	7/7	
Response rate	53.8%	100%	p = 0.015*
TTP(weeks); median (range)	6 (4−52)	8.5 (6−18)	p = 0.748**
OS(weeks); median (range)	23 (4−60)	41 (8−72)	p = 0.05**

TTP: time-to-progression; OS: overall survival. *Fisher's exact test; **log-rank test.

2657 POSTER

EGFR expression, but not mutation of EGFR, KRAS, BRAF, PIK3CA and MSI is prognostic factor in gastric cancer after surgical resection

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Background: Gastric cancer remains among leading cause of cancer death and the recurrence rate is still high even after curative surgical resection. Multidisciplinary treatment and novel targeted therapy could be potentially beneficial, however identification of new prognostic factors influencing such treatment is necessary. The existing molecular factors remain controversial.
We aimed at the evaluation EGFR expression, frequency and type of mutation in tyrosine kinase domain in *EGFR* gene (ex. 18−21) and also frequency and type of mutation of *KRAS* (ex.2,3,61), *BRAF* (ex.15), *PIK3CA* (ex.9,20) and microsatellite instability MSI status and their impact on prognosis after curative resection.
Material and Methods: We collected 107 tumor samples from pts. undergoing surgery because of adenocarcinoma of gastroesophageal junction (20) and stomach (89) between 2008–2011. Lauren type: intestinal-45, diffuse-38, mixed-22, unknown-2. 30 pts were treated multidisciplinary mainly with chemoradiotherapy. RNA and DNA was freshly isolated from tumor samples used concomitantly for routine histopathology examination and immunohistochemical staining for EGFR. Mutational status was examined by reverse transcription and polymerase chain reaction amplification (RT-PCR) followed by direct sequencing of its product. To detect microsatellite instability isolated DNA was amplified using the STR NGM kit and PCR. The PCR product was then sequenced and the results obtained were analyzed using GeneMapper 3.2.1.
Results: EGFR expression was detected in 73 samples (69.5% of evaluated samples) in the range from 1% to 100% cells. There were no *EGFR* mutations. However polymorphism 2361G>A, Gln787Gln was found in 80 samples (78.4%). 3 *KRAS* (2.8%), 2 *BRAF* (1.9%), 2 *PIK3CA* (2.2%) mutations and 12 MSI (12.9%) were detected. Median FU, DFS and OS were 910, 442, 520 days, respectively.
Conclusions: Neither mutations of *KRAS*, *BRAF*, *PIK3CA* and *EGFR* polymorphism nor MSI status were independent prognostic factors. EGFR expression was associated with shorter DFS and OS in the group with microsatellite instability and non-intestinal type ($p = 0.008$, $p = 0.06$ and $p = 0.04$ $p = 0.09$). Pts. who had microsatellite instability coexisted with lack of EGFR expression had a particularly good prognosis. There were no deaths in this group.
No conflict of interest.

2658 POSTER

Phosphorylated AMP-activated protein kinase and MAPK3/1 expression associated with prognosis for patients with gastric cancer

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Objectives: Phosphorylated AMP-activated protein kinase (pAMPK) plays a central role in cellular metabolic sensing and energy balance homeostasis, and interacts with various pathways [e.g., TP53, mTOR, NUAK2 (sucrose nonfermenting-like kinase), MAPK3/1 (ERK), and PDK]. Therefore, the present study analyzed the expression of pAMPK, NUAK2, MAPK3/1, and PDK-1 and their impact on the survival of patients with resected gastric cancer.
Methods: A total of 621 patients with surgically resected gastric adenocarcinoma and a curative intent were enrolled. Immunohistochemical staining for pAMPK, NUAK2, MAPK3/1, and PDK-1 was performed using tissue microarrays of operative specimens of gastric cancer.
Results: Positive pAMPK, NUAK2, MAPK3/1, and PDK-1 expression was observed in 379 (61.0%), 257 (41.4%), 327 (52.7%), and 67 (10.8%) cases, respectively. A multivariate survival analysis showed a significantly better survival for the patients with a positive pAMPK or MAPK3/1 expression than for the patients with a negative expression (pAMPK: disease-free survival [DFS], hazard ratio [HR]=0.750, 95% CI=0.568–0.970, p value=0.030; MAPK3/1: DFS, HR = 0.692, 95% CI=0.720–0.974, p value=0.021), while the expression of NUAK2 or PDK-1 had no effect on survival.
Conclusions: The expression of pAMPK or MAPK3/1 was found to be an independent prognostic marker for patients with resected gastric cancer.
No conflict of interest.

2659 POSTER

Iron-controlled cancer therapy: A new concept for anti-angiogenic drug (bevacizumab and sorafenib)

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Background: Iron is an essential element for both normal and cancer cells in humans. Iron overload is known to induce some kinds of cancer. Iron-depletion treatment is also known to suppress tumor growth in vivo. However iron-depletion mono-therapy has generally been thought to not be superior to ordinary chemotherapy and a standard therapeutic strategy in the treatment of cancer. We discovered that iron depletion inhibited the cancer cell proliferation and reciprocally induced angiogenesis in vitro and in vivo. Here we demonstrate that this new concept of iron controlled therapy induces a synergistic effect of anti-angiogenic drugs in the treatment of cancer.
Methods: A549, H1299 (lung cancer), TE4, TE8 (esophageal cancer), and HepG2, Hep3B (hepatocellular carcinoma: HCC) were used in this study. To stimulate iron depletion status, we used the iron depleted custom medium (passive iron depletion:PID) and deferasirox, an iron chilator, deferasirox (EXJADE® active iron depletion:AID). Bevacizumab and Sorafenib were used as anti-angiogenic drugs. We examined cell viability assay, flow cytometry, western blot analysis, and A549 and HepG2 subcutaneous tumor model in vivo.
Results: PID slightly inhibited proliferation of cancer cells, AID strongly inhibited them. Combination therapy (PID + Bevacizumab and AID + Sorafenib) -revealed a synergistic effect in vivo. In western blot analysis, AID affects the cancer cells as follows: increase VEGF expression via HIF-a, decrease N-cadherin expression. Moreover, AID + Sorafenib synergistically inhibited cyclin D1, cyclin E, CDK4 and CDK6, and induced apoptosis.
Conclusions: These results suggest that iron controlled cancer therapy has a potent synergistic anti-cancer effect with anti- angiogenic drugs.
No conflict of interest.

2660 POSTER

EGFR expression and prognosis in galbladder cancer

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Background: Gallbladder carcinoma (GBC) is the most aggressive of the biliary cancers with the shortest median survival duration. There is a lack of biomolecular level studies on this disease and few data on prognostic biomarkers.
Material and Methods: We evaluate the prognostic value of laboratorial (albumin level, CA 19.9 and CEA), surgical (type of resection, bleeding, tumor clearance), morphological (necrosis, perforation, nodal status, lymphatic embolization, perineural invasion, tumor grade and tumor localization at gallbladder) and molecular characteristics (EGFR, E-cadherin, p53 protein and COX2 immunoexpression) in a series of 42 pts with GBC treated from Jan 1995 to Jan 2006 at a tertiary cancer center in São Paulo, Brazil. Survival analysis was performed using the Kaplan–Meier method and Cox regression.
Results: A multivariate analysis disclosed EGFR expression +2/+3 (HR = 8.9; 95% CI 2.6 to 29.9; $p = 0.001$), presence of necrosis (HR = 20.7; 95% CI = 3.8 to 111.0; $p = 0.001$) and low albumin level (HR = 21.9; 95% CI = 2.5 to 194.7; $p = 0.006$) as independent prognostic factors.
Conclusions: Immunoexpression of epidermal growth factor receptor identified a poor prognostic subgroup of GBC patients, eventual candidates suitable to treatments based on molecularly targeted agents that inhibit EGFR pathways.
No conflict of interest.

2661 POSTER

The role of LDH serum levels in predicting global outcome in HCC patients treated with sorafenib: Implications for clinical management

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Background: In many tumour types serum LDH levels proved to represent an indirect marker of tumour hypoxia, neo-angiogenesis and worse prognosis. As we reported previously LDH is an important factor in hepatocellular carcinoma (HCC) patients undergoing transarterial chemoembolization (TACE). Sorafenib is at present the therapeutic stronghold in HCC patients in advanced stage. As a TKI mainly directed against the angiogenetic pathway, the correlation of sorafenib administration with markers of hypoxia could be an important tool in patients management. Aim of our analysis was to evaluate the role of lactate dehydrogenase (LDH) pre-treatment levels and its variation post-treatment for HCC patients treated with sorafenib.
Methods: 78 patients were available for our analysis. For all patients LDH values were collected within one month before the procedure and after treatment end. For study purposes we divided our patients into two groups, according to LDH median serum concentration registered (first group: LDH $\leqslant$380U/l; second group: LDH >380U/l). Patients were, also, classified according to the variation in LDH serum levels pre- and post-treatment (increased patients vs decreased patients).
Results: Patients proved homogeneous for all clinical characteristics analyzed. In patients with LDH values under 380 U/l median progression free survival (PFS) was 7.6 months, whereas it was 2.9 months in patients above the cut-off ($p = 0.026$). Accordingly median overall survival (OS) was 14.9 months and 11.2 months ($p = 0.019$). In patients with decreased LDH values after treatment median PFS was 6.8 months, and median OS was 13.2 months, whereas PFS was 1.2 months and OS 7.3 months in patients with increased LDH levels (TTP: $p = 0.0014$; OS: $p = 0.0096$).
Conclusions: In our experience, LDH seemed able to predict clinical outcome in terms of TTP and OS for HCC patients treated with sorafenib. Given the correlation between LDH levels and tumour angiogenesis we can speculate that patients with high LDH pretreatment levels may be optimal candidates for other emerging therapeutic agents or strategies.
No conflict of interest.

2662 POSTER

The effects of XPD /ERCC2, RAD51 and hOGG1 gene polymorphisms on overall survival of Turkish gastric cancer patients

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Aims: We assessed whether XPD /ERCC2, RAD51 and hOGG1 Gene Polymorphisms predicted clinical outcome in advanced gastric cancer patients.
Methods: DNA was isolated from parafin emedded tumor tissues and then SNPs analayses were done by MassARRAY® System (Sequenom). The data were statistically analyzed using SPSS software version 17.0 Statistical significance of the observed genotype frequencies was evaluated according to Hardy–Weinberg rule compared to the expected genotype frequencies.
Results: A total of 31 gastric cancer patients with locally inoperable or distant metastasis and performance status of 0−2 were enrolled in this study. We determined the XPD /ERCC2 Asp312Asn (rs1799793) single nucleotide gene polymorphism G23591A, RAD51(rs1801320) single nucleotide gene polymorphism G135C and hOGG1 Ser 326 Cys (rs1052133) single nucleotide gene polymorphism. Median age was 68 years: 74.2% male, 25.8% female. Docetaxel-based DCF regimen (docetaxel 75 mg/m(2) on day 1, cisplatin 75 mg/m(2) on day 1, and 5-fluorouracil 750 mg/m(2) for 5 days of continuous infusion every 21 days) with G-CSF were given to fourteen patients; all other patients received Mayo regimen.We found XPD /ERCC2 gene GA, GG, AA genotype and A, G allele frequencies in gastric cancer patients as 54.8%, 35.5%, 9.7% and 90.3%, 9.7%, respectively. Patients with GA genotype had a longer survival (11.96$\pm$2.177 months, 95% CI 7.69−16.23) than the other genotypes. However, this difference is not statistically significant ($p = 0.448$). We found that RAD51 gene GG, CG, CC genotype and G, C allele frequencies as 83.9%, 12.9%, 3.2%, 90%, 10%, respectively; for hOGG1 gene GC, CC, GG genotype and C,G allele frequencies as 48.4%, 45.2%, 6.5%, 69.4%, 30.6%, respectively. We didn't find any significant correlation between overall survival and genotype or allel for RAD51, hOGG1 genes ($p = 0.9$, $p = 0.307$, respectively). Cox regression analysis for overall survival showed that serum ALT level <33 IU/L (HR of ALT $\leqslant$33 IU/L vs >33 IU/Lis 2.705 $p < 0.001$);serum LDH level <214 IU (HR of LDH $\leqslant$214 IU/Lvs>214 IU/Lis1.247 $p = 0.007$) were the most important prognostic factors. The frequency of genotypes in these genes in patients did not show a significant deviation from Hardy–Weinberg equilibrium.
Conclusions: We could not find any significant association between the genotypes and clinicopathologic parameters; however, serum ALT and LDH levels were found to be the most important prognostic factors for overall survival.
No conflict of interest.

2663 POSTER

The changing of serum vitamin B12 and homocysteine levels after gastrectomy in patients with gastric cancer: Do they associate with clinicopathological factors?

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Bacground: After total or partial gastrectomy patients are at high risk of vitamin B12 (vit B12) deficiency, which results in elevation of homocysteine levels. However, the prevalence of the changing of serum vit B12 and homocysteine levels in patients with gastric cancer is not well investigated.
Methods: Sixty-two patients with gastric cancer who had undergone curative gastrectomy and fifty healthy controls were included. Serum vit B12 and homocysteine levels in gastric cancer patients were compared with those of healthy control subjects.
Results: Serum vit B12 level in gastrectomized patients was significantly lower than that of healthy controls (228.3$\pm$126.6 pg/mL vs. 309.9$\pm$174.3 pg/mL, $p = 0.002$), however, homocysteine levels were significantly higher in patients with gastric cancer compared with healthy controls (15.1 μmol/L vs. 12.5 μmol/L, $p = 0.016$). Mean serum folate level was found to be high in healthy controls (7.3 ng/mL) compared to patients (9.2 ng/mL, $p = 0.027$). Thirty-three (53.2%) patients received prophylactic vit B12 replacement after gastrectomy. Both serum vit B12 and homocysteine levels in patients receiving vit B12 treatment were similar with those in patients who are not receiving ($p>0.05$). When only patients who has not received vit B12 were analysed, we found significant low vit B12 and high homocysteine levels in gastrectomized patients compared to healthy subjects (231.8$\pm$97.2 pg/mL vs. 310$\pm$174.3 pg/mL, $p = 0.02$; 14.4 $\pm$6.1 μmol/L vs. 12.6$\pm$6.0 μmol/L, $p = 0.04$, respectively). Moreover, in patients transferin saturation was significantly found to be lower than controls ($p = 0.02$). There were no relationship iron parameters, vit B12 and homocysteine levels according to gastrectomy types ($p>0.05$).
Conclusions: Our results showed that gastric cancer patients who underwent total or subtotal gastrectomy had low vit B12 levels and hyperhomocysteinemia compared with healthy controls. In addition, the impact of vit B12 replacement on vit B12 and homocysteine levels could not be proved.
No conflict of interest.

2664 POSTER

Role of platelets in HCC cell growth: Clinical and experimental evidence

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Background: Thrombocytopenia has been reported to be both a risk factor for HCC and a prognostic factor. Many HCCs also occur in presence of normal platelets. The relevance of platelets for HCC is unclear.
Materials and Methods: Records were examined of 634 biopsy-proven HCCs patients without thrombocytopenia. Pooled human donor platelet extracts were then examined for their growth effects on human HCC cell lines in culture.

Results: 52 patients were identified with thrombocytosis (platelet levels >400 x 10^9/L) and compared to 582 patients with normal platelet levels. Average tumour diameters were 13.1 vs. 8.8 cm, $p < 0.0001$ and average total bilirubin levels were 0.9 vs.1.5, $p = 0.02$. There were significant increases in tumour size with increased platelet levels and a significant trend. In presence of 1% serum, platelet extracts stimulated HCC cell growth and migration. In presence of growth-inhibitory concentrations of either sorafenib or regorafenib, platelet extracts antagonised inhibition of HCC cell growth. Both clinical observations and experimental findings suggest that platelet factors may influence HCC growth.
Conclusions: Thrombocytosis in association with HCC occurs in patients with larger tumour sizes and better liver function. Platelets stimulate HCC growth in vitro. They are a source of several known HCC mitogens and their antagonism offers a potential new avenue for therapy.
No conflict of interest.

Proffered Papers Session (Sun, 29 Sep)
Genitourinary Malignancies − Other

2700 ORAL

Heterogeneous response and progression patterns of renal cell carcinoma metastases in individual patients reveal intra-tumour heterogeneity of anti-angiogenic drug resistance

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Background: We recently demonstrated genetic and functional intra-tumour heterogeneity (ITH) in advanced clear cell renal cell carcinomas (ccRCC) (Gerlinger et al, N Engl J Med, 2013). We hypothesize that ITH may also lead to differences in drug sensitivity of different metastatic sites within individual patients. To investigate this, we longitudinally assessed multiple metastatic lesions in patients treated with VEGFR-TKI therapy.
Patients and Methods: Multiple metastatic lesions from each of 19 treatment naive patients with ccRCC were followed by contrast CT scans during first line VEGFR-TKI therapy with sunitinib or pazopanib in the context of clinical trials. The diameter of each measurable lesion was quantified before treatment initiation and at regular intervals during treatment until disease progression (RECIST criteria). Individual metastases were categorized based on their best response to treatment into responding (RL:$\geqslant$20% decrease in diameter), stable (SL:<20% change) and progressing (PL:$\geqslant$20% increase in diameter) lesions. A heterogeneous response was defined as the presence of metastases in at least two of these categories.
Results: A median of 4 metastatic lesions per patient (90 lesions in total) were assessed longitudinally by regular CT scans. Heterogeneous responses were found in 42% of patients ($n = 8$). RLs and PLs were detected simultaneously in 5 of these patients. Progressive disease by RECIST criteria occurred through progression of existing metastases in one patient and through the appearance of new metastases in the other 18 patients. Synchronous progression of existing metastatic sites was detected in 10 of these patients; however, 70% (63/90) of the existing metastases remained controlled (RL/SL) at the time of RECIST progression, indicating ITH of acquired resistance.
Conclusions: Heterogeneous radiological responses of metastatic sites were detected in 42% of patients with ccRCC treated with VEGFR-TKI therapy. At disease progression, 95% of patients had developed new metastases but the majority of existing lesions remained controlled. The simultaneous presence of sensitive and resistant metastases in a large proportion of ccRCC patients reveals clinically relevant ITH, potentially driven by the molecular heterogeneity previously identified. ITH of VEGFR-TKI sensitivity suggests that single biopsies are likely to miss resistant lesions, hindering the identification of resistance mechanisms or predictive biomarkers in metastatic ccRCC.
Conflict of interest: *Corporate-sponsored research: GSK, Pfizer, Astellas, Bayer, Novartis*

2701 ORAL

Prognostic significance of nephrectomy in patients with synchronous metastases from renal cell carcinoma (RCC) treated with 1st line sunitinib: A European collaborative study

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Background: Nephrectomy was shown to be associated with improved outcome in patients with metastatic RCC (mRCC), treated with cytokines. Nevertheless, its role in the anti-VEGF targeted therapy era is controversial. This is the first study to evaluate the prognostic role of nephrectomy in patients with mRCC and synchronous metastases, treated with sunitinib.
Patients and Methods: Patients were selected from a multinational, multi-institutional database (Greece, France, Belgium), which includes 458 patients with histologically confirmed mRCC, treated with 1st-line sunitinib. Selection criterion for this analysis was the diagnosis of metastases prior to, at the time of or within 3 months from the diagnosis of RCC. Multiple Imputations were implemented for missing values. Correlations of baseline characteristics with OS were assessed through hazard ratios estimated from univariate Cox proportional hazards models. Significant factors were then included in a multivariate Cox proportional hazards model.
Results: 189 patients treated between 1/2006−3/2012, fulfilled the selection criteria. 38 patients (20%) did not undergo nephrectomy. Patients who had undergone nephrectomy were younger (<65 years 76% vs. 54%, $p = 0.011$), had better PS (PS 0 62% vs. 26%, $p < 0.001$), received IFN more frequently (40% vs. 10%, $p < 0.001$), had lower incidence of neutrophilia (45% vs. 73%, $p = 0.006$) and abnormal LDH (15% vs. 52%, $p < 0.001$) but had more frequently more than 2 metastatic sites (44% vs. 24%, $p = 0.02$). The location of metastases did not affect the decision of nephrectomy. Patients with nephrectomy lived significantly longer than those without nephrectomy (median OS 24 [95% CI: 20−28] vs. 10 [95% CI: 5−16] months, $p < 0.001$).
Multivariate analysis showed that age (<65 vs. >65), brain metastases, bone metastases and histology (clear cell vs. other) were independent prognostic factors. When nephrectomy was entered in a multivariate cox regression models including the above factors, it retained its significance (Table 1). When risk stratification according to IMDC or MSKCC was used in multivariate analysis, nephrectomy retained its independent prognostic significance.
Subgroup analyses suggested a more pronounced effect of nephrectomy in patients with clear cell histology or <2 metastatic sites, but these results are limited by the small number of patients included in each subgroup.

Table 1.

Model	Hazard ratio of nephrectomy after multiple imputation	95% CI	p
No risk stratification	0.478	0.297–0.771	.002
IMDC risk stratification	0.418	0.265–0.661	<0.001
MSKCC risk stratification	0.420	0.268–0.658	<0.001

Conclusions: In the targeted therapy era, nephrectomy is mainly offered to mRCC patients with synchronous metastases who have favourable prognostic features. Nevertheless, in this study nephrectomy retained its favorable prognostic significance independently of these factors. Information regarding the selection of patients likely to benefit from this approach may be derived by Prospective Phase III trials which are under way (CARMENA, SURTIME).
Conflict of interest: *Advisory board: Pfizer. Other substantive relationships: Pfizer*

2702 ORAL

Tumor response is an independent prognostic factor in patients (pts) treated for metastatic renal cell carcinoma (mRCC)

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Background: Pts treated for mRCC may have different outcomes based on tumor response. To explore whether extent of tumor shrinkage correlates with distinct clinical outcomes and may represent an early indication of treatment benefit, we investigated these questions in a pooled clinical trial population.
Materials and Methods: Data from pts treated in phase II (NCT00054886, NCT00077974, NCT00267748, NCT00338884, NCT00137423) and phase III (NCT00083889, NCT00065468, NCT00678392) trials sponsored by Pfizer from 2003 to 2011 were included. Pts were characterized by maximal tumor shrinkage from baseline (⩽100% to <-60%, ⩽60% to <-30%, ⩽-30% to <0%, ⩽0 to <+20%, ⩾+20%). Pts without post-baseline scans were also included. A Cox proportional hazard analysis as well as a 6-month landmark analysis were performed for the evaluation of prognostic factors with progression free survival (PFS) and overall survival (OS); Kaplan–Meier (K-M) plots were utilized to estimate median PFS and OS.
Results: 2749 pts (71% male) with median age 60 (33% ⩾65) were treated (median 162 days) with sunitinib (n = 1059), interferon-alfa (IFN) (n = 560), axitinib (n = 359), sorafenib (n = 335), temsirolimus (TEM) (n = 208), or TEM + IFN (n = 208). Most pts had baseline ECOG PS of 0 (47%) or 1 (51%), clear cell histology (91%), and nephrectomy (84%). Multivariate analysis of prognostic factors including age, performance status, LDH, hemoglobin, and calcium, showed that maximal tumor shrinkage was an independent predictor of OS. Median OS was 54.5 months in patients with the highest maximal tumor shrinkage (−100% to −60%), and was 7.3 months in patients with ⩾+20% increase in tumor size. Overall, the degree of tumor shrinkage correlated with OS (Table).

Maximal tumor shrinkage	N	HR (95% CI)	Median OS (months)
⩽−100% to <−60%	283	0.267 (0.201–0.354) [a]	54.5
⩽−60% to <−30%	547	0.697 (0.589–0.825) [a]	26.4
⩽−30% to <0%	1155	*	16.6
⩽0 to <+20%	390	1.618 (1.383–1.893) [a]	10.4
⩾+20%	156	1.918 (1.540–2.389) [a]	7.3
No post-baseline scan	218	4.369 (3.607–5.292) [a]	2.0

[a] p < 0.0001. *Reference in Cox proportional hazards model.

Conclusions: Tumor shrinkage is an independent predictor of OS. Patients with maximal tumor shrinkage achieve marked clinical benefit with prolonged OS, independent of systemic therapy. Achievement of maximal tumor response should be a therapeutic goal in patients with mRCC.
Conflict of interest: *Ownership: Pfizer. Advisory board: Astellas, Aveo, GlaxoSmithKline, Novartis, Pfizer, Roche. Other substantive relationships: Employee: Pfizer Pharma GmbH Germany, Pfizer Inc.Lecturer: Astellas, GlaxoSmithKline, Novartis, Pfizer, Roche*

2703 ORAL

Preliminary data on feasibility of vinflunine (VFL)-based combinations as 1st line in CDDP-unfit patients (pts) with advanced urothelial carcinoma (UC): VFL/gemcitabine vs. VFL/CBDCA in a randomised international phase II trial (JASINT1)

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Background: There is no standard treatment in patients unfit for a CDDP-based regimen as 1st line chemotherapy (CT) for advanced or metastatic UC. CBDCA-gemcitabine doublet or single agents are frequently used. VFL is a novel agent approved in the post-platinum setting that has shown to be safe in pts with impaired renal function. The aim of this study is to provide data of the benefit/risk ratio of two VFL combination CT regimens in UC.
Methods: The primary endpoint was to assess the disease control (DC) rate (CR + PR + SD by RECIST 1.1); 68 pts with a creatinine clearance (CrCl) <60 mL/min but ⩾30, PS 0/1, no prior systemic CT (except neoadjuvant or adjuvant CT if relapse occurred ⩾6 months after last dose) were to be randomised. Depending on CrCl, <40 or ⩾40 mL/min, pts received VFL 250 or 280 mg/m^2, plus Gemcitabine (Arm A) 750 mg/m^2, escalated to 1000 in cycle 2 (if no toxicity Grade (G) ⩾2) or plus CBDCA AUC 4.5 (Arm B). Other endpoints included safety, response rate, PFS, OS.
Results: We report on the safety data of the first 43 recruited pts (February 2011-February 2012), cut-off June 2012, median follow-up 7 months (21 arm A, 22 arm B). Median age was 70 yrs, PS 0 in 46.5% and PS 1 in 53.5%; 53% and 47% pts had bladder and upper tract primary sites, respectively; 14% had received prior CT. Pts characteristics were similar in both groups. The vast majority of pts had multiple co-morbidities, cardiac in 26%. Mean CrCl was 46.7 mL/min (<40 in 19%). Median [range] number of cycles was 5 [1−12] and the median VFL relative dose-intensity was 98% and 93% in arms A and B, respectively. Haematological G3/4 events were more frequent in arm B with neutropenia in 68% pts (vs. 43%) and febrile neutropenia in 9.1% (vs. 0%). Overall, most frequent possibly related non-haematological G3/4 adverse events were asthenia-fatigue (18.6%), infection (11.6%), and constipation (7.0%) without major difference between arms. The reason for treatment discontinuation was a non-haematological drug-related event in 9.5% and 18% pts, in arms A and B, respectively. DC was observed in 36/41 evaluable pts (17 A, 19 B) with ORR in 20/41 pts (confirmed in 16).
Conclusions: Preliminary data confirm that both doublets with VFL are feasible, safe and can be administered for ⩾5 cycles. The DC was similar between arms but haematological toxicity was more frequent with VFL-CBDCA. Collection of data on the whole cohort is ongoing.
Conflict of interest: *Ownership: Pierre Fabre M*dicament. Advisory board: M. De Santis. Corporate-sponsored research: Coordinator of trials involving vinflunine: M. De Santis, S. Culine. Other substantive relationships: Speaker: M. De Santis, S. Culine Employee of Pierre Fabre Research Institute: C. Lucas, N. Vaissi*re, J.P. Burillon*

2704 ORAL

Phase II study of eribulin in platinum-treated, tubulin naive advanced urothelial cancer (UC) − A California Cancer Consortium trial (NCI/CTEP 7435)

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Introduction: There is an unmet need for new agents in locally advanced and metastatic UC. Tubulin directed agents (vincas, taxanes) have activity in UC. We previously reported that eribulin, a microtubule modulator derived from the black Pacific sea sponge toxin, is active against UC in the frontline setting (D. Quinn, ASCO A4359, 2010). Here we report the initial results of a phase II study in UC patients (pts) with prior platinum-based therapy but with no prior anti-tubulin drug exposure, which has completed accrual. An ongoing parallel study is evaluating patients with prior anti-tubulin drug exposure.
Methods: Patients with a calculated CrCl ⩾20 mL/m, UC of any histological type & prior platinum-based cytotoxic therapy for advanced disease were eligible. Eribulin 1.4 mg/m^2 was given IV on d 1 & 8, q3 weeks. An overall response rate (RR) of >20% was considered promising for further study; 41 pts were required in a Simon 2-stage design. PFS and OS were Secondary endpoints.
Results: Of 46 pts entered, 39 were evaluable (7 too early).
Patient characteristics: Median age: 67 years (range: 25−86); Males: 87%; KPS ⩾90% in 64%, ⩽80% in 33%; Histology: Transitional 36 (92%), unclassified 2 (6%) adenocarcinoma 1 (2%); Bajorin risk groups: 0: 33%, 1: 62%, 2: 5%.
Overall RR was 36% (95% CI: 21, 53%), including 1 CR, 7 PR, and 6 unconfirmed PR. [Confirmed RR was 21% (95% CI: 9, 36%)]. Stable disease for ⩾12 weeks was seen in 12 pts (31%). PD was best response in 11 pts (28%). At median follow-up of 5.9 (1.4, 17.1) months, median PFS

was 4.1 months (2.6, 6.4). Median OS was 9.6 months (5.3, ∞) 16 pts dead). PFS was associated with Bajorin risk group (p = 0.005 for trend). Toxicities: 24 pts (62%) Gr 3/4 neutropenia, 3 pts (8%) Gr 3 febrile neutropenia, 14 pts (36%) and Gr 1/2 sensory neuropathy. Other non-hematologic toxicities: hyperglycemia (1 pts (3%) Gr 3), hyponatremia (8 pts (21%) Gr 1), alopecia (16 pts (41%) Gr 1/2), leg fatigue & aching (2 (5%) Gr1).

Conclusions: Eribulin has highly encouraging single agent activity in advanced UC pts with prior platinum-based chemotherapy and has the potential to improve outcomes in this disease. Phase III evaluation of eribulin in advanced UC is warranted. http://clinicaltrials.gov/show/NCT00365157 (U01 CA062505 P30 CA014089, P30 CA033572).

No conflict of interest.

2705 ORAL

Risk of cardiovascular disease, diabetes and death in germ-cell cancer survivors in a large cohort

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Background: Treatment of germ-cell cancer (GCC) imposes a risk of secondary cardiovascular disease (CVD) and increased mortality. Through collation of hospital files with national registries we present the most complete analysis to date.

Material and Methods: Danish patients treated for GCC 1984–2007 were included (n = 4697) in this study. Data on cause of death, CVD and diabetes were obtained from national registries and collated with information from hospital files. Type of treatment was registered; cisplatin, etoposide and bleomycin (BEP), (n = 1525), radiotherapy (RT) (adjuvant (n = 298) or curative (n = 366)) or combinations hereof and surveillance only (n = 2314). Patients were excluded if they died of GCC (n = 179) or if they received other types of treatment (n = 53). Only tobacco use had missing values with data available on 2063 patients and missing on 2402. Hazard ratios (HR) were calculated adjusted for age and tobacco use and compared to surveillance only.

Results: Median observation time was: 15.3 years (IQR, 9.8–21.3 years). Treatment with PEB increased the risk of all major cardiovascular diseases independently (table). RT given with curative intent increased the risk of diabetes significantly. If tobacco use was omitted from the analyses, HR on CVD remained significant in the chemotherapy group, whereas HR on CVD remained insignificant in the RT group.

Conclusions: We confirm that treatment with BEP increases long-term risk of CVD in GCC survivors compared to patients treated on a surveillance program. CVD was not increased in patients treated with RT, but patients with disseminated seminoma treated with RT had an increased risk of developing diabetes. With the present observation time, development of diabetes had no impact on CVD-risk. Death due to CVD was not significantly increased. The present data will be compared to an age-matched control group without GCC and these data will be presented at the meeting.

No conflict of interest.

Poster Discussion Session (Sun, 29 Sep) and Poster Session (Mon, 30 Sep)
Genitourinary Malignancies − Other

2706 POSTER DISCUSSION

Open-label phase II trial of first-line everolimus monotherapy in patients with papillary metastatic renal cell carcinoma: RAPTOR final analysis

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Background: Treatment options for patients with papillary metastatic renal cell carcinoma (mRCC) are limited. The RAPTOR (RAD001 in Advanced Papillary Tumor Program in Europe; ClinicalTrials.gov, NCT00688753) study evaluated first-line everolimus in patients with papillary mRCC. Preliminary results were presented at ESMO 2012.

Materials and Methods: RAPTOR is an open-label, multicenter phase II trial. Adult patients with type I or type II papillary mRCC, an ECOG performance status of $\leqslant$1, and no previous systemic therapy for RCC were enrolled. Central pathology review was performed for every patient. Patients received oral everolimus 10 mg once daily until disease progression or unacceptable toxicity. The primary end point was the proportion of patients progression free at 6 months. Secondary end points included progression-free survival (PFS), overall survival (OS), and safety.

Results: Study duration at time of analysis (Jan. 2013) was 3.5 years. The analysis included three populations: safety (N = 92, 100%), intention-to-treat (ITT, n = 83), and per protocol (PP, received $\geqslant$1 dose of study drug dose and had no major protocol violations; n = 63). Most patients were men (78%), most were white (92%), and mean age was 60 years (23−84 years). Among patients with papillary RCC per local review (99%), of whom 77% were confirmed centrally, 58% had type II and 16% had type I (25% missing) and per central review (76%), 59% had type II and 33% had type I (9% missing). In the PP population, the 6 month PFS rate was 58.7% per local review and 34.9% per central review. Median PFS was 7.8 months (95% CI: 5.5–10.8) per local review and 3.9 months (95% CI: 2.1−5.7) per central review in the PP population and 7.6 months (5.5−9.9) per local review and 3.7 months (2.3−5.5) per central review in the ITT population. Median OS was 21.0 months (95% CI: 15.4–28.0) in the ITT population and 20.0 months (95% CI: 11.1–28.0) in the PP population. Common grade $\geqslant$3 AEs included asthenia (10.9%), fatigue (5.4%), and anemia (5.4%); 27.2% of patients discontinued due to AEs.

Conclusions: These results demonstrated that everolimus provides clinical benefit with promising OS and is generally well tolerated by patients with papillary mRCC.

Conflict of interest: *Advisory board: Astellas, Aveo, Aveo-Astellas, Bayer, Bayer-Schering, Boehringer-Ingelheim, GlaxoSmithKline, Jansen, Novartis, Pfizer, Roche, and Sanofi-Aventis. Corporate-sponsored research: Pfizer and GlaxoSmithKline. Other substantive relationships: One author is an employee of Novartis Pharma GmbH.*

Table (abstract 2705).

Cause of admission/death	Hazard Ratio (HR) (95% CI), reference (HR = 1.0): surveillance only					
	BEP		RT, curative		RT, adjuvant	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Cerebrovascular accident (n = 121)	1.7 (1.0−2.8)	0.060	0.7 (0.3−1.8)	0.49	*	*
Coronary heart disease/Myocardial infarction (n = 306)	1.6 (1.1−2.3)	0.008	0.7 (0.4−1.4)	0.33	1.0 (0.5−2.0)	0.98
Venous thromboembolism (n = 78)	2.0 (1.0−4.1)	0.050	1.6 (0.6−4.3)	0.34	0.5 (0.1−4.1)	0.54
Heart Failure (n = 67)	2.2 (1.1−4.6)	0.031	2.1 (0.8−5.1)	0.11	0.6 (0.1−4.7)	0.64
Any above (n = 475)	1.8 (1.4−2.4)	<0.001	0.9 (0.6−1.5)	0.94	0.7 (0.4−1.3)	0.72
Other CVD (n = 455) [a]	1.5 (1.1−2.0)	0.012	0.8 (0.5−1.4)	0.50	0.5 (0.3−1.1)	0.079
Any CVD (n = 715)	1.5 (1.2−1.9)	0.001	0.8 (0.5−1.2)	0.27	0.6 (0.4−1.1)	0.096
Diabetes (n = 255)	1.2 (0.8−1.8)	0.42	1.7 (1.1−2.8)	0.025	1.4 (0.7−2.7)	0.29
Death by CVD (n = 80)	1.8 (1.0−3.5)	0.053	1.7 (0.7−3.8)	0.22	0.5 (0.1−2.5)	0.37

*No events. [a] Including dysrythmiae (n = 141), hypertension (n = 121), endocarditis/valve failure (n = 41), transient cerebral ischaemia (n = 39), arteriosclerosis (n = 33), pericarditis (n = 23), abdominal aortic aneurysm (n = 19), cardiomyopathy (n = 11), and other (n = 27).

2707 POSTER DISCUSSION

Sunitinib expanded-access trial in metastatic renal cell carcinoma (mRCC) − final Italian results

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Background: Sunitinib is established as a reference standard of care and is approved globally for patients (pts) with mRCC based on a randomized, phase III trial (Motzer et al, 2007). Prior to regulatory approval, more than 4,500 patients were enrolled between 2005 and 2007 in a global mRCC expanded-access trial (ClinicalTrials.gov, NCT00130897; Pfizer) in which sunitinib was given to pts ineligible for other sunitinib trials. Sunitinib was shown to have a manageable safety profile and encouraging efficacy in this broad population of pts (Gore et al, 2009). Here we report final efficacy and safety results for pts in Italy who enrolled in this trial.

Material and Methods: 521 pts aged ⩾18 years with treatment-naive or previously treated mRCC received oral sunitinib at 50 mg/day on a 4-wk-on/2-wk-off schedule. Tumor measurements were scheduled per local standard practice and measured using RECIST. Safety was assessed regularly. Objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and treatment-related adverse events (AEs) are reported. Analyses included all pts who received ⩾1 dose of sunitinib.

Results: Characteristics of 521 pts included 40% aged ⩾65 years, 14% with non-clear cell RCC, 11% with ECOG performance status (PS) ⩾2, and 11% with baseline brain metastases. Median treatment duration and follow-up were 7.4 and 12.3 months, respectively. 514 pts (99%) discontinued treatment; reasons included death (17%), lack of efficacy (46%), or AEs (13%). ORR was 12%, with ORR in subgroups of interest as follows: aged ⩾65 years, 8%; non-clear cell RCC, 7%; ECOG PS ⩾2, 2%; and baseline brain metastases, 4%. Median PFS and OS were 9.1 months (95% CI: 7.9–11.0) and 27.2 months (95% CI: 22.5–36.5), respectively. The most common any-grade treatment-related AEs were asthenia (44%; fatigue, 15%), thrombocytopenia and stomatitis (both 37%), diarrhea (36%), mucosal inflammation (29%), hypertension (26%), and dysgeusia (25%); the most common grade 3/4 treatment-related AEs were thrombocytopenia (10%), asthenia (9%; fatigue, 3%), neutropenia and stomatitis (both 6%), hypertension (5%), and hand–foot syndrome, mucosal inflammation, and diarrhea (all 4%).

Conclusions: Among 521 mRCC pts in Italy treated in the expanded-access trial, safety with sunitinib was comparable to, whereas OS was longer than, that of the overall population as previously reported.

Conflict of interest: *Ownership: K Fly, K Zhang and S Hariharan − Pfizer Inc stock ownership. Advisory board: CN Sternberg − Pfizer Inc, AVEO, Novartis, Bayer S Bracarda − Pfizer Inc, Bayer, Novartis, GSK, Boehringer-Ingelheim, AVEO-Astellas, Janssen, Sanofi-Aventis C Porta − Pfizer Inc, GSK, Bayer-Schering, Novartis, Astellas, AVEO, Boehringer-Ingelheim. Corporate-sponsored research: CN Sternberg − Pfizer Inc C Porta − Pfizer Inc, GSK, Bayer-Schering, Novartis, Astellas, AVEO. Other substantive relationships: K Fly, K Zhang and S Hariharan − Pfizer Inc employment C Porta − substantive relationships with Pfizer Inc, GSK, Bayer-Schering, Novartis, Astellas*

2708 POSTER DISCUSSION

Characterizing prior nephrectomy patients with metastatic renal cell carcinoma (mRCC) treated with first-line sunitinib versus interferon-alfa

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Background: In a randomized, phase III trial (Motzer et al, 2009), median progression-free survival (PFS; primary endpoint) was superior with sunitinib versus interferon-alfa (IFN-α) as first-line therapy of mRCC, 11 versus 5 months, respectively (P<0.001); median overall survival (OS) was 26.4 versus 21.8 months (P = 0.051). Prior nephrectomy was previously shown by multivariate Cox regression analysis to be an independent predictor of improved PFS with sunitinib in this trial (Patil et al, 2011). Here we report a retrospective analysis of the baseline characteristics and survival outcomes of patients in this trial with prior nephrectomy.

Material and Methods: 750 treatment-naive patients with mRCC were randomly assigned to sunitinib 50 mg/day on a 4-week-on-2-week-off schedule or IFN-α 9 MU subcutaneously thrice weekly. Median PFS (as assessed by central review of imaging studies) and OS were estimated by Kaplan–Meier method for the subset of patients with prior nephrectomy in each arm, with 95% confidence intervals (CIs) and hazard ratios (HRs) calculated for each. Median survival values were compared by 2-sided, unstratified log-rank test.

Results: Of 375 patients randomized to each arm, 90% had prior nephrectomy (sunitinib, n = 339; IFN-α, n = 335). Baseline characteristics were similar in each group; median age was 61 and 59 years, 71% and 72% were male, and the percentages of patients with ECOG performance status of 0/1 were 64%/36% and 64%/35%, respectively. Median PFS (95% CI) of sunitinib versus IFN-α in patients with prior nephrectomy was 11.5 months (10.7–13.6) versus 5.1 months (4.1−5.5), respectively (HR, 0.502; 95% CI, 0.407–0.618; P<0.0001). Median OS (95% CI) of sunitinib versus IFN-α in patients with prior nephrectomy was 30.0 months (23.7–not reached) versus 24.2 months (19.1–28.8), respectively (HR, 0.806; 95% CI, 0.650–1.000; P = 0.0496). Baseline characteristics and survival outcomes of patients with prior nephrectomy categorized by baseline ECOG performance status will also be presented.

Conclusions: In treatment-naive mRCC patients with prior nephrectomy, sunitinib maintained and improved upon its treatment effect over IFN-α in the overall population, with a statistically significant difference in median OS.

Conflict of interest: *Ownership: X. Lin, S. Pitman Lowenthal, B. Kortowsky and E. Matczak − Pfizer Inc stock ownership. Advisory board: R.A. Figlin − Pfizer Inc T.E. Hutson − Pfizer Inc, Bayer, GSK, Genentech, AVEO, Novartis G.A. Bjarnason − Pfizer Inc S. Oudard − Pfizer Inc, Bayer, Novartis, Janssen, Keocyt, Takeda, Roche. Corporate-sponsored research: T.E. Hutson − Pfizer Inc, GSK, AVEO, Novartis G.A. Bjarnason − Pfizer Inc S. Oudard − Bayer, Novartis. Other substantive relationships: T.E. Hutson − honoraria from Pfizer Inc, Bayer, GSK, Genentech, AVEO, Novartis X. Lin, S. Pitman Lowenthal, B. Kortowsky and E. Matczak − employed by Pfizer Inc*

Table (abstract 2710): STEPP analysis over anti-S (pmol/ml; median: 53.5) using IL-6 (pg/ml; median: 7.02) defined subgroups comparing Nap + IFN-α vs IFN-α on OS (HR (N))

anti-S IL-6	13.8–36.7	13.8–43.2	28.2–53.9	35.4−67	41.8–84.2	51.7–125	65.2–4705	81.5–4705
<3.24	0.26 (26)	0.25 (43)	0.59 (50)	1.21 (57)	2.84 (51)	3.45 (41)	2.04 (36)	2.1 (22)
<7.02	0.41 (73)	0.47 (104)	0.68 (102)	1.04 (100)	2.03 (92)	2.09 (91)	1.26 (81)	1.07 (54)
>7.02	1.83 (53)	1.46 (82)	1.48 (89)	1.31 (91)	1.5 (99)	1.18 (100)	1.5 (105)	1.25 (72)
All	0.83 (126)	0.82 (186)	0.9 (191)	1.22 (191)	1.61 (191)	1.44 (191)	1.28 (186)	1.09 (126)

2709 POSTER DISCUSSION

An update of the Renal Cancer Appropriateness-based treatment toolkit (ReCATT) based on the validated semi-quantitative RAND UCLA methodology

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Background: Since we developed the RAND-UCLA appropriateness-based treatment toolkit for the treatment of patients with advanced/metastatic renal cancer in 2011 (Gore ME et al, Eur J Cancer. 2012 May;48(7):1038−47), there have been several clinical studies conducted in patients with metastatic renal cell carcinoma (RCC). These clinical data comprises RCTs and other non-controlled studies. To ensure that the treatment toolkit is up-to-date with available clinical evidence, especially in light of outputs of the COMPARZ trial (Motzer RJ et al. ESMO, 2012 October: Abstract LBA8), we have undertaken an update of prior published work.
Methods: The decision support toolkit was updated using the RAND/UCLA method and employed a panel of 11 EU RCC experts who evaluated treatment strategies in 36 different case scenarios. Cases and treatments were updated based on outputs of the updated systematic review. Elimination of the 'clinical trial' treatment option makes the toolkit more relevant to practice outside specialist centres. Individual panel members scored the appropriateness and their preferences of several interventions for each case and treatment, 1 (inappropriate) to 9 (most appropriate). This was followed by a panel meeting to reconcile disagreements as per the RAND methodology.
Results: Outputs of this update, while generally in-line with the published results in 2011, showed a greater specificity of appropriateness in general. Only 41 of the 575 total treatment options scored were seen as appropriate. There was higher concordance among the panel for the appropriateness/in-appropriateness of therapies in general, compared to the scoring from 2011. Areas in which there was discordance among the panel were those with the least- available data and include
– Use of pazopanib and sunitinib in the neo-adjuvant setting
– Possibility of nephrectomy with or without systemic targeted therapies in patients who have a high ASA score (3 or 4) and, thus, have been identified as having poor surgical risk

A significant change over the previous scoring exercise was that pazopanib and sunitinib are now considered equal by the panel in every situation. Of the 101 peer-reviewed publications concerning the treatment of RCC in the past 2 years, 24 had grade 1 evidence (SIGN grading criteria; SIGN, 2010). Further analysis will be conducted to explore the association between this new grade 1 evidence and the greater specificity of the outputs from the toolkit.
Conclusions: Apart from an update on the outputs of the decision toolkit, the update has objectively assessed more updated expert opinion in the treatment of RCC. Large studies have a rapid impact on experts, which may not be translated to general oncology practice. Areas of uncertainty and disagreement among RCC experts warrant further clinical research. Discordance around the role of surgery in high-risk patients may be because decision-making in such patients is best done only when actually seeing the patient.

Conflict of interest: *Ownership: Astrazeneca. Advisory board: GSK, Pfizer, Bayer-Schering, Novartis, Astellas, Aveo, Boehringer-Ingelheim. Board of directors: None. Corporate-sponsored research: GSK, Pfizer, Bayer-Schering, Novartis, Astellas, Aveo. Other substantive relationships: GSK, Pfizer, Bayer-Schering, Novartis, Astellas*

2710 POSTER DISCUSSION

Baseline biomarker trend analysis of a randomized phase 2/3 study of naptumomab estafenatox plus IFN-a vs IFN-a in advanced renal cell carcinoma

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Background: Naptumomab estafenatox/ANYARA (Nap) is a fusion protein of an antibody (5T4) and a superantigen (SEA/E-120). After phase 1 studies a randomized phase 2/3 trial of Nap + IFN-α vs IFN-α was conducted. The main results were presented at ASCO 2013. The primary endpoint OS was not reached, HR = 1.08. In a subgroup of 130 patients (pts) having below median of baseline IL-6 and anti-SEA/E-120 antibodies (anti-S), prolonged OS (HR = 0.59, p = 0.02) was achieved. Plasma IL-6 was predictive of pazopanib and vaccine benefit in RCC pts.
Methods: 513 pts with RCC were treated. Baseline biomarkers IL-6 and anti-S were analyzed. Trend analysis (moving median, adapted STEPP) was performed for the biomarkers vs drug concentration, induced IL-2 (marker for drug induced T cell activation), PFS HR and OS HR (HR corrected by Heng risks).
Results: The STEPP analysis (see table) shows clear trends of decreasing HRs in pts with decreasing IL-6 and anti-S. The pts with IL-6 <3.24 pg/ml and anti-S <36.7 pmol/ml display an OS HR of 0.26. The pts defined by the three lowest anti-S blocks having IL-6 below median of the study display OS HRs $\leqslant$0.68. Pts with high anti-S or IL-6 have HRs >1, most pronounced at high anti-S and low IL-6. Similar trends are seen for PFS HRs. Plasma concentrations of Nap and induced IL-2 show matched trends.
Conclusions: The trend analysis clearly indicates that low baseline anti-S and IL-6 plasma levels independently predict anti-tumor efficacy after Nap + IFN treatment. The results warrant further studies with Nap in sequence or combo with e.g. TKIs in a biomarker IL-6/ anti-S defined subgroup. The results also emphasize the potential role of IL-6 as a predictive factor for the outcome on treatment with immunotherapies and TKIs in RCC.
Conflict of interest: *Advisory board: Tim Eisen & Robert Hawkins − Advisory Board Membership. Other substantive relationships: Gunnar Hedlund, Göran Forsberg & Örjan Nordle.*

2711 POSTER DISCUSSION

c-MET is an active target across all papillary renal cell carcinoma (pRCC): Results from a large genomic French study

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Background: C-MET, is a tyrosine kinase receptor involved in tumor cell proliferation and migration. C- MET gene copy number alterations or somatic mutations have been reported in sporadic type I pRCC. MET pathway activation has not been investigated in type II (or non type I) pRCC. We used high-resolution oligonucleotide comparative genomic hybridization (CGH) arrays and matching gene expression array data on a large collection of pRCC to investigate c-MET as a potential deregulated gene across all pRCC subtypes.

Methods: 220 frozen pRCC were collected through French RCC Network, quality controlled for percentage of malignant cells >70% and subsequently RNA and DNA extraction were performed. Gene expression data generated with human whole genome Agilent 8x60K arrays was assessed on 98 pRCC (47 type I, 45 type II and 6 unclassified pRCC). Copy number alterations were analysed using Agilent Human 2x400K array for Type II pRCC and using comparative genomic microarray analysis (CGMA) method from gene expression data for Type I pRCC. C-MET gene sequencing was performed on type I pRCC.

Results:

- Ten somatic mutations of MET gene were identified amongst 51 type I pRCC (19.6%), including 8 mutations previously reported and 2 new mutations strongly predicted to be damaging.
- Copy Number alterations (Gain or Kr 7 polysomy) were identified by CGMA in 71% of type I and in 46 % of type II pRCC (69% gain in low grade type II and 38% gain in high grade type II).
- Correlation between DNA copy number alterations (CGH) and mRNA expression level was highly significant (Cor = 0.6, adjP=3.5e-02)
- c-MET expression level was high across all pRCC (Fold change = 5.8/ 3.1/ 1.8; $p=1.4x10^{-14}/p=1.8x10^{-4}/p = 0.1$) respectively for pRCC I /pRCC II /clear cell when compared each to normal kidney expression)
- LRRK2 is a known kinase required for MET downstream pathway activation. We found that LRRK2 overexpression specifically correlates with elevated c-MET mRNA expression across pRCC (Fold change = 7.4/3.6/1.5; $p= 1x10^{-11}/ p=8x10^{-6}/p = 0.2$) in pRCC I /pRCC II /clear cell respectively when compared each to normal kidney expression).

Conclusion: The present report expends the role of c-MET activation as a potential target across all pRCC subtypes. Further evaluation of MET downstream pathway activation according to c- MET status (somatic mutation, copy number alteration) is ongoing. These data support investigating c-MET inhibitors in phase II trials in correlation with MET activation status.

Conflict of interest: *Corporate-sponsored research: Albiges: research grant from Novartis*

2712 POSTER DISCUSSION

Treatment and outcomes of non-transitional cell bladder cancer

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Background: Non-transitional cell (non-TCC) bladder tumours are characterised by advanced stage and poor prognosis. Their relative infrequency and exclusion from bladder cancer trials means there is lack of evidence regarding ideal treatment approach. We report on the tumour characteristics and treatment outcomes of patients with non-TCC treated at our institution.

Material and Methods: Retrospective analysis between January 1990 and June 2011 identified 1269 patients with bladder cancer, of those 94 (46 male, 48 female) had confirmed non-TCC tumour on centralised pathological review. Variant TCCs were not included. The association between survival and tumour characteristics was examined using descriptive statistics.

Results: Median age at diagnosis was 70 years (range 22−96). Most patients presented with locally advanced disease. There was no significance difference between gender, stage at presentation and pathological subtype.

Pathological variant	Stage					Total
	T1N0	T2-T3N0	T4N0	TxN+	TxNxM+	
Squamous (SQ)	2	28	19	15	3	67
Adenocarcinoma (AD)		8	4	3	1	16
Neuroendocrine (NE)		4		2	2	8
Sarcomatoid (SA)		2	1			3
Total	2	42	24	20	6	94

67 patients were offered treatment with radical intent. 54 patients were treated with cystectomy, 11 with radical radiotherapy. 11/67 received neo-adjuvant chemotherapy, 1 progressed on chemotherapy and was not treated radically and 1 opted for experimental HIFU. Of the 27 who were treated with palliative intent, 18 had radiotherapy, 3 had surgery (including palliative cystectomy), 2 had chemotherapy and 4 received supportive care alone. After median follow-up of 8 months (range 0.2–106), 22 patients were alive with no disease, 68 had died (46 from metastatic bladder cancer). 3 were alive with active disease. Median time to disease progression following treatment was 7 months (range 1−76).

Overall 2 and 5 year survival were 31.4% and 23.5% respectively. There was no significant difference in overall survival rates between pathological variants (SQ vs AD p = 0.47, HR 1.26 95% CI 0.67–2.39; AD vs NE p = 0.99, HR 1.0 95% CI 0.34–2.95; SQ vs NE p = 0.28, HR 1.67 95% CI 0.66–4.20) and when stratified for stage (T1−4N0 vs N+ p = 0.54, HR 1.2 95% CI 0.67–2.14; T1-T4N0 vs M+ p = 0.08, HR 1.48 95% CI 0.96–2.28; N+ vs M+ p = 0.12, HR 2.18 95% CI 0.82–5.82).

Conclusion: Patients with non-TCC bladder cancer present at more advanced stage and have poor survival regardless of pathological subtype. Clinical trials are needed to determine whether multimodality treatment can improve outcome.

No conflict of interest.

2713 POSTER DISCUSSION

Disparities in predictors of genitourinary cancer in men

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Background: Almost half of all cancers in men are genitourinary cancers with prostate as the most common site, bladder 4th, and kidney 7th. Prospective data about risk factor disparities for these 3 cancer types are sparse leading us to study them in one large multiethnic cohort.

Material and Methods: In our study, 56,764 men supplied baseline data at health examinations from 1978 to 1985 and were followed through 2008 for tumor registry diagnoses. We performed Cox proportional hazards models adjusted for age, ethnicity, alcohol intake, smoking, BMI, and education to estimate hazard ratios (HR) and 95% confidence intervals (CI).

Results: Increasing age was related to higher risk of all 3 cancer types and alcohol drinking was unrelated to any. Statistically significant relationships (most with p < 0.001) included: (1) Compared to whites, black men had almost twice the risk of prostate cancer but 40% lower risk of bladder cancer while Asian men had lower risk of both prostate and bladder cancer. (2) Smokers had increased risk only of bladder cancer. (3) Obesity [BMI $\geqslant$30 kg/m^2] was related to increased risk of bladder and kidney cancer. (4) Higher educational attainment was related to increased risk for prostate cancer.

Conclusions: There are noteworthy disparities in risk factors for different GU cancers in men including race/ethnicity, smoking, BMI, and education.

No conflict of interest.

Table: Adjusted relationships* of traits to GU cancers in 56,764 men

Trait	Prostate cancer (n = 3,031)	Bladder cancer (n = 524)	Kidney cancer (n = 181)
Age (X10 years)	2.0 (1.9–2.0)[c]	2.5 (2.3–2.7)[c]	1.7 (1.5–1.9)[c]
Black/White	1.9 (1.8–2.1)[c]	0.6 (0.4–0.7) [c]	1.2 (0.8–1.7)
Asian/White	0.7 (0.6–0.8)[c]	0.5 (0.3–0.7) [c]	1.2 (0.7–2.0)
$\geqslant$1 pack per day smoking/none	1.0 (0.9–1.2)	3.6 (2.8–4.8) [c]	1.3 (0.8–2.2)
$\geqslant$3 alcohol drinks per day/none	1.1 (1.0–1.2)	1.0 (0.7–1.2)	1.1 (0.6–1.8)
BMI $\geqslant$30 kg/m^2/ <25 kg/m^2	1.0 (0.9–1.1)	1.4 (1.2–1.8)[a]	1.9 (1.2–3.0)[b]
College graduation/none	1.3 (1.2–1.4)[c]	1.0 (0.8–1.2)	1.0 (0.6–1.4)

p-values <0.05[a],<0.01[b], <0.001[c].
*HRs (95% CI).

2714 POSTER DISCUSSION

Historical data in real life from patients treated by vinflunine for an advanced or metastatic urothelial carcinoma: Results of the CURVE study

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Background: Vinflunine (VFL) is a chemotherapy (CT) registered as second line treatment of advanced or metastatic urothelial carcinoma (UC) after failure of a platinum-based CT. VFL was made available in France in September 2010. The purpose of the study was to collect data on the use of VFL in real life for a comparison with the phase 3 study results.

Material and Methods: The CURVE study is a retrospective data collection. 88 French centres where at least 4 patients (pts) had been treated during the year 2011 were asked to participate.

Results: From November 2012 to February 2013, 20 sites included 134 pts.

At the initiation of VFL, the mean age was 66 years and 89% of pts were males. The performance status (PS) was 0 or 1 in 72 % of pts. Most of them had a metastatic disease (75%) with visceral sites (liver and/or lung in 57%). Most pts underwent initial radical surgery (84%). All pts received prior chemotherapy with 95.5% for advanced disease intent; only one patient did not receive a platinum salt (99%).
The median duration of treatment by VFL was 3.1 months [0.03; 15.2] and the median number of cycles was 5 [1; 23]. The median initial dose of VFL was 280 mg/m^2 [120; 320] and the relative dose intensity reached the median value of 92.7% [19; 126]. 16% of pts experienced at least one dose reduction.
Most frequent grade 3−4 toxicities were asthenia and fatigue (20.9%), neutropenia (17.2%), anemia (8.2%) and constipation (8.2%). Prophylaxis against vomiting and constipation were prescribed in 92 and 86% of pts respectively.
The median overall survival (OS) was 8.2 months [6.5; 9.4]. The response rate was 22% with 5% and 17% of complete and partial responses respectively. The disease control rate was 51% with a median duration of 7.7 months [6.0; 9.4]. Median progression free survival was 4.2 months [2.8; 4.8]. Following VFL, 46% of pts received from 1 to 3 additional lines of chemotherapy.
Conclusion: The study reflects the current second line management of UC in France, pts exhibiting worse conditions than in real life and clinical trials.
The results are consistent with those of the phase 3 study, better for OS; toxicity is manageable with a higher number of cycles per patient and few dose reduction or delay. VFL brings a real benefit in some pts where there is no validated alternative.
Conflict of interest: *Advisory board: Pierre-Fabre Research Institute*

2715 POSTER DISCUSSION

Prognostic risk stratification of men with advanced penile squamous cell cancer (PSCC) receiving first-line systemic therapy

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Background: Clinicopathologic factors are prognostic in men with PSCC undergoing surgery. The discovery of prognostic factors in men with for advanced (locoregional or metastatic) PSCC receiving primary systemic therapy may guide rational drug development in this orphan disease with substantial unmet needs.
Methods: We combined individual patient level data obtained from multiple institutions to study clinicopathologic prognostic factors in the context of first-line systemic therapy for advanced PSCC. Cox proportional hazards regression analysis was conducted to examine the independent prognostic impact of candidate factors on overall survival (OS). The candidate factors were age, stage, hemoglobin, neutrophil count, lymphocyte count, albumin, site of metastasis (visceral or non-visceral), smoking, circumcision, therapy (cisplatin or non-cisplatin), ECOG performance status (PS), lymphovascular invasion, precancerous lesion and surgery following chemotherapy. Statistical methods, including automated selection procedures and multiple imputation, along with expert knowledge to select an optimal model of prognostic factors.
Results: 147 men received first-line therapy for advanced disease. The number of patients with complete data on all candidate clinicopathologic factors was 96. There were no major differences in characteristics and outcomes between men with complete and incomplete data. Mean age across all men was 57.1 years; 10.2%, 21.8% and 68.0% had stage 2, 3 and 4 disease, respectively. 43.3% were ECOG PS $\geqslant$1, 41.0% had visceral metastases and 74.8% received cisplatin-based chemotherapy. On multivariable analysis, poor prognostic factors were visceral metastasis, treatment with non-cisplatin regimens and ECOG-PS $\geqslant$1. A risk stratification was constructed with 0, 1 and $\geqslant$2 poor prognostic factors which demonstrated moderate discriminatory ability (c-statistic=0.70).
Conclusion: In men with advanced PSCC receiving first-line systemic therapy, visceral metastases, non-cisplatin regimens and ECOG-PS $\geqslant$1 were independently prognostic for poor OS. A prognostic model including these factors exhibited moderate discriminatory ability. External validation of the risk model will enable interpretation of outcomes and guide rational drug development.
No conflict of interest.

Number of factors	N	Overall survival		
		Median (95% CI) months	6-month (%) (95% CI)	1-year (%) (95% CI)
0	36	Not Reached	94.4 (79.6–98.6)	70.4 (48.9–84.2)
1	39	9 (7−11)	88.0 (71.0–95.3)	7.2 (1.3–20.4)
$\geqslant$2	36	6 (5−8)	46.8 (28.6–63.0)	8.5 (1.5–23.5)

2716 POSTER DISCUSSION

Long-term platinum retention after treatment with cisplatin-based chemotherapy in testicular cancer survivors (TCSs)

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Background: Testicular cancer (TC) survivors treated with cisplatin-based chemotherapy have an increased risk for serious late effects as cardiovascular disease and second cancers. Apart from treatment burden, mechanisms explaining the increased risk are still unknown. To further elucidate possible mechanisms, we have evaluated long-term platinum (Pt) retention in TCSs treated with cisplatin-based chemotherapy.
Material and Methods: 456 men treated for unilateral TC (1980–1994) participated in a national follow-up study (2007–2008), with blood samples available for Pt analyses. Pt determinations in serum samples were carried out with high resolution inductively coupled plasma sector field mass spectrometry. The limit of quantification for this method was 15 ng/L. Patients were categorized in three treatment groups: Surgery (n = 134), and two chemotherapy groups: cumulative cisplatin dose $\leqslant$850 mg (cis$\leqslant$850; n = 269) and cisplatin dose >850 mg (cis>850; n = 53). The Pt plasma concentrations ([Pt]) were categorized into quartiles. Logistic regression was performed to evaluate the risk for having [Pt] in the highest quartile vs. the other quartiles, presented as odds ratio (OR) and 95% confidence intervals (CI).
Results: The median observation time was 20 years (range 13−28). The median level for the surgery group was 49ng/l (range 0–230 ng/l), for the cis<850 group 84ng/l (0–244 ng/l) and for the cis>850 group 112ng/l (21–247 ng/l). Only 5.2% of the surgery group had Pt levels in the highest quartile, while corresponding numbers were 27.5% and 62.3% for the cis$\leqslant$850 and cis>850 groups, respectively. There was a significant association between pt-level and both follow-up time and cisplatin dose ($p < 0.001$, both). The OR for having [Pt] in the highest quartile was positively associated with cisplatin dose (OR 1.31, 95% CI 1.22–1.41) per 100 mg increase in cisplatin dose), and negatively associated with follow-up time (OR 0.48, 95% CI 0.35–0.66 per every 5 year increase in follow-up time). Age, smoking and physical activity at follow-up were not associated with pt-level.
Conclusion: Our data suggest that pt is detectable in serum median 20 years after cytotoxic treatment. This is a novel finding, and future studieson the associations between Pt level, cisplatin dose and long-term toxicities as well as genetic factors are needed to identify those at increased risk for serious late effects.
No conflict of interest.

2717 POSTER DISCUSSION

Impact of testicular scatter radiation (TSR) on testosterone (T) and luteinizing hormone (LH) 11 and 18 years after abdominal radiotherapy for testicular cancer

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Background: Radiotherapy (RT) may compromise gonadal function in male cancer survivors (CSs). Testicular CSs are at increased risk of gonadal dysfunction after adjuvant abdominal RT as measured by declining

T and/or increasing LH. Testicular scattered radiation (TSR) dose is lower after abdominal RT for testicular cancer (<1 Gy), than after RT for rectal- or anal cancer (3−13 Gy). The long-term impact of low doses of TSR on gonadal function, has not been assessed in a longitudinal matter and may have consequences for planning of radiotherapy and follow-up of irradiated CSs.
Material and Methods: T and LH levels were retrieved from 111 testicular CSs median 11 and 18 years after adjuvant RT administered as a Dog Leg field (DL) in 96 CSs or Para aortal strip (PA) in 15 CSs. Differences in TSR between DL and PA were assessed by T-test. Hormone values were categorized into 6 scores according to cut off levels corresponding to quartiles and 2.5- and 97.5 percentiles from healthy controls matched for decadal age, yielding an ordinal score ranging from 1 to 6. The impact of TSR on hormone levels was assessed by ordinal logistic regression analysis with TSR dose as a continuous variabel.
Results: In general, the TSR dose was low (median 0.34 Gy, inter quartile range [IQR] 0.24–0.48 Gy) and significantly higher after DL (median 0.36 Gy, IQR 0.30–0.50 Gy) than after PA (median 0.09 Gy, IQR 0.08–0.12 Gy), $p < 0.001$. TSR dose was significantly associated with increasing LH scores 18 years after treatment, $p = 0.030$, whereas no significant associations emerged after 11 years. There were no significant associations between TSR and T scores at any of the time points.
Conclusion: Even small amounts of TSR may impair gonadal function in the long-term. The significant association between increasing scores of LH and TSR almost two decades after treatment may have implications for the follow-up of irradiated CSs in general, especially as the majority of patients receiving pelvic/abdominal radiation are exposed to higher scatter gonadal doses than testicular CSs. As a consequence, irradiated CSs should be screened for gonadal dysfunction in their follow up, since testosterone supplementation may prevent complications of hypogonadism.
No conflict of interest.

Poster Session (Mon, 30 Sep)
Genitourinary Malignancies − Other

2718 POSTER

Prognosis of screen failure for brain metastases in patients with metastatic renal cell carcinoma

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Background: Brain metastases (BM) are common exclusion criteria for clinical trials in metastatic Renal Cell Carcinoma (mRCC). However, real prognosis of asymptomatic BM, when discovered at screening is unknown. The goal of our study was to determine (i) if the prognosis of BM is different from that of other screen failure reasons, (ii) if the number of BM is an important prognostic factor.
Methods: We reviewed all the patients who signed an ICF for second and third line trials in mRCC in 8 different clinical trials at Institut Gustave Roussy (5 published trials: TARGET, RECORD-1, Sunitinib continuous dosing trial, AXIS, and INTORSECT; 3 ongoing: PIM, GOLD and BMS-CA209 025) and who failed screening. From each patient's chart, we reported: disease characteristics, reasons for screen failure and in case of brain mets: clinical and radiological features of BM, treatment received and overall survival (OS). The association between OS and these factors was evaluated by univariate analysis (Cox model).
Results: Among 283 pts screened, 55 pts had screen failure (19.4%) including 24pts (8.5%) for BM. All screen failure causes are reported in table 1.
Patients with BM had no neurological symptoms when signing ICF, but 12 of them developed symptoms during screening period while 12 remained symptom free. Median OS for all screen failure patients was 6 mths [20 days to 102 months], very similar to those with BM (5.7 mths). HR was 1.3, 95% CI [0.7−2.4], $p = 0.36$. Median OS was 6.9 mths and 3.7 mths for asymptomatic and symptomatic respectively, $p = 0.08$, HR = 0.47 95% CI [0.17–1.07]. Among the 12 asymptomatic patients, 7 had one BM, and 5 had multiple BM. Median OS in pts with unique BM vs multiple BM were respectively 6.9 mths vs 12.8 mths ($p = 0.44$), HR was 1.55, 95% CI [0.49−6.75].
Conclusions: Incidence of unknown BM during screening for 2nd line therapy in mRCC is not uncommon (8.1%) and this is the first cause of screen failure. Median OS is overall poor, even in asymptomatic patients with a unique BM, justifying excluding those patients from clinical trials.
Conflict of interest: *Ownership: 0. Advisory board: Escudier: Bayer, Pfizer, novartis. Albiges: Novartis, Pfizer. Board of directors: 0. Corporate-sponsored research: Albiges: Novartis. Other substantive relationships: Honoraria − Escudier: Bayer, Roche, Pfizer, genentech, Novartis, Aveo, GSK; honoraria − Albiges: Novartis, Pfizer*

Table 1.

Screen failure reason	Number (n = 55)	%
Brain metastases	24	43.6%
Biological abnormalities	12	21.8%
Rapid deterioration of PS	11	20%
Cardiovascular	3	5.5%
Others	5	9.1%

2719 POSTER

Adjuvant radiotherapy with or without chemotherapy in patients with nonmetastatic stage III/IV transitional cell carcinoma of the upper urinary tract

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Background: The role of adjuvant radiotherapy still remains undefined in patients with transitional cell carcinoma of the upper urinary tract (UTTCC). To evaluate the role of adjuvant radiotherapy, we updated the prior review of clinical outcomes of patients with advanced stage III or IV UTTCC.
Material and Methods: From 2007 to 2012, 36 patients with nonmetastatic (M0) stage III or IV UTTCC underwent nephroureterectomy (NU) with bladder cuff excision followed by adjuvant radiotherapy (RT) with or without chemotherapy. As a historic control group, we reviewed 91 patients underwent NU and bladder cuff excision alone for the same stage UTTCC between 2000 and 2010. Patients in adjuvant RT group had significantly higher rate of involved resection margin (33% vs. 9%, $p = 0.001$) and higher tumor grade (grade 2, 9% vs. 30%; grade 3, 91% vs. 69%, $p = 0.017$). Adjuvant RT was delivered to tumor bed and regional lymph nodes with median dose of 46 Gy (range 45−60 Gy). Differences in risk-adjusted rates of treatment outcomes between 2 groups were assessed using multivariable Cox proportional-hazards model and the inverse-probability-of-treatment weighting (IPTW).
Results: Three-year actuarial locoregional recurrence (LR) free survival rates were 88% vs. 61% in adjuvant RT group and surgery alone group, respectively ($p = 0.017$). Three-year actuarial bladder recurrence (BR) free survival rate was 70 % in adjuvant RT group and 51% in surgery alone group ($p = 0.021$). After adjustment for differences in baseline risk factors, crude risk of LR (hazard ratio [HR]: 0.18; 95% confidence interval [CI]: 0.05 to 0.59, $p = 0.005$), the risk of BR (HR:0.39; 95% CI: 0.15 to 0.99, $p = 0.048$), and the risk of disease recurrence (HR:0.45; 95% CI: 0.22 to 0.92, $p = 0.029$) were significantly lower in the RT group. However, the rates of death were similar between 2 groups (HR: 1.14; 95% CI: 0.562 to 2.30, $p = 0.723$).
Conclusions: Despite the similar overall survival rate between 2 groups, current study shows that adjuvant radiotherapy may have benefit for reducing LR & BR, and improving disease free survival in patients with nonmetastatic stage III/IV UTTCC. Further prospective study will be required to confirm the role of adjuvant radiotherapy in patients with advanced stage UTTCC.
No conflict of interest.

Table (abstract 2719).

		Unadjusted Univariate			Multivariable*			IPTW		
	Event/ Total	Hazard Ratio	95% CI	*P* value	Hazard Ratio	95% CI	*P* value	Hazard Ratio	95% CI	*P* value
Locoregional recurrence	39/127	0.304	0.108, 0.858	0.024	0.212	0.074, 0.611	0.004	0.178	0.054, 0.588	0.005
Bladder recurrence	51/127	0.421	0.197, 0.898	0.025	0.298	0.134, 0.663	0.003	0.390	0.153, 0.994	0.048
Distant metastasis	56/127	1.186	0.642, 2.190	0.585	1.022	0.545, 1.914	0.947	0.973	0.460, 2.056	0.942
Disease recurrence	79/127	0.592	0.341, 1.028	0.062	0.437	0.241, 0.792	0.006	0.453	0.223, 0.922	0.029
Death	60/127	1.097	0.572, 2.106	0.780	0.984	0.510, 1.898	0.960	1.136	0.562, 2.297	0.723

2720 POSTER

Does ultrasound tell everything about testicular cancer: A novel approach for detection for testicular cancer

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Background: Testicular cancer is the most common solid neoplasia in men in the 20−40-year age group. Ultrasound (US) has so far been accepted as the gold standard for the evaluation of scrotal pathologies and is basically an extension of the physical examination. On the other hand, US can recognize testicular lesions only when they reach a certain size. It is important to know the presence of intratubuler germ cell neoplasia (ITGCN) in the contralateral testis for patients with testicular tumor, however, ultrasound cannot delineate ITGCN. The uncertain relation between the presence of testicular calcification, ITGCN, and testicular tumor needs further information. The booming advances in full field digital technology has enabled the use of this modality in the diagnosis of different malignant tumors. The objective of our study is to compare US and full field digital orchiography (FFDO) in the evaluation of testicular tumors with special emphasis on calcifications and discuss their clinical significance.
Materials and Methods: Between December 2011–2012, 12 orchiectomy specimens which were obtained from patients who underwent orchiectomy for testicular solid mass and 6 ram testicles which were selected to simulate normal testicular parenchyma, were evaluated with high resolution US and FFDO. Institutional review board approved the study protocol.
The digital orchiographic images of the specimens were obtained as magnification views without compression. Ultrasound was performed with 13−5 MHz. Two radiologists that were blinded to the histopathology results reviewed images in consensus. Calcification types and locations and mass on US and other US findings were recorded. Then the specimens were send to pathology department. The tumor types were identified and the presence of ITGCN was specifically sought for.
Results: Histopathologic findings revealed 4 seminoma, 8 non-seminomatous germ cell tumors and 6 normal testicular tissue (ram testicles). 10 out of 18 (55%) cases, calcifications were found on US. FFDO revealed calcifications in 13 (72%) of cases.
Small and faint microcalcifications were not detected by US. Orchiography performed better especially for the faint calcifications. Ultrasound was better in the detection of solid mass from the normal appearing adjacent testicular parenchyma. In 7 cases ITGCN was detected and both diagnostic modalities were able to detect calcifications.
Conclusion: Despite the findings that US provide, calcifications may need additional attention whether they may provide useful information in the diagnosis of testicular cancer. Our results had showed that FFDO was better in the detection and analysis of calcifications compared to US. On the other hand, we found that ultrasound was better in the detection of intrascrotal masses especially in delineation from the normal appearing adjacent parenchyma.
No conflict of interest.

2721 POSTER

Treatment management of malignancy in end stage renal disease patients

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Background: End stage renal disease (ESRD) cancer patient have some difficulties in their treatment management. These are management of drug toxicities and side effects, providing effective dose intensity, electrolyte imbalance, hemodialysis procedure and balancing volume load. We retrospectively evaluated the patients on continuous hemodialysis program, who were admitted to our department and had administrated chemotherapy.
Methods: We evaluated the clinical features of patients on continuous hemodialysis program and administrated chemotherapy from March 2007 to December 2010 in our department.
Results: We retrospectively evaluated 10 cancer patient with ESRD, who were on continous hemodialysis program. Median age and hemodialysis duration of patient population was 55 years (32−67) and 36 (2−84) months, respectively. Six of patients were male and four of them were female. The primary diagnosis of patients as follows; 4 had lung, 2 had breast, 1 had ovarian, 1 had colon, 1 had bladder cancer and 1 had Ewing sarcoma. Six patients had metastatic disease at diagnosis. All of patients had systemic chemotherapy and 8 of them had up to 40 % dose reduction of chemotherapeutics. Eight patients had grade 3 or 4 side effects of chemotherapy. The most common side effects were hematological toxicities. In early period, two patients died due to toxic effects of chemotherapy and 1 patient had cardiomyopathy. Two patients had primary granulocyte stimulating factor prophylaxis. Partial, stable and progressive response was obtained in 5, 3 and 2 patients, respectively. Two patients, who had progressive disease, had second line chemotherapy. In follow up period 4 patients died.
Conclusion: There are no detailed data about the management of cancer in hemodialysis patients in literature. During treatment management in hemodialysis patients, fluid and electrolyte imbalance and increased risk of toxicity are difficulties encountered in clinical practice. Medical oncologist should have collaborated with nephrologists while treating these patients. The loss of chemotheurapeutic agents to dialysis solutions and fluid overload have to be considered in treatment planning and chemotherapeutic dose modifications have to be done. Therefore dialysis schedule should be programmed according to these properties of chemotherapeutics. In our small patient group, we observed 2 toxic deaths and 5 patients had partial response. Well recorded data of these patients, will contribute treatment management of other ESRD cancer patients. End stage renal failure is not contraindication for chemotherapy. However, further randomized controlled studies are needed in this patient group for more effective and safe chemotherapy administration.
No conflict of interest.

2722 POSTER

Retrospective multicenter French study of relapse after adjuvant carboplatin in 19 patients with clinical stage I testicular seminoma

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Background: Stage I testicular seminoma is the most frequent presentation of Germ Cell Tumors (GCT) with a rising incidence. Surveillance or adjuvant treatment (radiotherapy or carboplatin AUC7) can be offered. The eatimated 5 year relapse rates are 15−20%, 4% and 5% respectively. There are no well-defined factor to predict relapse.
Material and Methods: We identified retrospectively, from 11 French institutions, patients (pts) who relapsed after adjuvant carboplatin AUC7 for clinical stage I seminoma since April 2008. We report here their characteristics, treatment and clinical outcome. Theoric carboplatin doses were checked and compared to administered doses.
Results: Nineteen pts were identified. Median age at GCT diagnosis was 39.6 years (23.6−68). All pts had a pure seminoma and were classified as stage I disease except one pt who must be reclassified as initial stage IIA disease. Median testicular tumor size was 50 mm (16−90) with 14 tumors $\geqslant$40 mm. Involvement of the rete testis was identified in 8/17 pts. The median time to relapse after carboplatin AUC7 was 15.1 months (mo) (1.7−46.5). Eighteen relapses occurred in the retroperitoneum, only one was located in the mediastinum. We have recalculated carboplatin doses from blood creatinin clearance for 18 patients: two patients received a dose that was more than 10% lower than the theorical dose. All pts received first line cisplatin-based chemotherapy (CT) (BEP, EP or VIP) at relapse. One patient progressed again one month after CT (3 BEP) and was treated with 3 TIP followed by retroperitoneal lymph node dissection. After a median follow-up of 26.0 mo (2.4–50.2) after first seminoma relapse, 18 pts are alive without disease and 1 is on CT.
Conclusions: In this study we couldn't identify factors that could predict relapse after carboplatin AUC7 for clinical stage I seminoma. Especially, there wasn't a difference between theoric and administered carboplatin doses. All patients at relapse were cured with cisplatin-based CT.
No conflict of interest.

2723 POSTER

Resection of post-chemotherapy residual masses (RMs) in patients with advanced non-seminomatous germ cell tumors (NSGCT): prediction of outcomes

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Background: Multidisciplinary treatment of advanced NSGCT involves tumor resection of RMs following inductive chemotherapy. About 45% of RMs harbor necrosis/fibrosis (N/F), 40% teratoma (Te) and only 15% viable tumor (VT). The presence of Te in the primary tumor, the size of the RM and tumor marker values pre-chemotherapy have been proposed as predictive factors of RM histology. We analyze here the experience of two European tertiary hospitals and search for predictors of histology.
Methods: All NSGCT patients (pts) who underwent retroperitoneal lymph node dissection (RPLND) of RMs in the two institutions from 2004 to 2012 were reviewed. Histology of primary tumor, the size of RM as determined by CT and tumor marker values were analyzed as predictors of RM pathology. Three groups of pts according to RMs size were established for the analysis: (A) $\leqslant$2 cm, (B) >2-$\leqslant$5 cm, (C) >5 cm.
Results: 45 RPLND of RMs were performed in 40 pts. In 7 pts embryonal carcinoma was the only histology in the primary tumor. In those with mixed pathology (n = 27), 20 (74%) had teratoma components. According to the size of the RM (data available in 25) pts distributed in groups as follows: 3 in group A, 11 in group B and 11 in group C. The pathology of the RMs revealed VT in 0%, 27% and 0% respectively in groups A, B and C. All RMs in group A, 54.5% in group B and 63.6% in group C showed Te. The % of N/F ranged from 0% in group A to 18.2% and 36.4% in groups B and C respectively. When analyzed for correlation, only the presence of Te in the primary tumor approached statistical significance as a valid predictor for Te in the RM ($p = 0.064$).
Conclusions: No clinical or histological factor was able to predict with accuracy the pathology of RMs in our series. RPLND remains necessary even in minimal-size residual lesions in order to achieve long-term survival in this patient population.
No conflict of interest.

2724 POSTER

Sequential targeted therapy (TT) with sorafenib-sunitinib (SO-SU) versus sunitinib-sorafenib (SU-SO) in metastatic renal cell carcinoma (mRCC): Results from a case-series of patients

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Introduction: Up to now, there is no clear consensus on the most appropriate sequencing of drugs following disease progression in mRCC. This study was performed to investigate correlation between progression free survival (PFS) and overall survival (OS) in a consecutive series of mRCC pts treated with the sequence SO-SU versus SU-SO.
Methods: Characteristics and outcomes of 125 pts affected by mRCC treated with SO-SU or SU-SO at the Istituto Nazionale Tumori of Milan were collected between November 2005 and January 2012. The Kaplan Meier curves were used to describe the survival distributions and the log-rank test to detect a statistical significance between survival distributions (p-value<0.05); correlation between PFS and OS was measured with the Kendall's Tau non parametric index.
Results: The main characteristics of 104 (83.2%) pts treated with the SO-SU sequence were: ECOG PS 0/1/2 56 (53.8%)/47 (45.2%)/1 (1 %); clear-cell histology 88 (84.6%); previous nephrectomy 98 (94.2%); according to Motzer criteria 38.5% were low risk, 53.9% intermediate risk and 7.7% poor risk. The main characteristics of 21 (16.8%) pts receiving SU-SO were: ECOG PS 0/1/2 10 (47.6%)/10 (47.6%)/1 (4.8%); clear-cell histology 17 (81%); previous nephrectomy 20 (95.2%); according to Motzer criteria 14.3% were low risk, 61.9% intermediate risk and 23.8% poor risk. Median follow-up was 66.6 months (range 6−84) in the SO-SU arm and 37.1 months (range 4–60.1) in the SU-SO treatment. At the time of analysis 88/125 (70%) pts were dead and 98/125 (78%) pts reached the disease progression. No statistical difference in PFS was observed for the two treatment groups: median PFS for SO-SU was 26.1 months (95% CI: 21.8–34.0), while for SU-SO was 20 months (95% CI: 10.0–33.0); no statistical difference in OS was observed for the two treatment groups: median OS for SU-SO was 27 (95% CI: 10.0-nd), while for SO-SU was 35.3 months (95% CI: 26–44.4). For both SO-SU and SU-SO treatment sequences a low positive correlation between PFS and OS was observed, respectively τ=0.13 and τ=0.15.
Conclusions: These data suggest that the sequence SO-SU compared to the sequence SU-SO has comparable efficacy in terms of PFS and OS. No strong evidence of a correlation between PFS and OS was demonstrated.
Conflict of interest: *Advisory board: G. Procopio: Bayer, GSK, Astellas. Other substantive relationships: G. Procopio: Consultant for Pfizer, Novartis*

2725 POSTER

Cross-sectional observational study assessing the impact in daily clinical practice of the implementation of cooperative group (SOGUG) guidelines about management of targeted therapies in metastatic renal cell carcinoma (mRCC)(proTECT 2 Study)

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Background: Appropriate management of secondary effects has been proposed as a key factor for optimizing the outcome of patients (pts) with mRCC on targeted therapies. Aiming to improve such management the Spanish Oncology Genitourinary Group (SOGUG) launched in 2011 a program for the implementation of a clinical guide of recommendations for adverse event (AE) management. We report the impact of such program in the daily clinical practice of 32 Spanish hospitals.
Methods: This is a retrospective, cross-sectional, and multicenter study. Two populations were analyzed: A) pts with mRCC who initiated any targeted therapy before the guidelines were published (March 2010- March 2011) and B) pts who were treated after an educational program for the implementation of such guides was launched (Jan 2012- Dec 2012). The main objective of this study was to compare the adherence to the gold standard of care in the management of 10 key AEs in both populations. This study was approved by the Spanish Medicine Agency and Ethic Committees of each hospital.
Results: A total of 269 pts have been included: 54% received sunitinib (SU), 18% everolimus (EVE), 12% sorafenib (SO), 11% pazopanib (PAZ), 4% temsirolimus (TEM) and 1% bevacizumab (BEV). A total of 1231 cycles (605 before and 626 after the implementation program) were analyzed. The selected AEs were: Hypertension, cardiac, hepatic and cutaneous toxicity, hypothyroidism, diarrhea, proteinuria, hyperglycemia, dyslipaemia and neumonitis. Analisis was based on the adherence to the guides regarding baseline/follow up test performance, use of concomitant medication and policy for dose reduction/interruption or definitive suspension. After the implementation program there was a significant improvement in the adherence to recommendations regarding cardiac toxicity and diarrhea in pts treated with SU, 5.8% vs 12.9% ($p < 0.01$) and 84.8% vs 94.1% ($p < 0.001$) respectively. Also, there was a significant increase in guide overall compliance with EVE 36.8% vs 52.7% ($p < 0.05$). Regarding type of hospital, a significant improvement in management of toxicity was seen in those with higher number of renal cases per year and higher specialization after the program was launched 12.9% vs 34.6% ($p < 0.001$).
Conclusions: Educational programs focused on the implementation of clinical guidelines, may be of major help to the medical community in the therapy management and in the benefit of pts.
Conflict of interest: *Other substantive relationships: Dr. Morán is a Pfizer employee*

2726 POSTER

Residual masses in germ cell tumors and their impact in prognosis

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Background: Residual masses (RM) are common in patients with germ cell tumors (GCT) treated with orchiectomy and chemotherapy. Those

masses may be positive for tumoral cells, necrosis or teratoma and might be implicated in the prognosis of the disease.
Patients and Methods: We analized retrospectively 161 male patients diagnosed of GCT treated between 1974 and 2012 in our hospital with a median follow up of 8.1 years (0.3−23.6). We compared the evolution of patients with RM with those without.
Results: Of the 161, 159 had testicular tumors and 2 extragonadal tumors at diagnosis. All of them but one underwent standart orchiectomy. 41.5% were seminomas and 84.5% nonseminomatous tumors (the most prevalent were embryonal carcinoma and teratocarcinoma). Of the nonseminomatous, 57.4% were mixed tumors whereas just 4.5% in seminomas. The median tumor size was 4.4 cm. Most of them (60.1%) were diagnosed at stage one, of these, 16% had RM, 15% in stage two, 50% in three and 46% in stage four ($p < 0.001$). The most frequent chemotherapy schemes used (53.4%) were BEP (Cisplatin, etoposide and bleomicine), other conteining platin (14%) and carboplatine alone (6%). 8.7% of the patients recived radiotherapy as part of the treatment.
The rate of complete responses (CR) was 89.4%, parcial responses (PR) with negative tumoral markers was 7.5% and with positive markers 1.9%.
A total of 27 (16.8%) of the 161 had RM detected in computed tomography. In 22 (81%) were resected, in 5 (19%) watchful waiting was decided. In 40%t the histology was malignant tumor, in 32% teratoma, in 27% necrosis or other findings. Analizing this subgroup of patients with RM, no histological differences (linfovascular, rete testis or albugineal invasion) were found in those with malignant tumor. ($p = 0.13$). The histology of teratoma in prmary tumor (PT) was not associated with the presence of RM ($p = 0.31$). The median time to diagnosis of PT in the group without RM was 1.2 months, and in the RM group 2.1 ($p = 0.04$).
According to the GCT risk classification, intermediate or bad prognosis at diagnosis was associated to the presence of RM (55% vs 11.3%, $p < 0.001$).
Of the 133 patients without RM, only 27 (20.3%) relapsed whereas 13 (48.1%) out of the 27 did it in the RM group ($p = 0.001$).
The rate of progression free survival (PFS) in both groups (without and with RM) after two and ten years was 83% and 57% and 77% and 33% respectively (logrank test $p < 0.001$) HR: 3.1 (95% CI 1.7−5.6). Ten-year overall survival (OS) was 92% and 81% respectively ($p = 0.07$) HR: 2.5 (95% CI 0.9−6.9).
Conclusions: Forty per cent of RM were malignant tumors but we did not find any histological marker that may predict this. Bad or intermediate prognosis and advanced stages as well as elapsed time to diagnosis of PT were associated with the presence of RM. These patients had a raised risk of relapse and a lower rate of PFS but no differences were found in OS. In this serie, the finding of teratoma in primary tumor was not a predictor of residual masses.
No conflict of interest.

2727 POSTER

Best response (BR) may be predictive of progression-free survival (PFS) in patients with metastatic renal cell cancer (mRCC) treated with tyrosine kinase inhibitors (TKI) in first line

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Background: TKIs have quite recently brought innovation in the treatment of mRCC. Though TKIs' efficacy and tolerability has been proven in many trials, there is no current certain data about predictive markers (both clinical and biological) of response.
In this retrospective study we analyzed the correlation between BR and PFS in a cohort of patients subjected to first line TKI treatment for mRCC.
Patients and Methods: 36 patients affected by mRCC, stage IV, MSKCC good risk 6/36, moderate risk 21/36, poor risk 7/36, were treated since 2007 in three hospitals in Palermo, Sicily, Italy. Patients received the following treatment: 30 patients received sunitinib, 5 patients received sorafenib, 1 patient received pazopanib. Responses were evaluated using RECIST 1.1. Patients with a treatment follow-up longer than 24 months were included in the analysis, while patients with shorter follow-up were censored at the time of the last evaluation. Kaplan–Meier survival and log rank test were performed using MedCalc® software.
Results: 30/36 patients were evaluable for response and were included in the analysis. 6/30 patients did not respond to the treatment at the time of the first evaluation. Analysis showed Median PFS in PR group to be 22 months vs. 7 months in SD group ($p = 0.0003$).
Conclusions: In our study, patients affected by mRCC experiencing PRs to TKI treatment in first line appeared to have a better outcome in terms of PFS compared to patients experiencing SDs. These data do not reflect what we have seen in Gastro-Intestinal Stromal Tumors (GIST). Although the treatment approach to GIST is very similar to mRCC, patients who experience PR appear to have very similar outcome to patients who experience SD. Limits to these study are retrospectivity, small amount of cases, and short follow-up. Also, it is not clear whether a longer PFS is associated to a longer OS. Further studies will certainly follow.
No conflict of interest.

2728 POSTER

The preliminary result of combination of radiotherapy and cisplatin arterial infusion for bladder cancer

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Background: To evaluate the effectiveness of combination with radiotherapy and balloon-occluded arterial infusion (BOAI) for bladder cancer, we analyzed our preliminary clinical experience.
Methods and Materials: We investigated 160 patients (Male : Female 123 : 37) and the median age was 71 (range; 38−98) years old. The median follow-up time was 16 months. Using the UICC classification, 10 stage I, 82 stage II, 46 stage III, and 22 stage IV were identified. Transurethral resection showed urothelial carcinoma for 153 patients and the other histological types for 7 patients. All patients received external beam radiation therapy (EBRT) with the prescribed dose of 50 Gy to the whole pelvis and 10 Gy to the bladder as a boost. During EBRT, BOAI of cisplatin (100 mg/body) was performed from bilateral internal iliac artery.
Results: Complete response rate was 73% on 2 months after treatment. The 2-year local control and overall survival rates were 87% and 78%. The 2-year bladder preservation rate was 93%. Grade 3 acute complication occurred in 20 patients (13%) (genitourinary: 17; gastrointestinal: 3) and Grade 4 acute complication was not observed.
Conclusions: The combination of radiotherapy and cisplatin arterial infusion for bladder cancer showed promising preliminary results.
No conflict of interest.

2729 POSTER

Biological toxicity as a predictive factor of efficacy in metastatic renal cell carcinoma (mRCC) treated with sunitinib

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Background: Sunitinib is the standard of care for mRCC in first-line. There are no established predictive factors of efficacy. We investigated retrospectively the relationship between biological toxicities and sunitinib efficacy.
Methods: Clinical data were retrospectively collected in all clear cell carcinoma patients treated with sunitinib for mRCC (except 3 pts for papillary carcinoma) at the European Georges Pompidou Hospital in Paris, France, who started between 2005 and 2012. Only patients having received sunitinib in first-line for at least one cycle were eligible. Platelets, neutrophils/granulocytes, leukocytes counts, cholesterolemia, triglyceridemia, hemoglobin and biological hypothyroidism were recorded with onset date and higher grade (NCI-CTC3.0).
Time to highest toxicity and time to best response were also recorded. Efficacy was assessed with objective response according to RECIST criteria 1.0 and progression-free survival. Statistical tests were chi square for categorical variables and log rank or Cox test for censored variables.
Results: 150 patients charts were reviewed. Data for biological toxicities were available for 42 patients. Median age=61.5 y (42−80), sex ratio=6/1 (M/F). ECOG-PS= 0 (50%). Objective response rate: CR=2, PR=18, SD=17, PD=2, NE=3. Median treatment duration= 23 months (11.4–28.5). Median treatment follow-up time= 36.3 m. Median survival = 51 m (30.7−64). Median PFS= 28.5 m (17.5–35.5).
Efficacy and toxicity were studied with several approaches. Relationship between grade toxicity and RECIST criteria, duration of treatment and time to best response were considered. All those relationship were non significant. Delay of highest toxicity was shorter for SD and PD responses ($p < 0.05$). Absolute decrease of leukocytes was related to delay of best response ($p < 0.05$). All other tests were non significant.
Conclusions: There is no clear relationship between biological toxicities and radiological response to sunitinib. But, other efficacy criteria such as delay of highest toxicity and delay of best response seem to be of interest for efficacy evaluation.
No conflict of interest.

2730 POSTER

Sunitinib in patients (pts) from Latin America: Final results of the expanded-access trial in metastatic renal cell carcinoma (mRCC)

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Background: Sunitinib is approved multinationally for the treatment of mRCC. A global expanded-access trial (NCT00130897; Pfizer) confirmed the manageable safety profile and efficacy of sunitinib in a broad population of pts with mRCC (N = 4543; Gore et al, ESMO 2012). Using final data from this trial, we present sunitinib efficacy and safety results in pts from Latin America, the first such report from this region.
Material and Methods: Pts aged ⩾18 y with treatment-naive or previously treated mRCC received oral sunitinib at 50 mg/d on a 4-wk-on/2-wk-off schedule. Safety was assessed regularly, tumor measurements done per local practice, and survival data collected where possible. ORR, PFS, OS, and treatment-related (TR) AEs are reported. Analyses included all pts who received ⩾1 dose of sunitinib.
Results: 348 pts were the subject of this analysis (modified ITT [mITT] population), of whom 60% had received prior cytokine treatment. In the mITT population, 28% were aged ⩾65 y, 5% had non-clear cell RCC, 14% had an ECOG performance status ⩾2, 9% had baseline brain metastases, and 75% had ⩾2 sites of metastatic disease; 89% had prior nephrectomy. Median treatment duration and follow-up were 8.0 and 15.1 mo, respectively. 326 pts (94%) discontinued study participation for reasons including death (41%), lack of efficacy (22%), or AEs (13%). Among 311 pts with RECIST tumor assessments, the ORR was 17% (19% and 15% in pts with or without prior cytokine treatment, respectively). The clinical benefit rate (CR + PR + SD ⩾3 mo) was 57%. Median response duration among responders was 26.7 mo. Median PFS was 12.1 mo for the 311 pts with RECIST tumor assessments and for pts with or without prior cytokine treatment. Median OS was 16.9 mo (95% CI: 15.1–20.2) in the mITT population, and 16.6 mo (95% CI: 14.7–19.5) and 19.3 mo (95% CI: 13.8–28.5) among pts with or without prior cytokine treatment (P = 0.46). The most common TRAEs of any grade were mucosal inflammation (54%), diarrhea (53%), asthenia (41%), and decreased appetite (33%); the most common grade 3/4 TRAEs were asthenia (12%), neutropenia (10%), fatigue (9%), and thrombocytopenia (9%). Further analyses of pt subgroups with and without prior cytokine treatment, as well as other subgroups of interest, will be presented.
Conclusions: In this expanded-access trial, the efficacy and safety profile obtained with sunitinib in pts with mRCC in Latin America was comparable to that of the overall population as previously reported.
Conflict of interest: *Ownership: Mauricio Monaco, Peter Sajben and Ke Zhang − stock ownership: Pfizer. Advisory board: Daniel Herchenhorn − Pfizer, Sanofi, BMS, Janssen, Astellas Matías Chacón − Pfizer Paula Cabrera-Galeana − Pfizer, Novartis, Roche. Corporate-sponsored research: Carlos Barrios − Pfizer, Novartis, Astellas. Other substantive relationships: Mauricio Monaco, Peter Sajben and Ke Zhang − employment: Pfizer*

2731 POSTER

Taxanes in salvage and high-dose chemotherapy and autologous peripheral blood stem cell transplantation in patients with advanced germ cell tumors

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Paclitaxel-based combination became the standard in salvage settings and incorporated in high-dose regimens prior autologous stem cell transplant (ASCT). We report on docetaxel use in salvage regimen prior to high-dose chemotherapy (HDCT).
Materials and Methods: 44 procedures of HDCT and ASCT were performed in 28 relapsed or refractory germ cell cancer patients, judged to be incurable by standard salvage therapy. Two patients had seminoma and 26 nonseminomatous germ cell tumors.
50% of patients were heavily pretreated with ⩾2 lines of previous systemic therapy and median of 7.5 cycles of cisplatin-based chemotherapy (CT). 22 patients were cisplatin refractory and 9 patients had relapse. Treatment plan consisted of 2−3 cycles of salvage CT and two sequential cycles of high-dose (HD) etoposide (1500 mg/m^2) and carboplatin 1800 mg/m^2 (24 AUC). Salvage regimens were docetaxel (160 mg), ifosfamide (6 g/m^2) and cisplatin (100 mg/m^2) in 13 patients, standard TIP − in 4, VIP − in 5 and GOP (gemcitabine, oxaliplatin and paclitaxel) in 6 patients, depending on previous therapy or drug availability. Totally 36 taxanes-based salvage CT blocks were conducted.
Stem cells were successfully collected in all patients, but 5 of them required second mobilization. 14 patients received 2 HD regimens, 13 patients − one, and 1 patient received 3 cycles of HDCT. HD-paclitaxel was included in HD regimen in 7 cases.
Results: The median patients' age was 27.5 years (range 14−41 years). Response was achieved in 23 (82%) patients: partial in 19, complete − in 4 patients, 4 had stable disease and 1 progressed before HDCT.
The most frequent non-hematological toxicities of HDCT were nausea and vomiting, mucositis (Grade 3 mainly in patients receiving paclitaxel in HD regimen), ototoxicity and hepatic toxicity.
Transplant-related mortality was 3.57% (1/28), 1 patient died due to renal insufficiency after HDCT (ifosfamide was included in HD regimen). At a median follow-up of 2.3 years (range 2–141 mo.) a continuously disease-free status was achieved in 14 (50%) patients, in 7 patients residual tumor was removed. 12 patients died because of disease profession, one − from other reason.
Conclusion: Incorporation of docetaxel and paclitaxel in salvage treatment and HDCT appear to benefit patients with resistant germ cell tumors with manageable toxicity.
No conflict of interest.

2732 POSTER

Effect of adjuvant chemotherapy on survival in patients with urothelial bladder cancer undergoing radical cystectomy

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Patients with urothelial bladder cancer (BC) scheduled for radical cystectomy (RC) often are candidates for systemic therapy. Administration of chemotherapy in postoperative regimen requires additional evidence of its effect, as EAU guidelines do not provide proof of its benefit. We ran retrospective single center study on effect of adjuvant chemotherapy (CT) on 3- and 5-years cancer-specific survival (CSS) in series of patients after RC for BC.
Materials and Methods: 286 patients with BC underwent RC with pelvic lymph node dissection and subsequent urinary diversion from 2000 through 2011. Males were 259 (90.2%). Median age at surgery was 60.6±15 years (range: 30−79 years). Orthotopic intestinal urinary diversion was performed in 130 (45.5%) patients, heterotopic intestinal urinary diversion − in 30 (10.5%), and on-skin diversion of urine was done in 126 (44%) patients.
Patients with locally advanced or lymph node positive disease underwent adjuvant platinum-based chemotherapy in one of the selected modes (methotrexate with vinblastine, doxorubicin and cisplatin; or gemcitabine with cisplatin).
Logistic regression method was applied for data analysis. Statistical significance of independent variables (clinical stage pT, sex, age at surgery, adjuvant CT) on 3- and 5-yr. CSS was determined.
Results: Forty-six (15.8%) patients after RC received adjuvant CT: 38 (82.6%) patients with N+, 3 (6.5%) − with pT3a disease, and 5 (10.9%) − with M+.
Thirty (65.0%) patients died due to progression, with median survival of 14.8 months (range 3.4–55.3 mo., 95% CI: 5.0–36.7). At final follow-up only 3 out of 16 survived patients after CT are free from disease.
Among 174 patients who did not receive CT after RC 108 (62.1%) patients died due to all reasons including progression of cancer. Median survival was 34.3 mo. (12.9–88.6 mo., 95% CI: 13.4–82.7).
Logistic regression analysis revealed significant factors for 3-years CSS with AUC=0.847 to be age at surgery ($p < 0.00001$), pT ($p < 0.0001$), insignificant factors were: sex ($p = 0.259$) and adjuvant CT ($p = 0.233$). For 5-years CSS with the AUC = 0.784 significant factors were pT ($p < 0.0001$), age ($p = 0.001$), insignificant factors were adjuvant CT ($p = 0.127$) and sex ($p = 0.221$).
Conclusion: Adjuvant chemotherapy does not affect cancer specific survival in bladder cancer patients after radical cystectomy.
No conflict of interest.

2733 POSTER

Patience is a virtue: "wait and see" strategy for metastatic or recurrent renal cell carcinoma

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Background: Metastatic renal cell carcinoma (MRCC) often presents with very indolent course without any symptom, and treatment (Tx) for MRCC is mostly palliative rather than curative in a molecular target agents era. There exist several Tx options for MRCC, but all available agents have considerable toxicities, cause economic burden to patients (pts), and impair quality of life. For some cancers like indolent lymphoma, 'wait and see' strategy (W&S) is adopted for asymptomatic pts. We retrospectively evaluate clinical outcomes of W&S for asymptomatic MRCC pts.
Methods: We enrolled MRCC pts who was followed-up with deferred treatment for the purpose of W&S in our institution between 2000 and 2012. Clinical characteristics, response to W&S, predictive factor for time-to-progression (TTP), and response to succeeding first line Tx were analyzed.
Results: Of 44 pts found, 30 pts had recurrent disease and 13 pts initially metastatic disease. Most pts had good Karnofsty PS (KPS), 100% for 26 pts and 90% for 13 pts. Lung (38 pts), lymph nodes (16 pts), kidney (6 pts) were most common site of metastasis. During W&S, stable disease (SD) and progressive disease (PD) were the best overall response for 36 (82%) and 8 (18%) pts, respectively, and 37 pts had PD finally. With a median F/U period of 24.7 months, median TTP and OS were 12.5 months (95% CI, 6.7–18.4) and 91.1 months (95% CI, 41.3–141.0). After univariate and multivariate analysis for TTP, KPS <100, liver metastasis, time from diagnosis to W&S <1 year, and neutrophilia were found to be predictive factors for TTP during W&S. After PD, 27 pts proceeded to systemic treatment (13 sunitinib, 10 pazopanib, 3 immunotherapy, and 1 temsirolimus). Objective response rate were 54% for sunitinib, and 50% for pazopanib.
Conclusions: This study suggests that W&S could be a viable treatment option for the first-line approach in asymptomatic MRCC pts, especially for those who have good performance status without neutrophilia or liver metastases.
No conflict of interest.

2734 POSTER

Demographic and clinical data on nonseminomatous germ cell tumours and long-term (1993–2011) results: GATA experience

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Introduction: Male nonseminomatous germ cell cancers are frequently seen tumors in young patients between the ages of 20−40. Approximately 95% of them involve testes and 5% are extragonadal.
Methods and Patients: Demographic and clinical characteristics of 248 patients who applied to section of Medical Oncology, Gulhane Military Medical Academy between February 1993-December 2011were retrospectively reviewed and evaluated.
Results: Median age of patients was 26 (19−45 years) and 74 patients (29.8%) were living in Central Anatolia; Eastern Anatolia region drew attention to be the least one of living area (n = 14, 5.6%). 54 cases (21.7%) had noticed an asymptomatic testicular mass themselves and 39 percent of these cases (72.2%) were higher educated. In evaluation of body-mass indexes; 156 cases (62.9%) were normal weight, 45 (18.1%) were overweight, and 38 (15.3%) were obese. Two patients (008%) had testicular intraepithelial neoplasia, 32 patients (12.9%) were stage I, 126 patients (50.8%) were stage II, 88 patients (35.4%) had stage III disease. The primary place of tumor was as follows; 189 patients (76.2%), testis, 59 patients (23.8%) extragonadal [retroperitoneal in 38 patients (15.3%), mediastinal in 21 patients (8.4%)]. Histopathologically, embryonal carcinoma, yolk-sac and choriocarcinoma components accompanied mixt-germ cell components in the frequencies of 73%, 22%, 17% respectively. As first line therapy, PVB or BEP chemotherapy in all cases was performed. Number of patients who needed retroperitoneal lymph node dissection because of a residual mass after standard chemotherapy for stage II and stage III disease were 21 (8.4%) and 7 (2.8%), respectively. Median follow-up was 94 months (range: 19–228), 69 months (14 −176) and 31 months (11–134) for stage I, II and III patients, respectively. 10-year overall survival rate of patients with testicular tumors were 99%, 79% and 43% for stage I, II and III patients, respectively.
Conclusion: Germ cell cancers have high response and survival rates with conventional chemotherapy although they have heterogeneous characters in terms of histologic type and clinical behavior.
No conflict of interest.

2735 POSTER

Response to second line chemotherapy (Ctx) in advanced urothelial carcinoma: A pooled retrospective analysis of combination versus monotherapy

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Introduction: Second line ctx for advanced urothelial carcinoma (UC) constitutes a substantial unmet need. There are a number of agents used however with marginal activity in advanced UC. We examined the effectiveness of chemotherapy in the 2nd-line setting along with the effect on reported overall survival (OS). We also determined whether responses differed between combination and monotherapy regimens.
Methods: Published 2nd-line studies were identified from PubMed between 1997 and 2012. Manuscripts were reviewed for data extraction. Pooled weighted objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and median overall survival (OS) were calculated. Using Fisher's exact we determined the difference between the ORR and DCR of combination versus monotherapy.
Results: Twenty-five prospective studies of second-line ctx for progressive advanced UC were identified (22 non-randomised, 3 randomised) (n = 1297). The majority of studies (88%) were phase II. Twelve studies investigated combination regimens while 13 studies examined monotherapy. All studies allowed adjuvant and primary chemotherapy as 1st-line but only 12 reported breakdown while only 7 studies reported median time from last chemotherapy. The pooled ORR was 17.0% (95% CI 12.7–21.3%) and DCR was 47.7% (95% CI 36.8–58.6%). In terms of median PFS, the pooled median is 3.0 mos (range 1.6–11.0 mos) while the median pooled OS was 6.9 mos (range 3.0–14.4 mos). When we compared the combination regimens to monotherapy the ORR was 27.7% versus12.3% ($p < 0.001$) and DCR was 44.3% versus 32.3% ($p < 0.001$). There was numerical difference in PFS between combination and monotherapy, at3.9 mos (range 1.6−3.8 mos) versus 2.7 mos (range 2.6−11 mos), and in OS at 7.5 mos (range 4–14.4) versus 6.6 (range 3−1.8 mos). No formal comparison was performed.
Conclusion: The pooled analysis revealed that 2nd-line ctx for advanced UC can induce a response and good disease control. Combination ctx is still superior in 2nd-line and is an appropriate approach in patients with a good performance status. This may help relief symptomatic patients. However larger prospective study is needed to confirm this.
No conflict of interest.

2736 POSTER

Experience with Sunitinib in metastatic renal cell carcinoma (mRCC) patients: Pool analysis from 3 Spanish observational prospective studies

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Background: Sunitinib is a standard of care for favorable and intermediate risk mRCC patients (pts) in the firts-line setting. Here we report efficacy and safety results from a pooled analysis of 3 observational prospective studies involving 33 Hospitals.
Material and Methods: 224 evaluable pts who were enrolled between 2007 and 2011 and received Sunitinib in the 1st line setting following routine clinical practice were analyzed. 49 pts from SUT-IIG-09 study; 94 from SUT-REN-07 and 81 from MAR-SUT-2008−01. The primary objective of these studies was to evaluate the predictive value of different biomarkers in terms of PFS.
Results: 42% pts were metastatic at diagnosis and 93% were clear cell or showed a clear cell component. 81% had prior nephrectomy. 36% only one site of metastasis, 37.5% two sites, 25.5% $\geqslant$3 sites and 1% locally advanced disease. 25%, 63% and 12% were ECOG PS 0, 1 and

⩾2 respectively; 6%, 83% and 11% showed intermediate and poor risk (MKSCC criteria) respectively.
Time from diagnosis to Sunitinib interval was ⩽1 year in 58% of pts. 59% of pts had at least one dose reduction. Median treatment duration was 7.7 months (m) (95% CI: 9.3–11.3). At the time of the analysis 171 pts (76%) had discontinued treatment: 68% due to progressive disease (PD) and 20% due to toxicity. With a median time of follow up of 13.07 m (95%IC: 6.97–22.20) median PFS was 11.60 m (95% CI: 9.92–13.28) for the favorable-intermediate risk group. 208 pts were evaluable for response. As a best response: 5% complete responses (CR), 38.5% partial response (PR), 38.5% stable disease (80% lasting >6 m) and PD 17.8%. Objective response rate (CR+PR) was 43.5% (95% CI: 36.8–50.7). Median time to PR was 3.8 m (95% CI: 3.86–5.99) and to CR 8.2 (95% CI: 4.75–9.77). Median duration of response was 7.43 m (95% CI: 8.9–12.3). At the time of the analysis 102 pts had died and median overall survival was 21.9 m (95% CI: 17.2–26.6).
The most common related AEs were asthenia (72%), mucosal inflammation (56%), diarrhea (41.5%), neutropenia (36%), hypertension (HTN) (36%), hand food syndrome (HFS) (35%) and hypothyroidism (24%); the most common grade 3 toxicities (more than 10% of patients) were asthenia (25.5%), HFS (18%), HTN (16%) and neutropenia (12.5%). Only 3 cases of grade 4 toxicities were reported.
Conclusions: Efficacy and safety with Sunitinib in pts treated within an observational prospective study were comparable to those previously reported in clinical trials.
Conflict of interest: *Other substantive relationships: MV Bolos works at Pfizer*

2737 POSTER

Outcome of metastatic renal cell carcinoma (mRCC) patients in the era of new targeted therapies

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Background: Targeted therapies have improved the outcome in patients (pts) with mRCC in terms of progression-free survival (PFS) and overall survival (OS).
Material and Methods: A retrospective analysis from pts treated with targeted therapies between 2007 and 2011 in a single institution was carried out. The primary objective was to evaluate the efficacy of treatment with sunitinib and the different treatment sequences.
Results: 102 pts with mRCC were included, 84% had prior nephrectomy and most of the tumors were clear cell or showed a clear cell component (98%); 35%, 48% and 16% showed an ECOG PS of 0, 1 and 2 respectively; 48%, 27.5% and 24.5% were favorable, intermediate and poor risk, respectively, according to MSKCC criteria. 79% received sunitinib as a 1st line, 16% as a 2nd line and 5% in subsequent lines. 37% were treated only with Sunitinib (n = 38), 19% received 2 lines of treatment (n = 19), 26% 3 lines (n = 27) and 18% ⩾4 lines (n = 18), including sunitinib. 9 pts were rechallenge with sunitinib. 33% of pts were treated with a VEGF (vascular endothelial growth factor) inhibitor followed by a VEGF inhibitor (n = 34); 19% of pts (n = 19) received the sequence VEGF-mTOR inhibitors and 7% the sequence mTOR-VEGF inhibitors (n = 7). Sunitinib starting dose and schedule was 50 mg/day 4-wk-on-2-wk-off (4/2) in 75.5% of cases. 46.5% of pts experienced at least one dose reduction during sunitinib treatment. Median time of follow up was 19.32 months (m) (95% CI: 8.63–34.67). 93% of patients had discontinued sunitinib at the time of this analysis: 68% due to progressive disease and 19% due to toxicity. Best response: 5% complete response, 33% partial response and 38% stable disease (61% lasting >6 months). Median PFS was 9.5 m (95% CI: 6.73–12.21) in the favorable-intermediate risk group and 3.8 m (95% CI 1.4−6.2) in the poor risk group. Median OS for the favorable-intermediate risk group was 33.9 m (95% CI: 26.9–40.9) and 11.7 m (95% CI: 2.7–20.7) for the poor risk group. The 3 yrs OS rate was 22.6%. An exploratory analysis to evaluate the efficacy in terms of PFS and OS of different treatment sequences is underway.
Conclusion: The outcome of mRCC has improved markedly with targeted therapies. Multiples lines of treatment have increased survival to close to 3 years in patients with good-intermediate prognosis. Patients with poor prognosis also obtain a survival improvement when compared to historical data.
Conflict of interest: *Other substantive relationships: Mari Victoria Bolós and Andrea Viqueira are Pfizer employees*

2738 POSTER

Hand–foot syndrome (HFS), a potential biomarker of efficacy in patients (pts) with metastatic renal cell carcinoma (mRCC) treated with sunitinib (SU)

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Background: HFS and related skin toxicities are common side effects of tyrosine kinase inhibitors such as SU, a multitargeted inhibitor of VEGF and PDGF receptors plus other receptor tyrosine kinases. In the treatment of naive mRCC pts, SU showed superior progression-free survival (PFS) and objective response rate (ORR) over interferon-alfa, with a median PFS of 11 mo and median overall survival (OS) of 26.4 mo, establishing SU as a reference standard of care (Motzer et al, 2009). In this analysis, correlations between SU-associated HFS and efficacy endpoints were investigated in mRCC pts from January 2009 to January 2011 in the first- and second-line treatment settings.
Methods: A total of 23 patients who received single-agent SU as 50 mg/d on a 4-week-on/2-week-off schedule (n = 17; 73.9%) or 37.5 mg (n = 6; 26%). Median PFS and OS were estimated and compared between pts with vs without HFS. Adverse events were recorded regularly.
Results: Of 23 pts, 9 (39%) developed any-grade HFS, compared with 14 (60.8%) who did not. Most HFS (58%) initially occurred during the first 3 treatment cycles. Pts who developed HFS had significantly better ORR (55% vs. 32%), PFS (12 vs. 8 mo), and OS (23 vs. 11 mo) than pts who did not develop HFS.
Conclusions: In mRCC pts, SU-associated HFS was significantly and independently associated with improved clinical outcomes. Overall, pts who did not develop HFS still had substantial benefit from SU. However, the presence of HFS identified a subset of pts that manifested highly favorable efficacy results with SU. This is suggesting that development of HFS may serve as a predictive biomarker of SU efficacy.
No conflict of interest.

2739 POSTER

SUVmax evaluated by FDG-PET/CT predict survival for patients with advanced renal cell carcinoma

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Background: Recently, various molecular targeting therapeutics were developed and improved the prognosis of patients with advanced renal cell carcinoma (RCC). When molecular targeting therapies have become the mainstay of treatment, assessment of the biological activity of cancer becomes important. Because the antitumor action of targeting therapeutics is not cytotoxic, like classical antitumor therapeutics, but rather cytostatic, suppressing biological activity by inhibiting critical biological pathways. ^{18}F-2-fluoro-2-deoxyglucose positron emission tomography (FDG PET/CT) is a useful non-invasive tool to evaluate glucose metabolic status, which can be the index of biological activity of cancer. We evaluated the impact of the maximum standardized uptake value (SUVmax) from pretreatment FDG PET/CT, which was a semiquantitative simplified measurement of the tissue FDG accumulation, on survival for patients with advanced RCC.
Material and Methods: A total of 71 patients with advanced RCC were enrolled in this study. The impact of pretreatment SUVmax from FDG PET/CT (Aquiduo 16; Toshiba Medical Systems, Tokyo, Japan) on patient survival was analyzed prospectively.
Results: The SUVmax of 71 patients ranged between undetectable level and 16.6 (median 8.1). The patients with RCC tumors showing high SUVmax demonstrated poor prognosis ((P<0.001 hazard ratio 1.289, 95% CI 1.161–1.430). The SUVmax of 36 patients (51%) were <7.0 and their median overall survival (OS) was 1218±248 days. The SUVmax of 24 patients (34%) were 7.0⩽and <12.0 and their median OS were 676±291 days. The SUVmax of 11 patients (15%) were 12.0⩽and their median OS were 129±43 days. The OS for these patient subgroups were statistically different (<7.0 vs. 7.0⩽<12.0: $P = 0.0257$, 7.0⩽<12.0 vs 12.0⩽: $P = 0.0181$).
Conclusions: The survival of patients with advanced RCC can be predicted by evaluating their pretreatment SUVmax using FDG-PET/CT. In the era of molecular targeting therapy, FDG-PET/CT has potency as an

'imaging biomarker' to provide helpful information for the clinical decision-making.
No conflict of interest.

2740 POSTER

Health-related quality of life among patients with metastatic renal cell carcinoma in daily clinical practice

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Background: Real-life data on mRCC patients' health-related quality of life (HRQoL) have not been available. It is recognized that the every-day patient population may differ from those in clinical trials. Sunitinib is normally administered in 6wk cycles including a 2wk rest period. Previous studies have indicated an improvement in the HRQoL during the 2 weeks off the treatment.
Materials and Methods: A prospective follow-up study of patients using sunitinib as the first line mRCC treatment (N = 54) was carried out. The data were collected in 5 oncology clinics in Finland. The patients were asked to fill in the generic 15D HRQoL questionnaire at baseline, at day 28 of the 1st sunitinib treatment cycle, 1st day of 2nd cycle, and thereafter in 3 month intervals. The 15D produces a HRQoL score on a 0−1 (dead-full health) scale. After exclusion due to missing HRQoL questionnaires, data from 49 patients were available for final analysis. The mean age among the responders was 65.3 years [range: 46.4–80.5], and 73% were men.
Results: At baseline the mRCC patients' mean 15D score was slightly lower than that of the age-standardized general population (0.854 vs. 0.865). The difference was neither statistically significant nor clinically important. The patients were statistically significantly worse off than the general population on the dimensions of usual activities, mental function, distress, and sexual activity. The mean 15D score declined from the baseline level by 0.040 when a full 28 days of sunitinib was administered (a statistically significant and clinically important decline), and returned back to the baseline level (0.860) after the 2 week rest period. The HRQoL fluctuated during later phases of treatment, but this was not clinically important in magnitude. No trend was observed between the time on sunitinib and HRQoL.
Conclusions: The 2wk rest period included in the 6wk treatment cycle is relevant from the perspective of patients' HRQoL. The decline in HRQoL during treatment days was clinically important and could be captured with the generic 15D instrument.
Conflict of interest: *Other substantive relationships: The data collection was partly supported by Pfizer*

2741 POSTER

Validation of imaging biomarker in multi-centric study to predict PFS in mRCC treated with sunitinib

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Background: Tyrosine kinase inhibitors including sunitinib are the most effective treatments of metastatic renal cell carcinoma (mRCC). A multi-centric study of 539 patients (different tumors treated anti-angiogenic treatments) evaluating dynamic contrast-enhanced ultrasound (DCE-US), showed that a decrease of AUC (Area under the curve) correlated to the blood volume at one month is predictive of response. Our objective was to validate the correlation between this parameter and the PFS in a sub-group of mRCC treated with Sunitinib.
Material and Methods: Each Patient had CT-scan every 2 months in order to evaluate the Response assessment using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1).
DCE-US were performed at baseline and at D30. At each examination, we quantified 7 DCE-US parameters after bolus injection of contrast agent and mathematical modelization of raw linear data recorded during 3 minutes. We also estimated the variation between baseline and D30. The main endpoint was progression free survival assessed according to RECIST. We first selected the best parameters. We studied the trend between the parameter value and freedom from progression. After, the best cut-points were searched through a grid search. The best single cut-point was that with the lowest P-value for progression free survival. We performed this analysis in the sub-group of patients with mRCC treated with sunitinib.
Results: A total of 81 mRCC patients treated with sunitinib were selected. All had DCE-US at baseline and one month. The median of follow-up was 18 months. For DCE-US, the decrease of 90 % of AUC at D 30 was correlated to the PFS (p = 0.01). The difference of PFS between the groups defined by this cut-point was 4 months (bad responders) and 14 months (good responders).
Conclusions: The decrease of more than 90% of AUC with DCE-US at one month is a potential predictive biomarker of response in mRCC patients treated with sunitinib.
No conflict of interest.

2742 POSTER

Important differences for fatigue and quality of life questionnaires in advanced renal cell carcinoma patients

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Background: The Functional Assessment of Chronic Illness Therapy − Fatigue (FACIT-F) is a widely used 13-item questionnaire assessing fatigue that is validated for use in the general population, cancer patients, and other chronic disease populations. Past analyses suggest 3−4 points constitute an important difference. A Supplementary Quality of Life Questionnaire (SQLQ) assessing mouth/throat, hand, and foot soreness and limitations due to soreness was created for use in PISCES, an ongoing trial in advanced renal cell carcinoma (RCC) patients (NCT01064310). The FACIT-F and SQLQ were administered at baseline and every 2 weeks thereafter. This project evaluates important differences on the FACIT-F and SQLQ in 168 advanced RCC patients enrolled in PISCES.
Material and Methods: We used distribution- and anchor-based approaches to estimate important differences. We compared baseline mean scores across levels of baseline ECOG performance status. Effect sizes (ES) were calculated as the mean group difference/pooled standard deviation (SD). Mean change from baseline to Week 8 was calculated for patient subgroups defined by worst fatigue (or hand–foot syndrome) adverse event (AE) grade during that period. ES was calculated as mean change/SD of change. Distribution-based measures, 1/3 SD and 1/2 SD, were also calculated at each assessment.

Table: Score changes by AE grade

Worst grade	N	Mean score change	ES
FACIT-F (fatigue grades)			
0	81	−0.52	−0.07
1	17	−4.68	−0.59
2	19	−9.21	−0.93
3	9	−10.22	−1.29
Limitations due to mouth and throat soreness (hand–foot syndrome grades)			
0	94	0.36	0.27
1	13	0.77	0.62
2−3	13	0.77	0.45
Limitations due to foot soreness (hand–foot syndrome grades)			
0	92	0.15	0.08
1	13	0.38	0.34
2−3	13	1.31	0.62

Results: ECOG 0 and 1 patients differed by 8.6 FACIT-F points (ES=1.06), 0.45 points for SQLQ limitations due to mouth/throat soreness (ES=0.45), and 0.94 points for limitations due to foot soreness (ES=0.48). Change for patients categorized by worst fatigue or hand–foot syndrome AE are summarized in the table. For the FACIT-F, 1/3−1/2 SD equaled 3−5.6 points, 0.3−1.0 points for limitations due to mouth/throat soreness, and 0.2−0.3 points for limitations due to foot soreness.
Conclusions: In advanced RCC patients, FACIT-F and SQLQ are valid and responsive measures. Group differences on clinical anchors range from small to large in magnitude, and are therefore often larger than one would

consider 'minimally' important. These results inform future judgments of the clinical relevance of group differences on these measures.
Sponsor: GlaxoSmithKline
Conflict of interest: *Ownership: (JD) GlaxoSmithKline stock (FM) GlaxoSmithKline stock. Advisory board: (DC) GSK, Pfizer, Aveo, Novartis, Bayer. Corporate-sponsored research: (KK) Research sponsored by Daiichi Sankyo, Biogen Idec, Janssen Pharmaceuticals (DC) GSK, Pfizer, Aveo. Other substantive relationships: (JD) employed by GlaxoSmithKline (FM) employed by GlaxoSmithKline*

2743 POSTER

First-line treatment in the management of advanced renal cell carcinoma: Systematic review and network meta-analysis

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Background: A systematic review (SR) and network meta-analysis (NMA) were conducted to assess the efficacy and safety of first-line treatments for advanced renal cell carcinoma (RCC) building on previous published analyses.
Materials and Methods: Database searches (accessed November 2012) were conducted to systematically identify randomised controlled trials (RCTs) in the first-line treatment of RCC. Indirect comparisons using a fixed-effect Bayesian model were used to assess the relative effectiveness of treatments, reported as hazard ratio (HR) and 95% credible intervals (CrI). All eligible studies were included in the model to minimise the introduction of potential bias.
Results: Seventy-nine publications of 43 RCTs met the pre-specified criteria for inclusion in the SR. Hand-searching of conference proceedings identified efficacy results from three additional RCTs. Eight RCTs were eligible for inclusion in the basecase NMA. In terms of progression-free survival (PFS) sunitinib was superior compared with sorafenib, bevacizumab + IFN and temsirolimus + bevacizumab (see table). Sunitinib also showed benefit over pazopanib and tivozanib, though these results were not significant. Sensitivity analysis based on re-estimating the HR from one study was performed, which impacted the results of the NMA. A robust analysis of overall survival (OS) was not performed due to difficulties in identifying OS data for individual treatments when many results include post-study treatment.
Conclusions: Based on available comparative clinical trial data the analysis results suggest that sunitinib continues to be an important treatment option to extend PFS in the management of advanced RCC in the first-line setting. While results from the current analysis can guide clinicians regarding the relative efficacy of currently available treatments, the results should be interpreted with the following caveats. Due to the lack of individual patient level data it was difficult to test the validity of the proportional hazards assumption. Also, as each treatment pair is connected by just one study, the results can be sensitive to changes in a single trial result.

Treatment comparison [a]	Mean HR	Median HR	95% CrI
Sunitinib vs. Pazopanib	0.94	0.93	0.80–1.08
Sunitinib vs. Bevacizumab + IFN	0.79	0.78	0.64–0.96
Sunitinib vs. Sorafenib	0.57	0.56	0.40–0.78
Sunitinib vs. Tivozanib	0.76	0.74	0.48–1.13
Sunitinib vs. Temsirolimus + bevacizumab	0.74	0.73	0.56–0.96

[a] Results include independently assessed data (where available).

Conflict of interest: *Other substantive relationships: James Larkin received an honorarium from Pfizer in connection with the development of this abstract. Grace Foley and Connie Chen are employees of Pfizer Ltd. Stephen Mitchell and Abby Paine were paid consultants to Pfizer in conjunction with development of this abstract.*

2744 POSTER

Prospective, multicenter and epidemiological study to determine prognostic factors in patients with renal cell carcinoma: A stroma-related SNP located at FGFR2 as a potential prognostic biomarker

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In renal cell carcinoma (RCC) the MSKCC criteria are the most widely used classification for stratifying patients (pts) into different risk categories. Although generated from pts treated with cytokines, this classification is still widely used in the era of molecular targeted therapy. Moreover, there is little information on non-clinical characteristics that might have a prognostic significance; recently the role of stroma has been reported as crucial to define the patient outcome. This study evaluates the role of the MSKCC prognostic classification in pts treated with targeted therapies and explores the prognostic potential of some molecular, genetic and stroma-associated biomarkers.
A prospective, observational and multicenter study in pts with treatment naive RCC was carried out. Baseline clinicopathological characteristics were recorded; a baseline blood sample was extracted from all pts in order to evaluate the molecular, genetic and stromal factors. The primary objective of the study was to identify the pre-treatment prognostic factors associated with progression free survival (PFS) in pts with RCC.
From May 2009 to September 2010, a total of 145 pts (137 evaluable) were included. Pts had a median age of 64 years, 65% were male, 72% had clear cell RCC and 75% had a prior nephrectomy. According to MSKCC criteria, 23% had a favorable prognosis, 56% an intermediate prognosis and 21% a poor prognosis. All pts were treated with targeted therapies: 71% with sunitinib, 23% with temsirolimus and 6% with sorafenib. Median PFS according to prognostic group were: not yet reached, 10.9 and 4.1 months for pts with good, intermediate and poor prognosis, respectively, with statistically significant differences between the 3 categories. In a multivariate analysis, non-clear histology, Karnofsky performance status and time from diagnosis to treatment were shown to be independent prognostic factors of poor PFS. Regarding stroma-associated factors, a SNP located at FGFR2 gene at position 906C>T (rs2981582) provides independent prognostic information identifying two clinical patterns ($p = 0.009$) regardless of other significant clinicopathological variables.
MSKCC criteria are still a valid tool for stratifying pts into prognostic categories. Additionally, non-clear histology, Karnofsky performance status, time from diagnosis to treatment and FGFR2 SNP at 906-nt (C>T) were shown to be independent prognostic factors that might be useful to classify pts with RCC.
Conflict of interest: *Other substantive relationships: Dr. Viqueira is a Pfizer employee*

2745 POSTER

Smoking habit and its impact on the efficacy and safety of sunitinib in metastatic renal cell carcinoma (mRCC) patients

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Background: Sunitinib is a tyrosin kinase inhibitor with proven efficacy in mRCC. The impact of the smoking habit on the efficacy and safety of novel anti-angiogenic agents is not still clear.
Material and Methods: We conducted a retrospective analysis on 102 mRCC patients (pts) who received Sunitinib in a single Institution (Hospital Universitario Central de Asturias) with a high incidence of mRCC. The main objective of the study was to explore the impact of the smoking habit on treatment response in terms of progression free survival (PFS) and overall survival (OS).
Result: 42% of pts ($n = 43$) were never-smokers, 38% ($n = 39$) former-smokers and 20% ($n = 20$) current-smokers. Most of the pts showed clear cell tumors (83%) or with a clear cell component (15%). 74.5% ($n = 76$) of pts were male, median age was 62 (range 58−62).
Although different groups according to smoking habit were not well-balanced in terms of ECOG PS, prior nephrectomy, sites of metastatic

Table (abstract 2747): Clinical outcome by AUC_{study} threshold

	AUC_{study} threshold (ng·h/ml)							
	⩾200	<200	⩾300	<300	⩾400	<400	⩾273*	<273*
n	123	44	73	94	49	118	82	85
ORR	53%	34%	48%	48%	53%	46%	52%	44%
mPFS, mo	14.5	11.5	12.2	16.6	12.2	16.3	13.8	14.6
HR† (95% CI); *P*	0.719 (0.478–1.08); 0.111		1.1 (0.751–1.62); 0.621		1.01 (0.662–1.53); 0.975		0.94 (0.642–1.38); 0.751	

*Median AUC_{study}; †Hazard ratio ⩾ vs < threshold.

disease, MSKCC risk groups and number of patients under 1st line Sunitinib, these differences were not statistically significant.
Statistically significant differences in terms of PFS were found among never-smoker, former-smoker and current-smoker groups: a median PFS of 5.9 months (95%IC: 4.1 −7.65), 10.2 months (95%IC: 7.7–12.6) and 10.2 months (95%IC: 2.2 −18.1) $p < 0.05$ was found respectively. Although an improvement in PFS was found in those patients with any smoking history, a multivariant analysis doesn't confirm it as independent factor for achieving a longer PFS. Non significant differences in terms of clinical benefit rate (complete and partial responses+ disease stabilizations) were found among these groups: 69% in never-smoker and former-smoker groups and 85% in the current smoker one ($p = 0.286$).
At the time of the analysis 93% of pts had discontinued Sunitinib. Reasons for discontinuation were: progression disease (68%), toxicity (19%) and others (17%).
Incidence of adverse events (AEs) with Sunitinib was as expected, with asthenia, hand food syndrome and mucosal inflammation as main toxicities (more than 40% of patients). Incidence of most Sunitinib associated AEs was greater in patients with any smoking history, although these differences were not statistically significant.
Conclusions: Additional prospective studies in well-balanced populations of patients are required to confirm if the smoking habit really impacts on the efficacy and safety with anti-angiogenic agents in mRCC.
No conflict of interest.

2746 POSTER

Determination of chromosome aberration as a factor of prognosis in treatment of bilateral renal cell carcinoma

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Background: To study cytogenetic features of peripheral blood lymphocytes in patients with bilateral renal cell carcinoma (RCC) in order to determine the degree of tumor aggressiveness.
Material and Methods: The results of examination and treatment of 37 patients with bilateral RCC have been studied in urological departments National center of oncology, regional center of oncology. There were 23 (62.1%) males and 14 (37.9%) females. The age of patients ranged from 22 to 83 years, mean 59.5±4.2 years. In order to determine chromosome changes in peripheral blood lymphocytes metaphase plate were studied in the corporative aspect.
Result: Analysis of the research results according to the number of metaphase plate with aberrations showed that in patients with local bilateral RCC metaphase plate with single chromosome aberrations are revealed more often (in 91.7% of cases), metaphase plates with plural aberrations are revealed more seldom (in 8.3% of cases) differences are statistically reliable ($p < 0.05$).
In patients with primary generalized form of bilateral RCC metaphase plate with plural chromosome aberrations occur on the contrary more often (in 57.1% of cases) than single ones (in 42.9%of cases), differences are statistically reliable ($p < 0.05$).
Conclusion: Marked tumor aggressiveness and chromosome disturbances in peripheral blood lymphocytes are specific for patients with bilateral RCC. The study of genetic alterations in lymphocytes in bilateral RCC due to discovery of their qualitative and quantitative changes is the method of early diagnostics and screening for cancer and it probably reveals the cause of bilateral RCC.
No conflict of interest.

2747 POSTER

Randomised phase II trial of axitinib with or without dose titration in first-line metastatic renal cell carcinoma (mRCC): Efficacy and pharmacokinetic (PK) analyses

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Background: Prior PK analyses suggest higher axitinib exposure correlates with efficacy in mRCC. Dose titration based on tolerability may optimise axitinib exposure and improve outcome.
Material and Methods: In a phase II trial (NCT00835978; sponsor: Pfizer), patients with treatment-naive mRCC received axitinib 5 mg BID for 4 wk (cycle 1). Patients with blood pressure ⩽150/90 mmHg, no axitinib-related toxicities grade >2, no dose reduction, and ⩽2 antihypertensive medications were randomised (double-blind) to axitinib 5 mg BID + dose titration to 10 mg BID maximum (n = 56) or placebo titration (n = 56). Those ineligible for randomisation continued ⩽5 mg BID (n = 91). Primary endpoint was objective response rate (ORR) in active vs placebo titration arms. Axitinib exposures (AUC 0−24 h) prior to randomisation (AUC_{cycle1}) and throughout treatment (AUC_{study}) were estimated by population PK analyses.
Results: ORR was significantly higher (1-sided *P*=.019) with active (54%) vs placebo (34%) titration. Patients eligible for dose titration had lower mean AUC_{cycle1} (active vs placebo titration: 248 vs 214 ng·h/ml) at 5 mg BID vs those not eligible (382 ng·h/ml). Mean AUC_{study} was 300 ng·h/ml with active titration, due to dose increases, and 207 ng·h/ml with placebo titration. Exploratory analyses indicated that progression-free survival (PFS) and AUC_{study} were not strongly correlated across the range of observed exposures. AUC_{study} thresholds (Table) showed the largest difference in ORR and PFS hazard ratio in patients ⩾ vs <200 ng·h/ml. When retrospectively grouped by AUC_{study} quartiles, patients in quartile 2 (199–272 ng·h/ml) had longer median PFS (mPFS; 22.2 mo) vs other quartiles (11.5–13.9 mo).
Conclusions: Axitinib titration significantly improved ORR vs placebo titration. Patients eligible for titration had lower AUC_{cycle1} at 5 mg BID, which increased with active titration, indicating the dose titration scheme identified patients with lower exposures at the starting dose. Results suggest PK is not the only driver of clinical outcome; pharmacodynamic and/or patient-specific factors likely contribute to axitinib efficacy in mRCC.
Conflict of interest: *Ownership: Y Pithavala, Y Chen, G Andrews, AH Bair, and S Kim (stock ownership in Pfizer). Advisory board: BI Rini (Pfizer) B Melicar (Roche, Astellas) MN Fishman (Aveo, Bayer, Eisai, GlaxoSmithKline, Novartis, Pfizer, Prometheus) V Grünwald (Pfizer, Novartis, GlaxoSmithKline, Astellas, Bayer, Roche). Board of directors: None. Corporate-sponsored research: BI Rini (Pfizer) MN Fishman (Amgen, Aveo, BristolMyersSquib, Eisai, SWOG [Bayer/Pfizer], Pfizer). Other substantive relationships: B Melicar (lecture fees from Roche, Novartis, Pfizer, GlaxoSmithKline) T Ueda (lecture fees from Pfizer) Y Pithavala, Y Chen, G Andrews, AH Bair, and S Kim (employment with Pfizer) MN Fishman (Immatics) V Grünwald (lectures for Pfizer, Novartis, GlaxoSmithKline, Astellas, Roche)*

2748 POSTER

Long-term safety with sunitinib (SU) in metastatic renal cell carcinoma (mRCC)

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Background: SU is approved globally for mRCC. Here we report long-term safety with SU in mRCC patients (pts) using pooled data from 11 prospective clinical trials.
Material and Methods: Pts received SU 50 mg/d on a 4-wk-on/2-wk-off schedule or 37.5 mg/d continuous dosing. Three analyses of treatment-related adverse events (TRAEs) were conducted, both in pts on SU $\geqslant$2 y and in all pts: (1) interval analysis, in which AEs were evaluated over successive 6-month intervals, with each AE counted once per interval; (2) cumulative analysis, in which each successive interval was defined from the start of treatment plus an additional 6 months; and (3) time to onset of common TRAEs.
Results: At the data cutoff, 5,292 pts had received SU, including 189 (4%) for $\geqslant$2 y ('long-term' pts), whose mean treatment duration was 964 days. Among long-term pts, most AEs initially occurred in the first 6 mo to 1 y and were stable and/or decreased in frequency over time in the interval analysis (table), except for hypothyroidism. There were minor differences in AE patterns between long-term pts and all pts in the interval analysis; however, the cumulative analyses showed that new occurrences of AEs plateaued in both groups. Most common TRAEs occurred within the first 6 mo, except for hypothyroidism, for which median time to onset was 9.4 mo. Among long-term pts, most common grade $\geqslant$3 TRAEs, except leukopenia, were stable or decreased in frequency in the interval analysis. No new grade $\geqslant$3 TRAEs were reported in the cumulative analysis of long-term pts, and there were no clinically significant differences between the grade $\geqslant$3 TRAE profiles of long-term pts and all pts. Most cardiovascular TRAEs occurred during $\leqslant$1 y, with the most common, hypertension, reported within 3 mo. Among long-term pts, only one new cardiovascular TRAE was reported after 2 y, ventricular dilation.
Conclusions: Prolonged SU treatment was not associated with new types or increased severity of TRAEs in mRCC pts. Only hypothyroidism appeared to be cumulative and delayed, possibly due to increased awareness of this TRAE.

Table: Most common TRAEs in long-term pts by 6-mo interval (N = 189)

	0–<6 mo	6 mo–<1 y	1–<1.5 y	1.5–<2 y	2–<2.5 y	⩾2 y
Diarrhea	59%	70%	65%	65%	56%	59%
Fatigue	59%	55%	51%	50%	43%	49%
Hand–foot syndrome	28%	35%	38%	36%	26%	31%
Hypothyroidism	5%	10%	19%	25%	26%	29%
Nausea	38%	31%	28%	25%	18%	22%
Dyspepsia	40%	31%	25%	23%	19%	20%
Hair color changes	21%	19%	16%	17%	18%	18%
Hypertension	29%	24%	24%	21%	16%	18%
Dysgeusia	49%	40%	31%	24%	15%	16%
Anorexia	34%	27%	23%	20%	15%	16%

Conflict of interest: *Ownership: L.P. Charles, L. Chen and S. Hariharan − stock ownership with Pfizer Inc. Advisory board: C. Porta − Pfizer Inc, GSK, Bayer-Schering, Novartis, Astellas, AVEO, Boehringer-Ingelheim M.E. Gore − Pfizer Inc, Bayer B.I. Rini − Pfizer Inc B. Escudier − Bayer, Pfizer Inc, Novartis R.J. Motzer − Pfizer Inc, Genentech, AVEO Oncology. Corporate-sponsored research: C. Porta − Pfizer Inc, GSK, Bayer-Schering, Novartis, Astellas, AVEO B.I. Rini − Pfizer Inc R.J. Motzer − Pfizer Inc, Novartis, GlaxoSmithKline. Other substantive relationships: C. Porta − Pfizer Inc, GSK, Bayer-Schering, Novartis, Astellas M.E. Gore − has received honoraria from Pfizer Inc, Bayer B. Escudier − Bayer, Roche, Pfizer Inc, Genentech, Novartis, AVEO L.P. Charles, L. Chen and S. Hariharan − employed by Pfizer Inc*

2749 POSTER

A prospective phase II study of pemetrexed in combination with cisplatin in patients with advanced urothelial cancer: PECULIAR study

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Background: Pemetrexed has demonstrated a favorable response at the rate of about 30% with minimal toxicity when used as single agent as first-line and second-line treatment for advanced urothelial carcinoma. This trial was performed to evaluate the efficacy and safety of pemetrexed plus cisplatin in advanced urothelial carcinoma.
Methods: Eligible criteria included chemotherapy-naive advanced urothelial carcinoma, ECOG PS 0−2 and measurable disease. Pemetrexed 500 mg/m^2 on day 1 with cisplatin 70 mg/m^2 on day 1 were administered every 3 weeks till disease progression or a maximal of 8 cycles. Primary endpoint was response rate (RR), and secondary endpoints were progression-free survival (PFS), overall survival (OS) and toxicities. Response was evaluated every 6 weeks according to the RECIST critieria v.1.0 and toxicities were assessed with NCI CTCAE v.3.0 (ClinicalTrials.gov identifier NCT01490437).
Results: At the time of this analysis, a total of 40 patients were enrolled and 34 patients (median age 66.5 years, ECOG 0−1 100%, visceral metastasis 70.6%) were evaluable; 6 patients were too early to assess. Two received one or fewer cycles leaving 32 evaluable for outcomes. Nineteen partial responses and five complete responses for an overall response rate of 75% [95% confidence interval (CI) 60.5–89.6%] were documented. Three patients had stable disease. The median PFS was estimated to be 7.0 months [95% CI 6.2−7.8 months]. The median OS was 14.4 months [95% CI 9.1–19.7 months]. The most common grade 3 or 4 toxicities were neutropenia in 35% of patients. No one experienced febrile neutropenia. Other grade 3 or 4 hematological and non-hematological toxicities were rarely observed (thrombocytopenia 6%, anemia 6%, LFT elevation 6%, nausea 3%, anorexia 3%, edema 3%, dyspnea 3%).
Conclusion: The combination of pemetrexed and cisplatin is clinically very active, with an overall response rate of 75% and well tolerated in patients with advanced urothelial cancer who have not been previously treated.
No conflict of interest.

2750 POSTER

Methods of immunocorrection as accompanying therapy in patients with ovarian and cervical cancer

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Background: Chemoradiation therapy in cancer patients often leads to immunosuppression, reflected in the inhibition of the cellular and humoral immunity, which leads to an increase in complications of the treatment. Modern methods allow immunocorrection greatly reduce the side effects of chemotherapy by increasing immunological reactivity.
Material and Methods: There were evaluated the results of treatment of 183 patients with cervical cancer and 97 patients with ovarian cancer of stages $T_{2-3}N_{0-2}M_0$. All patients with cervical cancer received concomitant radiotherapy in split course, systemic and intraarterial chemotherapy. Patients with ovarian cancer had a combined therapy, including chemotherapy (cisplatin and cyclophosphamide for 4−6courses), as well as surgical treatment. 87 (47.5%) patients with cervical cancer and 43 (44.3%) patients with ovarian cancer were treated by methods of immunotherapy. Methods of extracorporeal immunepharmacotherapy (EIPhT) was carried out by exfusion of 200–250 ml of autologous blood, incubation with thimalin a total dose of 30 mg (for 3treatments) followed by reinfusion of the conjugate. The method of intermittent plasma exchange included exfusion of 500–1000 ml autologous blood followed by centrifugation and incubated with thimalin.
Results: The severity of the general condition of patients on a scale of ECOG(WHO) in patients with plasma exchange followed by EIPhT was very minimal incomparison with other groups of patients. Patients with EIPhT without plasma exchange had significantly reduced indicator in comparison with patients without immunocorrective therapy. In the study of quality of life of patients after treatment, which was conducted according to the questionnaire SF-36showed that the scores of physical health component in patients with plasma exchange followed by EIPhT was 284.5$\pm$39.1, in patients with EIPhT without plasma exchange − 362.7$\pm$41.0, and in the control group − 162.4$\pm$30.2 ($p < 0.01$). The total score of mental health component in these groups of patients, respectively, amounted

to 258.5±43.8, 234.0±46.1 and 196.3±35.9($p < 0.01$). Chemoradiation therapy led to an acceleration of erythrocyte sedimentation rate (ESR) in patients, decreased number of erythrocytes, leukocytes, development of lymphopenia with a predominance of suppressor cells, there is marked increase in IgG. CD4/CD8 parameter decreased from 1.257±0.03 to 1.08±0.02 ($p < 0.05$). In evaluating the hematological parameters after EIPhT there is observed their positive trend with an increase in the number of erythrocytes and leukocytes, ESR is decreasing to 17.3±1.27 mm/h (at the level of 24.2±1.46 mm/h). At the same time patients had an increase in CD4/CD8 immunoregulatory index to1.38±0.01, reduced level of IgG and a decrease in disimmuneglobulinemia, some increase in the level of phagocytosis.

Conclusions: Studies have shown that the methods EIPhT are highly effective in reducing the side effects of chemotherapy and radiation in combined treatment of patients with cervical cancer and ovarian cancer of III stage by improving the blood, normalization of the immune system and improvement of the life quality of patients.

No conflict of interest.

2751 POSTER

Early results of a phase 2 study of neoadjuvant cisplatin and gemcitabine plus sorafenib (S-CG) for patients with muscle-invasive transitional cell carcinoma of the bladder (INT52/10, NCT01222676)

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Background: Despite surgery with curative intent, about 50% of patients (pts) with muscle-invasive transitional cell carcinoma of the bladder (MIBC) die for distant metastases. Improvements with neoadjuvant chemotherapy are still limited. A rationale exists for inhibiting the RAF/MEK/ERK pathway, the VEGFR1−3, and PDGFR in urothelial cancer. The S-CG combination is being investigated in an ongoing open-label, single-group, single-center, Phase 2 trial.

Methods: Chemonaive pts with T2−4N0 MIBC were given 4 cycles of cisplatin 70 mg/m^2 on day 1 and gemcitabine 1000 mg/m^2 on day 1 and 8, every 3 weeks. Sorafenib 400 mg q12 h was administered daily from day 1 until surgery (radical cystectomy). Pts were staged with computed tomography (CT) and positron emission tomography (PET)/CT scan at baseline and after treatment, and with CT after 2 cycles. An optimal 2-stage Simon's design is applied whereby 6 pathologic complete responses (pT0, primary endpoint) should be observed in 24 patients before moving to full enrollment of 45 cases. Residual carcinoma in situ with no evidence of concurrent invasive tumor (T1-T4) was considered as pT0. Intention-to-treat analysis was applied. 10 mL blood samples were collected at baseline and at each cycle for exploratory circulating tumor cell (CTC) analysis adapting the AdnaTest Prostate Cancer Select kit (AdnaGen®) and testing for gene expression of EPCAM and some other selected markers (5 ml blood) and for filtration on the ScreenCell®Cyto device (2x2.5 mL blood samples).

Results: 21 pts were enrolled from 04/11 to 03/13. Thus far, 17 completed the treatment and are evaluable. Median age was 61 yrs (IQR: 54−66). 11 had T2, 9 T3, and one a T4 disease. 6 pts had hydronephrosis at presentation. 15 pts underwent radical cystectomy. Six pts (35.3%, 95% CI: 14.2–61.7) had a pT0 and 3 pts a residual pT1. G1−2 hand–foot syndrome (HFS) occurred in 4 pts, rash in 2, and diarrhoea, increase of liver transaminases, fatigue and hypertension in one patient each. Grade 3 adverse events were thrombocytopenia in 7 pts (41.2%), fatigue in 2 pts (11.7%), HFS, anemia and hypertension in one pt each (5.8%).

CTC evaluations were carried out in 11 pts. The two methods used for CTC evaluation likely recognized different CTC populations and additional data are necessary to fully evaluate the correlation with clinical outcomes for each type of CTC measure. However, in 4 pts with pT<2 evaluable by the ScreenCell method (range 7−21 cells) a stepwise reduction prior to cystectomy was observed.

Conclusions: S-CG combination is tolerable and endowed of substantial antitumor activity that justifies full study enrollment in pts with muscle-invasive bladder cancer. Preliminary results on the contribution of sorafenib were obtained and warrant further investigation on a larger sample size. Mature results on the CTC and further biomarker analyses with longer follow up will be available in September 2013.

No conflict of interest.

2752 POSTER

Phase II study of dovitinib in first line metastatic or (non resectable primary) adrenocortical carcinoma (ACC) − SOGUG study 2011−03

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Background: Dovitinib is a novel targeted therapy that inhibits the fribroblast growth factor receptor(FGFR). Preclinical studies have pointed to a major role of this pathway in adrenocortical carcinoma (ACC) thus we aimed to test its clinical efficacy in this tumor.

Methods: A phase II proof of concept trial was designed. Since this is an extremely infrequent disease sample size calculation was done taking as a basis the first stage of a two-stage Gehan model. Thus 15 patients needed to be included to show a treatment efficacy of at least 15% (probability of Type I error α = 0.05, power [1 − β] = 0.8). Main inclusion criteria was advanced non-resectable ACC, histologically confirmed, with no prior therapy other than mitotane. Primary endpoint was response rate (RR) by RECIST 1.1 assessed by an independent radiologist. Secondary endpoints included clinical benefit (RR plus stable disease), progression free (PFS) and overall survival (OS). Dovitinib was administered at 500 mg daily dose 5 days on 2 days off for 6 months. Continuation of therapy was permitted at physician criteria.

Results: From January 2012 to August 2012, 17 patients (5 male and 12 female) have been included in 7 institutions. Median age was 53 years (range 26−72); ECOG was 0−1 in 15 patients, 2 in one patient and N/A in one patient. 77 cycles, defined as one month on treatment, have been administered with dose reductions in 6 (7.8%). Grade 3−4 adverse events deemed as related to the drug were: rash (6%), asthenia (12%), diarrhea (6%), GGT elevation (18%), nausea (6%),hypertriglyceridemia (6%), hypertension (6%), hyperkalemia (6%). 13 patients withdrew treatment because of disease progression and 4 remain on dovitinib. No toxic death was reported. After a median follow-up of 5.2 months (range 2.27−9.7) no objective response has been observed. Median PFS was 1.8 months (95% CI [1.35–2.25]), median OS has not been reached and clinical benefit has been achieved in 30% of patients with long lasting stable disease (>6 months) in 23%.

Conclusions: Though no objective response was observed, a significant number of long lasting stabilizations have been achieved with an acceptable toxicity. These encouraging results and merit further study.

***Conflict of interest:** Ownership: Novartis INC. Other substantive relationships: employed by Novartis INC*

2753 POSTER

Phase II trial of bevacizumab and erlotinib in patients with advanced hereditary leiomyomatosis and renal cell cancer (HLRCC) or sporadic papillary renal cell carcinoma

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Background: There are no standard systemic options for patients with advanced papillary renal cell carcinoma (pRCC). Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) is a familial syndrome that results from germline mutations in the gene for the Krebs cycle enzyme fumarate hydratase and is associated with an aggressive variant of pRCC. Recognition of hypoxia inducible factor upregulation in HLRCC and reliance of these tumors on aerobic glycolysis suggests that therapy targeting these pathways may be beneficial in this population. Herein, we report interim results from an ongoing phase II trial of bevacizumab plus erlotinib in patients with advanced HLRCC-associated or sporadic pRCC (ClinicalTrials.gov Identifier: NCT01130519).

Materials and Methods: Subjects with advanced pRCC (Cohort 1 − HLRCC-associated; Cohort 2 − sporadic) were enrolled on an IRB-approved protocol for treatment with bevacizumab 10 mg/kg IV q2 weeks,

and erlotinib 150 mg daily until disease progression or unacceptable toxicity. Eligibility included ECOG performance status $\leqslant 2$ and no more than 2 prior VEGF-pathway antagonists. The primary endpoint was overall response rate (ORR) assessed by RECIST 1.1. Secondary endpoints included evaluation of progression-free survival (PFS) and disease control rate (DCR) at 24 weeks.
Results: To date, a total of 34 subjects have been enrolled, including 14 in cohort 1 and 20 in cohort 2. Sixteen subjects had received at least one prior systemic therapy. The majority of subjects (24/34, 70%) belonged to the MSKCC intermediate risk category. ORR was 32.4% (11/34) in the entire cohort with a DCR (PR plus SD at 24 weeks) of 64.7% (22/34); 6/14 (42.9%) with HLRCC and 5/20 (25.0%) with sporadic pRCC had a partial response, respectively. With a median follow-up of 10.7 months, median PFS was 10.5 months (95% CI, 7.4–18.6 months). Median PFS was not reached at the time of this analysis in cohort 1, and was 7.3 months in cohort 2; several durable responses were observed in both groups. Most adverse events (AEs) were grade 1−2, with the most frequent grade 3−4 AEs being hypertension (17.6%) and proteinuria (8.8%). One subject died of gastrointestinal hemorrhage, possibly related to bevacizumab.
Conclusions: The combination of bevacizumab and erlotinib demonstrates significant activity in patients with advanced pRCC, particularly in those with HLRCC, and is associated with an acceptable toxicity profile. This regimen should be evaluated further as a possible standard of care option in pRCC.
No conflict of interest.

2754 POSTER

Liver toxicity in patients with metastatic renal cell carcinoma treated with pazopanib therapy

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Background: Pazopanib is a vegf tyrosine kinase inhibitor used in the treatmnet of metastatic renal cell carcinoma. It is associated with liver toxicity, athough timing, severity management and consequences of this toxicity is not known.
Material and Methods: Sequential patients who were treated with first line pazopanib for their metastatic renal cell cancer were identified from a prospective database. Four weekly liver monitoring occurred. Specific protocols for the management of grade 1−4 toxicity were followed. Toxicity was graded based on the clinical toxicity criteria (CTC) grading classificaion, but only patients who develped clinically significant grade 2 or more toxicity had a structured treatment interruption and dose reduction according to local policy.
Results: 125 patients were identified as having received pazopanib treatment as first line therapy between 2009–2012, 44 (35%) of whom developed clinically siginificant liver toxicity (grade 2 and above) as evidence by either a raise in bilirubin and alkaline transaminase levels [maximum CTC grade 2 = 16 (21%], 3 = 23 (31%), 4 = 5 (7%), 5 = 0 (0%). Maximum toxicity occurred a median 6.0 weeks after commencing therapy ((IQR 3.6–10.2 weeks). Resolution occured in all but 5 patients (grade 1 or less after stopping treatment for a median 2.0 weeks (IQR 1.0−4.0).
68% patients restarted pazopanib treatment, with 22% having a dose reduction. Recurrence of raised liver function occured in 27% of patients [maximum CTC grade 2 = 4 (18%), 3 = 2 (9%)].
114 patients progressed after 42 days, 44 patients (39%) had no liver toxicity, 29 (44%) patients developed grade 1 liver toxicity and 41 (36%) patients developed clinically significant liver toxicity (grade 2 and above). Patients who developed grade 1 liver toxicity had an improved progression free survival ($p = 0.011$, HR 0.43 (0.23–0.82), whereas patients who developed clinically significant liver toxicity had no significant survival benefit ($p = 0.459$, HR 0.81 (0.47–1.41).
Conclusions: Patients who developed only grade 1 liver toxicity was associated with an improved progression free survival, most likely secondary to the fact that these patients did not have any treatment interruptions or dose reductions.
Conflict of interest: *Corporate-sponsored research: GSK − Prof Tom Powles, Prof Brian Rini*

2755 POSTER

Treatment sequencing following first-line sunitinib in patients (pts) with advanced renal cell carcinoma (RCC)

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Background: In a randomized phase III trial, sunitinib had superior progression-free survival over interferon-alfa (median, 11 vs. 5 mo; $P<0.001$) as first-line metastatic RCC therapy with a median overall survival (OS) of 26.4 mo (Motzer et al, 2009). In a randomized phase II study of advanced RCC pts, time to tumor progression was compared between sunitinib intermittent versus continuous daily dosing as first-line therapy (median, 9.9 vs. 7.1 mo; $P = 0.090$) and median OS was more than 23 mo in both arms (Motzer et al, 2012). Here we report a retrospective analysis of post-study treatment using pooled data from pts in both trials to determine the optimal treatment sequence following first-line sunitinib.
Material and Methods: Data were pooled from 213 treatment-naive advanced RCC pts who received sunitinib 50 mg/d on a 4-wk-on-2-wk-off schedule and any post-study treatment. Pts were divided into 4 groups based on the following post-study treatment regimens: (1) a single tyrosine kinase inhibitor (TKI; n = 129); (2) a single mammalian target of rapamycin (mTOR) inhibitor (n = 35); (3) multiple TKIs (n = 11); and (4) a combination of TKI/mTOR inhibitors (n = 38). Median OS was estimated by Kaplan–Meier method for each group with 95% confidence intervals (CIs) calculated.
Results: Baseline characteristics were similar in each group; median age ranged from 59−61 yr, 71−82% were male, and 82−97% were white. Post-study treatments used in each group were as follows: single TKI: sorafenib (57%) and sunitinib (43%); single mTOR inhibitor: sirolimus (43%), temsirolimus (37%), everolimus (20%), and SGN-75 (3%), a humanized anti-CD70 monoclonal antibody used in combination with mTOR inhibitors; multiple TKIs: sorafenib and sunitinib (both 100%); and TKI/mTOR inhibitors: sorafenib (82%), sunitinib (39%), sirolimus (58%), temsirolimus (29%), and everolimus (21%). Median OS (95% CI) in each group was as follows: single TKI: 32.2 mo (26.9–not reached); single mTOR inhibitor: 34.6 mo (22.3–39.0); multiple TKIs: 25.5 mo (20.2–45.3); and TKI/mTOR inhibitors: 32.9 mo (28.8–42.7).
Conclusions: In a subgroup analysis of sunitinib-treated pts with advanced RCC, post-study treatment with a single TKI or regimens containing mTOR inhibitors showed similar prolonged OS. Pts who received multiple TKIs appeared to have shorter OS; however, these findings require further investigation due to sample size limitations and potential differences in disease aggressiveness and/or durations of therapy.
Conflict of interest: *Ownership: X. Lin, B. Korytowsky, M.J. Lechuga and E. Matczak − stock ownership with Pfizer Inc. Advisory board: M.E. Gore − Pfizer Inc, Bayer, Roche, GSK, Novartis, AVEO, Astellas T.E. Hutson − Pfizer Inc, Bayer, GSK, Genentech, AVEO, Novartis R.A. Figlin − Pfizer Inc R. Bukowski − Pfizer Inc, Novartis, GSK R.J. Motzer − Pfizer Inc, Genentech, AVEO Oncology. Corporate-sponsored research: T.E. Hutson − Pfizer Inc, GSK, AVEO, Novartis R.J. Motzer − Pfizer Inc, Novartis, GlaxoSmithKline. Other substantive relationships: T.E. Hutson − has received honoraria from Pfizer Inc, Bayer, GSK, Genentech, AVEO, Novartis X. Lin, B. Korytowsky, M.J. Lechuga and E. Matczak − employed by Pfizer Inc R. Bukowski − has served as a speaker/consultant for Pfizer Inc, GSK, Novartis, Argos, BMS, Genentech*

2756 POSTER

Use of bisphophonates in combination with sunitinib in renal cell cancer patients with bone metastases from the Expanded Access Study

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Background: Evidence suggests that bone metastases in metastatic renal cell cancer (mRCC) patients are a negative prognostic factor for survival and a negative predictive factor on the outcome of VEGF-targeted therapy (TKI). Common practice in these patients is bone-directed therapy with bisphosphonates (BPS) that showed a potentially synergistic effect with TKIs. More osteonecrosis of the jaw (ONJ) was reported when combining TKIs and BPS.
Materials and Methods: This retrospective study investigated the clinical effects of BPS in sunitinib treated mRCC patients with bone metastases. Patients enrolled into the sunitinib expanded access protocol were divided into 3 groups: those with bone metastases without BPS (group 1, n = 1147) or with BPS (group 2, n = 446) and those without bone metastases nor BPS (group 3, n = 2817).
Results: The groups were well balanced in terms of age, sex, histology, cancer surgery, sunitinib exposure and dose reductions. Group 2 seemed to have more advanced disease and be more heavily pretreated. The median overall survival (OS) of group 1 and 2 was 14.1 months (95% CI; 12.1, 15.6) and 12.9 months (95% CI; 11.4, 15.0) respectively. In a univariate analysis the hazard ratio (HR) for OS was 1.2243 (p = 0.0025) favoring group 1 over group 2. However, when adjusted for covariates like age, histology, prior cytokines, prior angiogenic therapy and MSKCC risk in a Cox Proportional Hazards analysis the results were not statistically significant (HR 1.132, p = 0.082). Group 3 showed superior OS over group 1, namely 22 months (95% CI; 20.8, 23.5) vs 14.1 months (95% CI; 12.1, 15.6). Univariate analysis showed HR = 0.7004 (p < 0.0001). This statistically significant difference was maintained in a multivariate analysis with a HR = 0.841 (p value <0.001).
The percentage of patients with ⩾1 adverse event or ⩾1 serious adverse event was similar between group1 and group 2. ONJ was reported in 18 (4%) patients in group 2 and 2 (<1%) in group 1.
Conclusion: Our study shows that having bone metastases is a predictor for worse clinical outcome. BPS treated mRCC patients with bone metastases had inferior OS in a univariate analysis compared to patients with bone metastases without BPS. When adjusted for covariates there was no statistical difference.
Conflict of interest: *Advisory board: Pfizer. Corporate-sponsored research: Pfizer*

2757 POSTER

Adverse events among patients treated for metastatic renal cell carcinoma (mRCC): Data from a real world, multicenter registry

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Background: Data on the experience and rate of adverse events (AEs) among mRCC patients treated in routine practice (RP) are lacking. It is postulated that AEs in randomized clinical trials (RCTs) may vary considerably from those in RP. Data on these differences are critical to understanding and optimizing care delivery.
Methods: A retrospective, multicenter registry of mRCC patients treated in RP in the U.S. was developed between academic (Duke) and community (ACORN) partners. Data were collected on 466 patients between 2007–2011. 270 patients received 1st line sunitinib (SU), 53 sorafenib (SO), and 25 pazopanib (PA). AEs meeting the threshold of identification in the medical record (MR) were abstracted. Rates of AEs occurring in >10% of patients were contrasted with all grades of AEs reported on the package insert (PI), focusing on SU in 1st line therapy because of the large number of patients who received it.
Results: The AEs identified in the MR are reported in the Table. For some AEs the event rates were consistent between the MR and all grade AEs on the SU PI including fatigue (56% in MR vs 62% in PI), vomiting (42% vs 39%), and hand foot syndrome (24% vs 29%), while others varied widely such as diarrhea (37% vs 66%), mucositis (26% vs 47%), and hypertension (18% vs 34%). Variations were also noted between alternative first line agents and respective PIs.
Conclusions: These data shine light on the patient experience in RP. There are multiple potential explanations for the variations seen between RP and the PI including inconsistent clinician reporting of AEs, differences in dosing and real world management of AEs, and variations in patient populations between RP and RCTs. As these data reveal, we must first understand patterns of AEs in RP and their real-world clinical management, in order to provide guidance and optimize care. Prospective capture of AEs in RP is a critical first step.
Conflict of interest: *Corporate-sponsored research: Pfizer, Novartis, Bristol-Myers Squibb, Exelixis, Prometheus, Bayer, Genentech/Roche, AVEO, Astellas, Alexion, Amgen, Biovex, DARA. Other substantive relationships: Pfizer (employees)*

Table: Rates of AEs (%) abstracted from the MR for 1st-line therapies.

	SU (N = 270)	SO (N = 53)	PA (N = 25)
Fatigue	56	55	64
Vomiting	42	34	60
Diarrhea	37	38	48
Aesthenia	32	17	60
Mucositis	26	15	4
Hand–foot syndrome	24	38	12
Gastroesophageal reflux	21	8	48
Hypertension	18	21	32
Rash	12	21	0
Dysgeusia	9	0	24
Decreased appetite	5	4	16
Constipation	4	0	24

2758 POSTER

Adverse events (AEs) by age: data from a real world, multicenter registry of patients treated for metastatic renal cell carcinoma (mRCC)

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Background: There is no data on the experience of elderly patients (⩾65 yrs) treated with targeted therapies for mRCC in routine practice (RP) across multiple treatment lines. Patients in randomized clinical trials (RCTs) are younger than patients who do not go on RCTs and may experience different rates of AEs. Do AEs vary by age in RP?
Material and Methods: A retrospective, multicenter registry of mRCC patients treated in RP was developed between academic (Duke) and community (ACORN) partners. Treatment data was collected on 462 patients who received systemic therapy for mRCC from 2007–2011. AEs across 3 lines of therapy deemed clinically significant were abstracted from the medical record and broken down by age (<65 or ⩾65 yrs), organ system class, and AE term. P values were calculated using the Fisher Exact test.
Results: There was no difference (P = 0.39) in the fraction of patients with ⩾1 AE between those <65 (n = 242, 90.6%) and ⩾65 yrs (n = 182, 93.3%). However, there were significant differences between age groups for some organ systems, with the <65 group having higher AE rates in these systems (Table). AE numbers were small.

Table: Significantly different AEs by age group

Organ system (n)	Lines 1, 2, and 3		
	Age <65 (%)	Age ⩾65 (%)	P value
Skin (207)	50	38	P = 0.004
Nervous system (64)	17	10	P = 0.035
Respiratory (52)	37	15	P = 0.009
Musculoskeletal (43)	9	4	P = 0.002
Endocrine (16)	5	2	P = 0.045
Hepatobiliary (9)	3	0.5	P = 0.029

Conclusions: These data provide reassurance that elderly patients do not experience more AEs in RP. Although overall frequency of AEs was not significantly different by age group (<65 or ⩾65), the <65 group had

increased rates of AEs in several organ systems. Since toxicity may be a surrogate for dose intensity, we hypothesize that elderly patients may be subject to lower dose intensity; the <65 group may also have been preferentially selected as 'healthier' individuals, thereby better tolerating therapy. Limitations include the retrospective approach and physician reporting of AEs. A strength is the real world population (vs RCTs). Prospectively captured patient reported outcomes in addition to physician-assessed AEs are needed improve understanding of the patient experience in RP.

Conflict of interest: *Ownership: Pfizer. Advisory board: Pfizer, Novartis, Aveo, Astellas, Bayer, Genentech/Roche. Board of directors: Advoset, Orange Leaf Associates, LLC. Corporate-sponsored research: Pfizer, Bristol-Myers Squibb, Helsinn, Amgen, Kanglaite, Alexion, Biovex, DARA, MiCo, Novartis, Genentech/Roche. Other substantive relationships: Prometheus, Exelixis*

2759 POSTER

Impact of antiangiogenic treatment on cognitive functions and fatigue in metastatic renal cancer patients

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Purpose: Antiangiogenic treatments (AT) are currently standard in metastatic renal cancer (mRCC). Although these therapies improve outcome, they can induce some important, but commonly underreported adverse effects such as fatigue, concentration and attention disorders. Our goal was to assess the incidence of cognitive impairments and severe fatigue induced by AT and their evolution over time.

Methods: mRCC patients starting AT were eligible. Episodic, working memory, executive functions, information processing speed, cognitive complaint, anxiety, depression and fatigue were assessed with neuropsychological tests and self-reported questionnaires before AT(T0), 3 and 6 months later (T3, T6). Cognitive impairment was defined as a score <1.5 standard deviation (SD) of normative data on $\geqslant$2 tests, or <2 SDs on $\geqslant$1 test. Severe fatigue was defined if at least one score was $\geqslant$40 at the MFI20. Levels of hormones dosage, albuminemia, hemoglobinemia, CRP and cytokines were correlated with cognitive impairment and fatigue.

Results: Results concern 75 patients (63$\pm$10 years): males/females were 49/26 and 80% of the patients had good and intermediate prognostic. Brain imaging was normal in all the patients. A majority of patients received sunitinib (41 patients, 75%), and most of them were enrolled during first line treatment (55 patients,73%). At baseline, 38 (51%) patients had cognitive disorders (episodic memory and executive functions mainly impaired), independent from the line of treatment. Severe fatigue was expressed in 45 patients (67%). Only 3 and 1 patients experienced anxiety and depression, respectively.

Among the 58 patients with evaluations at T0 and T3 or T6, 18 (31%) had $\geqslant$1 domain of cognitive functions that became pathological over AT (mainly executive functions and episodic memory). Among these 18 patients, 13 (72%) had no initial cognitive disorder. Severe fatigue appeared in 41% of patients and an increase of fatigue was observed in 50% of patients with initial severe fatigue. Cognitive complaint was not related to objective cognitive performances but was associated to fatigue. Correlations with biologic parameters will be presented at the meeting.

Conclusions: Our study is the first to prospectively describe the incidence of both cognitive impairments and fatigue and their deterioration over AT. More than half of mRCC patients report cognitive impairments and severe fatigue before AT. In addition, AT induces cognitive decline and severe fatigue.

No conflict of interest.

2760 POSTER

Metastatic chromophobe renal cell carcinoma: Outcome with targeted agents

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Introduction: Chromophobe renal cell carcinomas (ChRCC) represent less than 5% of all RCC, and are commonly excluded from large clinical trials. Localized ChRCC have been communly reported to be associated with better outcome and a lower risk of metastases compared to clear cell RCC. However, little is known about the outcome of metastatic ChRCC in the era of targeted therapies.

Patients and Methods: A retrospective analysis performed amongst the French Kidney Group and the GETUG group was conducted to establish a clinical database of metastatic ChRCC. Data recorded included date of diagnosis, age at diagnosis, sex, date of first metastases, number and location of metastatic sites, prognostic factors, systemic and focal treatments performed and associated response.

Results: We report the preliminary results of 23 patients treated between 2005 and 2013 centers. Median age at diagnosis was 55. 3 years (24−78), with a majority of men (60%). Most of patients had nephrectomy (83%) and only 8/23 (35%) had synchronous disease; in overall population median time from diagnosis to metastasis was 25.6 months (range 0–122). Number of metastatic sites in the metastatic setting was >1 in 74 % of the patients, abdominal lymph nodes being the most common site of metastasis (70%), while lung (39%) and (35%) liver metastases, appeared to be less common than in ccRCC. Overall survival (OS) for the entire population from metastatic disease was 28.8 months. Median follow up for entire population was 3.7 years [0.3–12.4]. Nine patients received VEGFR TKI as first line (7 sunitinib, 2 sorafenib) with a medain PFS of 9.2 months; 6 patients received mTOR inhibitors (5 temsirolimus, 1 everolimus) with a median PFS of 8.1 months. Four patients received different therapy (roferon, vinfluinine, IFbevacizumab and bevacizumab alone). Eleven patients received second line (5 TKI, 3 mTOR inhibitors, 3 another therapy), and three received a third line. Interestingly, first line systemic therapy could be delayed more than 6 months in 7/19 pts (37%) thanks to focal treatment such as metastasectomy.

Conclusion: Metastatic ChRCCs is a rare situation and prognosis as well as specific therapeutic results in the era of targeted therapies remain scarce. We report the largest cohort of mChRCC to date and investigate PFS and OS with VEGFR-TKI and mTOR inhibitors treatments.

Conflict of interest: *Ownership: 0. Advisory board: Escudier: bayer, Pfizer, Novartis. Albiges: Novartis, Pfizer. Bigot: novartis. Bathelemy: Roche, Novartis, Jannssen. Board of directors: 0. Corporate-sponsored research: Bigot: Astellas. Albiges: Novartis. Other substantive relationships: Honoraria- Escudier: Bayer, Roche, Pfizer, Genentech, Novartis, Aveo, GSK. Honoraria − Albiges: Novartis, Pfizer, Amgen*

2761 POSTER

What is the best treatment option for second-line in long-responders to the first line TKI in metastatic renal cell carcinoma (mRCC) patients (pts): TKI-TKI or TKI-mTORi? Final results of a European retrospective study

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Background: Benefit of a TKI rechallenge versus switch to an mTOR inhibitor (mTORi) in mRCC pts who responded to a previous line of TKI is still debated. We report final results of a multicenter retrospective study.

Methods: This study retrospectively investigated Progression Free Survival and Time to Treatment Failure (PFS/TTF) in mRCC pts treated with sequence TKI-TKI or TKI-mTORi. Eligibility criteria: TKI in 1st line (L1)

followed by TKI or mTORi in 2nd line (L2), ongoing L2>6m. Prior L1 immunotherapy was allowed but no L1-L2 intermediate line (any drug). Pts characteristics and MSKCC/Heng risk group (RG) were collected at L1 L2 initiation. Long Response was defined as PFS/TTF>6m with objective response upon RECIST (OR) =SD/PR/CR. L2 PFS/TTF was analyzed with time to event and categorical analysis of L1 PFS/TTF at 6−12, 12−18, 18−24, 24−36, >36m. Cox model covariates: center, age, RG, Fuhrman, number of metastatic sites, presence of bone mets, L1 PFS/TTF, prior L1 and L2 ECOG, L1 best OR, interaction L2 therapy X prior L2 RG. Model was subject to sensitivity analysis (SA) with C-index (Ci) at cut-off 6, 12, 18, 24 and 36m. Analysis was performed both with case deletion and multiple imputations to deal with RG related missing data. Corrections for multiple testing were applied.
Results: Data for 313 pts from 10 European centers were collected and 242 were eligible. L2 therapy: 118 pts received a TKI and 123 a mTORi. Prior L2 Favorable + Intermediate RG (MSKCC): TKI=70%, mTORi=54%. Median L2 PFS (m, 95% CI): TKI=7.4 (5.5−9.5), mTORi=5.3 (3.8−6.5). Benefit of a 2nd TKI vs mTORi increased with L1 TKI PFS/TTF (p = 0.02, Mann-Whitney), largest difference being observed for L1=12−18m interval. Despite prior L2 unbalanced RG, interaction RG x L2 therapy was not significant. Among all covariates, only L2 therapy and prior L2 ECOG were predictive factors for PFS/TTF: HR (TKI/mTORi)=0.64 (0.45–0.90) and 0.62 (0.45–0.85) for PFS and TTF, respectively; stratified HR across 6−12, 12−18, 18−24, 24−36, >36 =0.55 (0.38–0.81) and 0.55 (0.39–0.77) for PFS and TTF. SA(TTF): HR L2 therapy(Ci): 12m=0.65(0.67), 18m=0.54(0.69), >18m=NS.
Conclusions: These results suggest a benefit of TKI rechallenge in patients with long response to a 1st line TKI.
No conflict of interest.

2762 POSTER

DILIGENCE-1: Dovitinib in 1st-line renal cell carcinoma, an investigation into tumour gene status and correlation with efficacy − 1st exploratory study

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Background: Dovitinib is a multi-targeted tyrosine kinase inhibitor which, in addition to VEGFR blockade, also has affinity to FGFR-1,-2,-3 and PDGFRβ. We sought to evaluate the activity of dovitinib as first-line therapy in patients with metastatic clear-cell renal cell carcinoma (mCCRCC) and correlate this activity with the status of genes relevant to its mechanism-of-action.
Material and Methods: 30 treatment-naive patients with mCCRCC have enrolled in this single-arm, single-site, phase II study (DILIGENCE-1, ACTRN12612000140853, sponsor Auckland City Hospital). Dovitinib was administered at 500 mg 5 days on/2 days off until progression. An optional post-treatment biopsy is also being offered to patients. The primary endpoint is PFS using RECIST 1.1. Secondary endpoints include response rate (RR) and efficacy by FGFR gene status (FISH and DNA sequence using Sequenom ® OncoCarta™ panel) by Spearman's rho correlation coefficient.
Results: The 1st patient was enrolled in March 2012 and the 30th in February 2013. Median patient age was 64 years and 72% were male. ECOG PS was 0 in 45% and 1 in 55%. Heng prognostic group was in favourable-risk in 38%, intermediate-risk in 52% and poor-risk in 10%. 38% of subjects had bone metastases (an adverse prognostic feature). Four patients discontinued treatment because of toxicity and one further patient was withdrawn (investigator decision), therefore target accrual was increased to 31 patients and is expected to be complete by May 2013. 93%, 59% and 51% of study patients have tumour tissue available for analysis from primary, metastatic and both sites respectively. As of April 2013, 15 primary and 12 metastatic pre-treatment samples have been assessed for FGFR gene status by FISH. Samples from16% of patients showed FGFR-1 or −3 amplification (when defined as a target:control >2.0 and FGFR copy number >6) and 21% showed loss of FGFR-1. Discordance in FGFR-1 status between primary and metastatic samples was seen in 3 patients (of 7 matched pairs). Polysomy for FGFR was also frequently seen, especially for FGFR-3.
Conclusions: 30 patients with mCCRCC have been treated 1st-line with dovitinib. Abnormal FGFR-1 and −3 gene status has been seen in a reasonable proportion of tumour samples and analysis continues. RR and correlational data with gene status including PDGF/PDGFRβ will be presented.
Conflict of interest: *Ownership: Oei P owns shares in IGENZ LtdBroom R owns shares in IGENZ Ltd. Advisory board: Broom R has done a previous Advisory Board for Novartis Oncology in 2012. Board of directors: Oei P is a director of IGENZ Ltd*

2763 POSTER

Clinical practice outcomes of patients treated with pazopanib for metastatic renal cell cancer (mRCC) − 6 year experience at a referral centre in Manchester, UK

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Background: Pazopanib is the most recently licensed first-line therapy for patients with mRCC. While there is good evidence of the efficacy and safety of Pazopanib within clinical trials, there is little evidence of treatment outcomes among the wider population. Here we characterize and present the outcomes of Pazopanib treated patients in routine clinical practice.
Methods: We identified 104 patients who commenced treatment with Pazopanib within the licensed indications from July 2006 to October 2012 with follow up to January 2013. The demographic data was extracted from the Christie kidney cancer database and clinical information was obtained from the patient's records. No patient was lost to follow-up. We explored the clinical features of the patients who receive this treatment. Median OS and PFS were estimated using the Kaplan–Meier method.
Results: 23% of patients were 75 years or older (range 42−87 median 66), 60% male and 29% performance status of 2 or more. A high proportion of patients had metastatic sites carrying an adverse prognosis at start of treatment (7% brain, 22% liver, and 25% bone metastases; half of these were spinal) and significant co-morbidities were frequent (13% mild, 22% moderate, 27% severe according to the ACE 27 Comorbidity Index), 69% had a Nephrectomy. All patients experienced side effects from treatment but 16 patients (15%) discontinued Pazopanib as a result of treatment toxicity. There was no statistical difference in the discontinuation rate due to toxicity in the different prognostic groups.
Table 1 shows the efficacy outcomes by MSKCC and Heng prognostic factors.

Table 1.

	%	PFS (mo)	OS (mo)
All Patients		13	19
MSKCC (ver 2)			
Favorable	19	NR*	25
Intermediate	63	12	17
Poor	18	6	6
Heng			
Favorable	17	NR	NR
Intermediate	51	12	25
Poor	32	6	7

*NR, Not Reached.

Conclusions: The population treated reflects the nature of patients with mRCC (often frail, elderly and with comorbidities) but these poorer prognosis groups tend to be under-represented in clinical trials. The patients that we see in clinical practice are challenging not only due to disease burden but due to existing severe pre-existing ilnesses, altough this is a familiar problem to the clinicians it is not often explored in the literature, often these patients are ofered Pazopanib as first line treatment due to the toxicity profile reported in large trials.
It was therefore encouraging that OS and PFS for the favorable/intermediate prognostic groups were similar to that reported in trials. Whilst the PFS in patients with poor prognosis is short, a proportion of patients appeared to benefit from Pazopanib; it was encouraging to see that treatment was generally well tolerated with rate of discontinuation due to toxicity not being different from the trial population.
No conflict of interest.

2764 POSTER

Pre-treatment neutrophil to lymphocyte ratio as an independent prognostic factor in patients with advanced urothelial cancer

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Background: Increased pre-treatment neutrophil to lymphocyte ratio (NLR), an index of systemic inflammation, is associated with poor outcome

for various types of cancers. We aimed to assess the association between pre-treatment NLR and progression free survival (PFS) and overall survival (OS) of patients with advanced urothelial cancer (UC) treated with first-line chemotherapy.
Materials and Methods: We retrospectively reviewed the records of 149 patients with advanced UC treated with first-line chemotherapy between January 2003 and December 2012 in our two Institutions. The NLR cut-off value was defined as ⩽3 (group 1) vs >3 (group 2). PFS and OS were estimated using Kaplan–Meier method. After univariate analysis a multivariate analysis was carried out by Cox regression model and included the following variables: Eastern Cooperative Oncology Group (ECOG) performance status (⩾2 vs 0−1), visceral disease (present vs absent), hemoglobin (<12 g/dL vs. ⩾12 g/dL), and NLR (>3 vs ⩽3).
Results: The median age was 68.8 years (range, 46.9–86.6) and 124 (83.2%) were male. The primary site was bladder in 123 cases (82.6%), renal pelvis in 20 (13.4%) and ureter in 6 (4%). First-line chemotherapy consisted of a platinum-based regimen in 105 cases (69.8%). The median PFS was 4.8 months (95% confidence interval (CI) 3.8−5.3) and the median OS was 9.7 months (95% CI 8.6–11.1). The median PFS was 3.8 months (95% CI 3.2−4.8) in the group 1 and 6.2 months (95% CI 4.5−8.1) in the group 2 ($p = 0.0002$). The median OS was 7.9 months (95% CI 5.7−9.1) in the group 1 and 15.9 months (95% CI 11.2–19.2) in the group 2 ($p < 0.0001$). In multivariate analysis, ECOG performance status, hemoglobin and NLR were predictors of PFS (hazard ratio (HR) = 1.78 (1.18–2.69) $p = 0.006$, HR = 1.48 (1.04–2.10) $p = 0.027$ and HR = 1.85 (1.28–2.68) $p = 0.001$, respectively) and OS (1.79 (HR = 1.16–2.76) $p = 0.008$, HR = 1.56 (1.07–2.28), $p = 0.022$, and HR = 2.70 (1.79–4.07) $p < 0.0001$, respectively).
Conclusions: Increased pre-treatment NLR is an independent prognostic factor for patients with advanced UC treated with first-line chemotherapy.
No conflict of interest.

2765 POSTER

Prognostic factors of patients treaded by vinflunine for an advanced or metastatic urothelial carcinoma: Results of the CURVE study

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Background: Vinflunine (VFL) is a chemotherapy (CT) registered as second line treatment of advanced or metastatic urothelial carcinoma (UC) after failure of a platinum-based CT. Based on the phase 3 data, performance status (PS), haemoglobin level and liver metastasis had been identified as predictors for overall survival (OS). The CURVE study included a search for prognostic factors.
Material and Methods: The CURVE study is a retrospective data collection involving 20 French centres where at least 4 patients (pts) had been treated during the year 2011.
Several potential pre-treatment prognostic factors for OS were investigated in univariate and multivariate analyses: PS (⩽1 or >1), hepatic function (normal or abnormal), previous history of pelvic radiotherapy (yes or no), haemoglobin level (⩽10 or >10 g/dl), creatinine clearance (⩽60 or >60 ml/min), previous lines of CT (⩽1 or >1), metastases at diagnosis (yes or no), visceral metastases (yes or no), liver metastases (yes or no), lung metastase (yes or no), previous treatment by cisplatin (yes or no), previous treatment by versus carboplatin (yes or no), progression free interval before VFL (<3 or ⩾3 months), previous surgery (bladder or kidney/ureter), relative dose intensity (⩽90 or >90 %), initial dose of VFL (<280 or ⩾280 mg/m^2), further lines of CT (post VFL) (0 or ⩾1), neutropenia (yes or no), asthenia/fatigue (yes or no),nausea (yes or no), constipation (yes or no) and PS at the end of VFL (⩽1 or >1).
Results: From November 2012 to February 2013, 134 pts were included. The median OS was 8.2 months [6.5; 9.4]. The study population and the main results are presented in a separate abstract.
The main identified prognostic factors were PS, haemoglobin level and hepatic function. In addition, four subgroups were formed based on the presence of zero, one, two, or three prognostic factors; the median OS times for these groups were 11.0, 5.7, 2.7, and 1.1 months (P<.001), respectively.
Conclusion: The CURVE study reflects the current second line management of UC in France, pts exhibiting worse conditions (age, PS) than in daily practice.
The current analysis of prognostic factors for OS is consistent with the data published from the phase 3 study. PS, haemoglobin and hepatic function appear to be the prominent parameters to take into account for the identification of patients having a potential higher benefit from VFL.
Conflict of interest: *Advisory board: Pierre-Fabre Research Institute*

2766 POSTER

Biological processes after discontinuation of VEGFR TKI in metastatic renal cell cancer (mRCC)

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Background: In mRCC there is no definite proof of the optimal treatment in case of PD during treatment with a VEGFR TKI. After discontinuation of a VEGFR TKI an accelerated growth is described in some patients and reintroduction of (the same) VEGFR TKI is sometimes effective. This study was performed to gain more insight into the biological mechanisms of this phenomenon.
Methods: mRCC pts on treatment with sorafenib or sunitinib with PD, were randomized to either directly stop the VEGFR TKI or to continue for two weeks. At baseline (*i.e.* at the moment of PD) and after two weeks VEGF plasma levels, CRP, D-dimer and regulatory T cells were measured and FDG-PET/CT and functional-MRI were performed. Differences between both groups were assessed by using the Mann-Whitney test. The association between parameter changes were tested using Spearman's correlation test.
Results: 16 mRCC pts (13M, 3F) were included and randomly assigned to direct stop (n = 9, 6 sunitinib, 3 sorafenib) or continue treatment (n = 7, 4 sunitinib, 3 sorafenib). Median age was 61.5 (range 48−79 yrs). Before PD occurred pts were treated for a median of 86 weeks (range 10–219). Overall the median change in tumor size according to RECIST in two weeks was +6% (range −5 to +19%). No significant difference in tumor size change was found between pts who stopped and pts who continued treatment (7 vs 1%, $p = 0.35$).
A median rise in K^{trans} of 1.6s^{-1} (range −0.9 to +4.2s^{-1}) was observed in pts who stopped versus a decrease of 1.1s^{-1} (range −34.6 to +0.6s^{-1}) in pts who continued ($p = 0.03$). A negative correlation between the change in VEGF and change in K^{trans} ($r = -0.70$, $p = 0.036$) and K_{ep} ($r = -0.72$, $p = 0.030$) was observed. In pts who stopped therapy the median decrease in LDH was 18.6% versus an increase of 11.7% in patients who continued ($p = 0.008$). Hemoglobin levels decreased in both groups, but more in the group who stopped treatment (−10.3 vs −1.1% $p = 0.005$). Results of PET, CRP, D-dimer and Tregs were not significantly different between both groups.
Conclusion: Within two weeks after VEGFR TKI discontinuation because of PD, a rise in K^{trans} accompanied by a decrease in LDH and a negative correlation with VEGF was observed.
This indicates a higher perfusion or permeability, denoting an increase in tumor vascularization. Although all pts had PD, only the pts who stopped showed increased perfusion and permeability, implying that at the moment of PD the effect of the VEGFR TKI is not completely exhausted.
No conflict of interest.

2767 POSTER

Efficacy and safety of first-line sunitinib in patients with late recurrence (>5 years) of clear cell renal cell carcinoma: Results from LateR study

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Background: The effect of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) in patients (pts) with late recurrence of clear cell renal cell carcinoma (ccRCC) is not well-known. Aim of this retrospective study was to investigate the efficacy and safety of first-line sunitinib in late-relapsing metastatic ccRCC pts.
Material and Methods: Data were collected from 11 Italian centers involved in the treatment of mRCC. MSKCC prognostic categories were assessed before starting first-line treatment with sunitinib. Overall survival

(OS) and progression free-survival (PFS) were estimated with the Kaplan-Meyer method with 95% CI and curves were compared with log-rank test.
Results: A total of 2021 pts were screened and 151 pts (7%) were included in this retrospective analysis. The median age was 64 years (range 43−87) and 119 (78%) of pts were male. Median time to recurrence was 7.6 years (range 5.3–23.4). Motzer prognostic categories were good in 59%, intermediate in 36% and poor in 5% of these pts. Median OS of these groups were 52.9, 40.6 and 16.9 months, respectively. Median PFS was 37.3, 16.4 and 3.6 months in the three groups. In the good risk group, pts relapsed >7.6 vs <7.6 yrs had a PFS of 40.2 and 15.3 months, respectively ($p = 0.009$). No differences were observed in terms of OS or in the other prognostic groups. Fifty-five percent of pts had a partial response, 36% stable disease and 9% progressive disease. The most commonly reported grade 3 adverse events were hand–foot syndrome (9%), hypothyroidism (8%), hypertension (7%), fatigue (6%), neutropenia (6%), thrombocytopenia (4%) and diarrhea (4%). Eighty-five pts (56%) underwent a second-line treatment with a VEGFR-TKI (46%) or a mTOR inhibitor (54%). Sunitinib-related PFS was significantly associated with the OS of these patients (p <0.001).
Conclusion: Patients with late relapsing ccRCC treated with first-line sunitinib showed consistently longer PFS and OS than reported in previous studies with sunitinib. Our data should be considered before enrolling these patients in randomized clinical trials.
No conflict of interest.

2768 POSTER

Vinflunine maintenance therapy vs best supportive care after platinum combination in advanced bladder cancer: A phase II, randomized, open label, study (MAJA study), SOGUG 2011−02

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Background: Vinflunine (VFL) is a novel microtubule inhibitor currently approved by EMA as treatment after platinum progression, in metastatic bladder cancer. It is distinguished from the other vinca-alkaloids because it binds relatively weakly to tubulin, suggesting an improved tolerance profile as a result of less neuropathy. Based on the fact that no cumulative toxicity is expected and the results reported in second-line, we aim to test the role of vinflunine in first-line therapy, as maintenance treatment for patients who obtain clinical benefit after platinum.
Material and Methods: Multicenter, randomized, open label, proof-of-concept study that is being performed in 21 institutions members of the Spanish Oncology Genitourinary Group (SOGUG). Subjects are randomized to receive VFL 320 mg/m^2 (280 mg/m^2 for patients with PS=1, age $\geqslant$75 years, prior pelvic radiotherapy or creatinine clearance Cr <60 ml/min) every 21 days plus best supportive care (BSC) vs BSC alone until disease progression. Main inclusion criteria: Subjects $\geqslant$18 and<80 years of age with histological diagnosis of transitional cell carcinoma of the urothelial tract and measurable disease whith radiological response or stabilization after 4 to 6 cy of a cisplatin-containing doublet for metastatic/advanced disease (carboplatin allowed on cy 5−6). Primary objective: progression free survival (PFS). A sample size of 86 patients allocated in a 1:1 ratio is planned. Recruitment started on April 2012. A pharmacogenomic translational study will be conducted.
Results: To March 2013, 29 pts have been enrolled, 14 in the VFL+BSC group (VFL dose 320 mg/m^2, 36%; 280 mg/m^2, 64%), 15 in the BSC group. Median age 65 years (range 47−78, 41.4% under 65); PS 0/1, 48.3%/51.7%; CrCl <60 ml/min 20.7%; liver metastasis 20.7%; prior pelvic RT 6.9%. Median time from the initial diagnosis to study entry was 8.2 months. Primary tumour location: bladder 85.7%, upper urinary tract 9.5%, urethra 4.8%. Pure transitional cells 90.5%. Metastatic/locoregional disease, 76.2%/23.8%. We analyzed 32 cy in the chemotherapy arm. Hematological toxicities (% cy): Anemia g2, 16.7%; leucopenia g2, 6.7%, neutropenia g3−4, 10%. Non-hematological toxicities (% cy): alopecia, 15.6%, constipation g3−4, 12.5%, fatigue g3, 6.2%.
Conclusions: These preliminary data show a good safety profile with low myelosupression for vinflunine as maintenance therapy for patients with advanced TCCU who obtained clinical benefit after platinum. Recruitment is ongoing, interim analysis will be presented.
No conflict of interest.

2769 POSTER

Long-term progression-free-survival (PFS) under sunitinib (SU) treatment for metastatic renal cell carcinoma (Sulong study): Analysis of two populations − long term responders (LR) vs. primary refractory (PR) patients

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Background: It would be useful for the management of patients (pts) with renal cancer to identify factors at the time of diagnosis that would enable us to identify prognostic groups and select the optimal therapeutic approach of the disease. We look at clinical and tumor characteristics in two extremely different groups: those with the highest benefit and those who show drug resistance.
Methods: Retrospective, observational and multicenter study of pts treated with SU under clinical practice. Two groups were included: pts with metastatic renal carcinoma (mRCC) who achieved PFS $\geqslant$22 months, and pts who showed progressive disease at first radiological evaluation. The objectives were to compare the clinical and molecular characteristics at tumor level (activation status of cancer stem cell signaling pathways) in LR vs. PR pts. This study was approved by the Spanish Medicines Agency and Ethic Committees of each hospital.
Results: A total of 82 pts in 12 centers were included, 70 were LR and 12 were identified as PR. Clinical factors that showed statistical significance between LR vs. PR are shown in Table 1.
In the LR cohort, median PFS was 45 months. Median time to best response was 10.2 months for complete response (CR) and 4.42 months for partial response (PR). CR and PR rates were 21% and 59% respectively. Median duration of response was 27 months. No differences in PFS between pts who received prior cytokines and those who did not. Significantly longer PFS was seen in LR who developed hypertension (36 vs.52, $p < 0.05$) and hypothyroidism (50 vs. 61, $p < 0.05$). 38 pts discontinued treatment: 8% due to toxicity, 41% progression and 3 pts for other reasons. Molecular assessment is still ongoing and will be presented.

Table 1 (abstract 2769).

Clinical factors	LR (70 patients)	PR (12 patients)	p-value
Metastasis at the time of 1st diagnosis, pts (%)	23	58.3	0.05
Age of diagnosis, median (years)	57	63	<0.05
Time from primary to metastatic diagnosis, median, months	38.17	2.07	<0.01
LDH value, median (U/L)	254	355	<0.01
Hemoglobin value, median (g/dL)	13.90	12.55	<0.05
Time from primary diagnosis to treatment, median, months	39	3.8	<0.01
Initial dose of Sunitinib, mg/day (% pts)	37.5 (3%) 50.0 (97%)	37.5 (17%) 50.0 (83%)	<0.01
Dose reductions, pts (%)	83.6	45.5	<0.01

Conclusions: Sunitinib achieves long-term response in a subset of pts with mRCC. MSKCC risk criteria, hypertension and hypothyroidism were confirmed as prognostic factors. Treatment initiation with 50 mg/day of SU and better drug management may improve clinical outcomes.
No conflict of interest.

2770 POSTER

Treatment outcome and relevance of palliative chemotherapy in urachal cancer

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Objective: Urachal cancer is rare malignancy accounting for less than 1% of bladder cancer and is no consensus in diagnosis and management of urachal cancer. Especially in unresectable, recurrent urachal cancer, there were few reports on the use of palliative chemotherapy. We delineate clinical feature and treatment outcome of resectable urachal cancer and relevance of palliative chemotherapy in recurrent, metastatic urachal cancer.
Methods: Between January 1996 to December 2010, 29 patients were diagnosis of urachal cancer. We collected clinicopathologic variables and treatment outcome were retrospectively.
Results: Among 29 patients, 25 patients were localized disease, 3 patients were metastatic disease at initial diagnosis. Among patients of localized disease, 21 patients got curative PC(partial cystectomy) or RC(radical cystectomy), 4 patients got curative tumor excision, 1 patients were followed up loss. The median overall survival in resectable disease and in unresectable disease were 110.0 months and 7.8 months (p value=0.001). Lung was the most common metastatic site in 5 (17.2%) patients followed by liver, bone, peritoneal seeding. Among patients of localized disease, 13 patients were no recurrence, 2 patients were follow up loss, 10 patients recurred disease. 9 patients who recurred disease after curative operation and 1 patient who presented metastatic disease at initial were received palliative chemotherapy. Fluropyrimidine(5-FU) based regimens, taxane based regimen and gemcitabine based regimen were most commonly used. The response of chemotherapy was poor (16.6%), but fluropyrimidine(5-FU) based regimens had most favorable response activity. One patients who had mucious mixed with small cell component adenocarcinoma showed partial response both etoposide based regimen and taxane based regimen.
Conclusions: In urachal cancer, curative operation is significantly associated with better overall survival. Fluropyrimidine based regimen could be considered as chemotherapy for metastatic, recurrent disease.
No conflict of interest.

2771 POSTER

Targeted therapies (TTs) in metastatic renal cell carcinoma (MRCC): Role of metastatic site as a prognostic and predictive factor

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Background: The prognostic/predictive role of metastatic sites in mRCC patients (pts) treated with TTs is not clearly understood. Aim of this study was to investigate whether metastatic sites were statistically associated to progression-free survival (PFS) and overall survival (OS).
Patients and Methods: We retrospectively collected data of consecutive mRCC pts treated with TTs at Istituto Nazionale Tumori of Milan. All pts received at least one targeted agent including: sunitinib, sorafenib, bevacizumab plus interferon-alfa, pazopanib, everolimus, temsirolimus or axitinib. Multivariate Cox regression models were used to estimate hazard ratios (HRs) and to test the association between predictors and PFS and OS. In the first model metastatic sites categorized into liver, lung, brain, bone, lymphnode and other site were contemporary introduced as binary predictors; in the second model the previous predictors and the Motzer score were evaluated. Statistical significance was reached when p value was less than 5%. Survival was estimated through the Kaplan–Meier method.
Results: From January 2004 to October 2012 a total of 366 mRCC pts were treated with TTs at our centre and a total of 358 (97.8%) pts were evaluated. After a median follow-up of 56.1 months (range: 1.0–93.2 months) median PFS was 11 months (95% CI: 8.1–12.0) and median OS was 24.2 months (95% CI: 20–27.8). Metastatic sites were associated to the PFS as follows: lymphnodes (HR: 1.43; 95% CI: 1.12–1.83, p = 0.004); liver (HR: 1.41; 95% CI: 1.05–1.90, p = 0.021); bone (HR: 1.26; 95% CI: 0.96–1.65, p = 0.091); brain (HR: 0.81; 95% CI: 0.46–1.43, p = 0.474); other sites (HR: 1.07; 95% CI: 0.83–1.38, p = 0.589). Number (n) of metastatic site were statistically associated to the PFS (HR: 1.16; 95% CI: 1.04–1.29, p = 0.008). Metastatic sites were associated to the OS as follows: lymphnodes (HR: 1.73; 95% CI: 1.31–2.29, p < 0.001); liver (HR: 1.71; 95% CI: 1.23–2.37, p = 0.002); bone (HR: 1.48; 95% CI: 1.10–1.98, p = 0.009); brain (HR: 1.21; 95% CI: 0.64–2.28, p = 0.568); other sites (HR: 1.09; 95% CI: 0.81–1.47, p = 0.568). Number of metastatic sites were statistically associated to the OS (HR: 1.27; 95% CI: 1.13–1.44, p=<0.001).
Conclusions: mRCC pts with liver, lymphnodes and bone metastases treated with TTs had poorer outcome than pts with metastases to other sites. Liver, lymphnodes and bone metastases may be considered independent negative prognostic factors.
Conflict of interest: *Advisory board: Giuseppe Procopio for: Astellas, Bayer, Glaxo Smith-Kline. Other substantive relationships: Giuseppe Procopio, Consultant honoraria for: Pfizer, Novartis*

2772 POSTER

Sunitinib expanded-access trial in metastatic renal cell carcinoma (mRCC) − final results from Spain

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Background: Between 2005 and 2007, more than 4,500 patients (pts) were enrolled in a global mRCC expanded-access trial (NCT00130897; Pfizer) in which sunitinib was given to pts ineligible for other sunitinib trials. Sunitinib was shown to have a manageable safety profile and encouraging efficacy in this broad population (Gore et al, 2009). Here we report final results for pts in Spain who enrolled in this trial.
Material and Methods: Pts $\geqslant$18 years of age with treatment-naive or previously treated mRCC received sunitinib 50 mg/d on a 4-wk-on/2-wk-off schedule. Tumor measurements were scheduled per local standard practice and measured using RECIST. Safety was assessed regularly. Objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and treatment-related adverse events (AEs) are reported. Analyses included all pts who received $\geqslant$1 dose of sunitinib.
Results: 231 pts received treatment, including 36% aged $\geqslant$65 years, 16% with non-clear cell RCC, 8% with baseline brain metastases, and 16% with Eastern Cooperative Oncology Group performance status (ECOG PS) $\geqslant$2 (29% and 47% had ECOG PS 0 and 1, respectively). 61% and 12% had received prior cytokine and antiangiogenic therapy, respectively, and 84% had prior nephrectomy. The proportions of pts classified as favorable, intermediate, or poor risk based on published MSKCC data were 29%, 35%, and 9%, respectively (data missing, 27%). Median treatment duration and follow-up were 6.6 and 12.8 months, respectively. 193 pts (84%) discontinued treatment; reasons included death (43%), lack of efficacy (15%), or AEs (6%). ORR was 16%. Median PFS was 9.7 months (95% CI: 7.3–12.2) overall and 17.9 months (95% CI: 11.6–22.7), 7.2 months (95% CI: 4.3−8.6), and 2.3 months (95% CI: 1.4−2.6) in favorable, intermediate, and poor risk groups, respectively. Median OS was 15.1 months (95% CI: 11.6–19.4) overall and not reached (95% CI: 22.5–not reached), 9.4 months (95% CI: 6.8–13.8), and 3.2 months (95% CI: 1.5−5.0) in favorable, intermediate, and poor risk groups, respectively. The most common grade 3/4 treatment-related AEs were asthenia (21%), neutropenia (10%), thrombocytopenia (10%), mucosal inflammation (8%), hand–foot syndrome (8%), diarrhea (6%), and hypertension (5%).
Conclusions: Among 231 mRCC pts in Spain treated in the expanded-access trial, efficacy and safety with sunitinib were favorable for a non-selected population and comparable to that of the overall population as previously reported.
Conflict of interest: *Ownership: K. Zhang, K. Fly and S. Hariharan − stock ownership with Pfizer Inc. Advisory board: M.A. Climent − Pfizer Inc. Other substantive relationships: K. Zhang, K. Fly and S. Hariharan − employed by Pfizer Inc*

2773 POSTER

The difference in adverse event profiles between the mammalian target of rapamycin inhibitors, everolimus and temsirolimus, in advanced renal cell carcinoma

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Background: Everolimus and temsirolimus have proven their efficacy and are used for patients with advanced renal cell carcinoma (RCC). They both are rapamycin derivatives and are categorized as mammalian target of rapamycin (mTOR) inhibitors. There have been few reports that examined the difference between these two agents regarding adverse events. Our objective was to investigate the difference in the safety of both agents on the basis of our real-world clinical experience.
Material and Methods: We identified patients with advanced RCC who had been treated with everolimus or temsirolimus at four major Japanese medical centers. Treatment duration, relative dose intensity, laboratory data, and adverse events during treatment with each agent were evaluated.
Results: A total of 176 patients were evaluable. 118 of those had been treated with everolimus and 58 with temsirolimus. There was no significant difference in age, gender, histological type, number of metastatic sites, and Memorial Slone-Kettering Cancer Center (MSKCC) risk between the two treatment groups. Median treatment durations of the everolimus and temsirolimus groups were 17.4 weeks and 12.1 weeks, respectively ($P = 0.192$). Relative dose intensities of the everolimus and temsirolimus groups were 75.4% and 80.5%, respectively ($P = 0.990$). Interstitial pneumonia ($P = 0.010$), stomatitis ($P = 0.010$), and increased serum aspartate aminotransferase ($P = 0.015$) of all grades were detected with significantly higher frequency in the everolimus group. Grade 3 or higher interstitial pneumonia was reported in 11.9% of the everolimus group and 1.7% of the temsirolimus group ($P = 0.022$). Frequencies of any adverse events of grade 3 or higher in the everolimus and temsirolimus groups were 45.8% and 22.4%, respectively ($P = 0.003$).
Conclusions: Adverse event profiles of everolimus and temsirolimus may differ from each other. Interstitial pneumonia may occur more frequently and severely in patients treated with everolimus than temsirolimus. These findings suggest that the difference in the pharmacodynamics, pharmacokinetics, and treatment regimen of these two agents may result in different adverse events even though they target the same molecule.
No conflict of interest.

2774 POSTER

Bleomycin lung toxicity in patients with male germ cell cancer

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Background: Germ cell cancer is a highly curable disease and the most common solid malignancy in young men. Combination of bleomycin, etoposide and cisplatin (BEP) remains the standard chemotherapy. The use of BEP is limited by the lung toxicity of bleomycin (BLT). Some probable predictive factors of BLT have been described.
Methods: Retrospective analysis of all consecutive patients (pts) treated with BEP regimen for germ cell cancer in our cancer center (Jan 2000-Aug 2012). Our aim was to evaluate the incidence of BLT during BEP up to six months after completion. BLT was defined by chest CT features (reviewed by expert) with or without symptoms, in the absence of other causes. Secondary aim was to validate in our population the risk factors reported for BLT: age, clearance creatinine (ClCr), lung metastases, smoking habits, bleomycin dose, lung disease, mediastinal primary and use of G-CSF.
Results: Of the 114 pts treated with BEP, 37 (32%) had seminoma, 77 (68%) non-seminoma. Median age at beginning of BEP was 29 years (range 15−61). Clinical stage was I in 32 pts (28%), II in 40 (35%), III in 36 (32%); 6 pts (5%) had mediastinal primary; 31 pts had multiple lung metastases; Prognostic staging (IGCCCG) was good in 71%, intermediate in 13% and poor in 16%; 45 pts had smoking habits. Median ClCr was 131 ml/min (range 39–231); 15% pts did G-CSF during BEP. Eight pts had underlying lung disease. Eighty-nine pts (78%) completed 3 or more BEP cycles. Median dose of bleomycin administered was 270U (range 30–360). BLT occurred in 17 pts (15%; 95% CI: 9−23%), in 6 pts during treatment and in 11 immediately after BEP completion. BLT radiologic patterns were interstitial pneumonia in 12 pts, organizing pneumonia in 3 pts and fibrosis in 2 pts. BLT symptoms were dyspnea in 8 pts and dry cough in 8 pts. Six pts were asymptomatic. Carbon monoxide diffusing capacity (DLCO) was done in 14 of the 17 BLT pts. Of these, only 6 pts had a reduction of at least 40%, all were symptomatic. Five pts needed hospitalization. Nine (53%) received steroids. All BLT pts had a full radiological and clinical recovery. BLT pts were older (median age 33 and 29 yrs, respectively; $p = 0.021$). In our data we couldn't demonstrate association between the other evaluated risk factors and BLT.
Conclusion: Our BLT incidence is in accordance with literature (3−14%). Despite age, the described risk factors were not useful for predict BLT. DLCO was not a relevant parameter for the diagnosis of BLT. Valid BLT predictive markers are needed.
No conflict of interest.

2775 POSTER

Evaluation of safety, tolerability and activity of temsirolimus in patients with advanced or metastatic renal cell carcinoma (a/mRCC) in routine clinical practice

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Background: Temsirolimus (TEMS), an i.v. mTOR inhibitor, is approved in the EU for the first-line treatment of patients with a/mRCC who have at least 3 of 6 prognostic risk factors. A pivotal study demonstrated significantly increased overall survival with TEMS in poor risk patients compared to the former standard Interferon (10.9 vs. 7.3 mo; $p = 0.0078$). To evaluate the safety profile and efficacy of TEMS in a clinical routine setting, collection of data in a post-approval non-interverntional trial is useful.
Methods: A German multicenter registry for a/mRCC patients treated with TEMS was started in Jan 2008 (NCT00700258). Objectives are evaluation of safety, tolerability and anti-tumor activity of TEMS, patients' profile, and sequence of systemic therapies. Inclusion criteria are histologically confirmed a/mRCC treated with TEMS and written informed consent.
Results: From Feb 2008 to Mar 2013, 122 active study centers recruited 466 patients. Preliminary data are available for 464 patients: 68.6% male, median age 66.8 years, median Karnofsky index 80%. Histological subtype: 73.5% clear cell, 11.6% papillary, and 2.8% chromophobe RCC. According to modified MSKCC criteria 94.9% of the patients were classified as poor risk and 5.1% as intermediate risk (n = 353). Adverse events (AE) and drug-related serious adverse events (SAE) were observed in 41.6% and 9.9% of the patients, respectively. Most common AEs of any grade were skin disorders, fatigue, nausea, stomatitis, anemia, thrombocytopenia, and mucosal inflammation. Median progression-free survival for the total patient population was 4.9 months, for the subgroup of 1st line patients 5.1 months, and for patients $\geqslant$65 years 5.1 months. Median overall survival for all patients was 11.4 months.
Conclusions: The population in our registry represents the expected pattern in a/mRCC patients regarding distribution of age, sex, and histology. Safety profile and clinical efficacy of TEMS in routine clinical practice confirm the phase III data. Besides, safety and clinical efficacy of TEMS for patients $\geqslant$65 years of age are comparable to the results for the overall study population.
Conflict of interest: *Ownership: none. Advisory board: Bergmann, Steiner (Pfizer). Board of directors: none. Corporate-sponsored research: Bergmann, Steiner (Pfizer). Other substantive relationships: Woike, Kalanovic (employees of Pfizer Pharma GmbH)*

2776 POSTER

Real world experience with axitinib in renal cell carcinoma at Institut Gustave Roussy (IGR)

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Background: Axitinib has shown activity in metastatic renal cell carcinoma (mRCC) in a large phase III, and has been approved in patients (pts) who failed sunitinib. It is available in France since mid November 2012, with recommended starting dose of 5 mg bid, and dose titration every 2 weeks up to 10 mg bid in pts without hypertension or grade >2 toxicity.
Material and Methods: We report IGR preliminary real world experience with axitinib in mRCC. Each time possible, Dynamic Contrast Enhanced ultrasonography (DCE-US) was performed at baseline, days 15 and 30. CT scans will be performed at month 2, and every 2−3 months thereafter.
Results: From 14 November 2012, 21 mRCC pts were treated with Axitinib for second or subsequent line. ECOG performance status was 0/1/>1 in

6/11/4 pts. Patients were classified as good (n = 6), intermediate (n = 6) or poor prognostic (n = 9) by Heng criteria. The number of prior therapies was 1 (n = 9), 2 (n = 4), or ⩾3 (n = 8), varying from 1 to 6 and included prior antiangiogenic therapy and/or immunotherapy. 18 pts (86%) had prior nephrectomy. The number of pts that had surgery, radiotherapy and radiofrequency/cryotherapy for metastases was 12, 9 and 4 respectively. The number of metastatic sites was 1/2/⩾2 in 3/2/16 pts. Dose titration could be performed in 29% pts at 2 weeks (7 mg bid) and in 16% pts at 4 weeks (10 mg bid). Hypertension was the most common adverse event (AE) according to CTC, with 9% grade 3. No other grade 3−4 AEs have been observed so far. The incidence of Grade 2 AEs was 52% and included hypertension (24%), fatigue (14%), diarrhea (5%), dysphonia (15%), abdominal pain (10%) and articular pain (10%). Efficacy: 76% of pts have been currently evaluated at 2 months. 5 patients progressed within 8 weeks. 11 pts had stable disease with tumor shrinkage ranging from −7 to −27%. DCE-US was performed in 9 pts. In 6 pts blood volume was evaluated in days 0, 15 and 30 through AUC quantification. In 5 pts vascularization decreased both in D15 (−55% to −92%) and D30 (−68% to −99%) and in 1 patient increased in D15 (+33%) and D30 (+152%). When compared to RECIST criteria all 6 pts presented SD. Data about efficacy will be updated, as well as correlation between DCE US and efficacy/toxicity.
Conclusions: Dose titration of axitinib is possible in only 29% of pts at 7 mg bid, and 16% at 10 mg bid in real world experience. Efficacy of Axitinib is observed, even in late line of treatment.
No conflict of interest.

2777 POSTER

Treatment-induced hyperlipidemia and pneumonitis could be meaningful clinical biomarkers during treatment with mTOR inhibitors (everolimus, temsirolimus) in metastatic renal cell cancer

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Objective: Objective of this analysis was to evaluate both, efficacy and toxicity of mTOR inhibitors in metastatic renal cell carcinoma patients and evaluate of treatment outcome predictive biomarkers.
Methods: This is a retrospective analysis of metastatic renal cell carcinoma patients treated with at least one regimen with mTOR inhibitor from December 2008 to November 2012 at the 2nd Oncology Department in National Cancer Institute in Bratislava. Therapy with mTOR inibitor was according usual standard guidelines and was conducted by a treating physician. Median PFS and OS were estimated using Kaplan–Meier method and compared with log-rank test. We perfomed univariate analysis of correlation of treatment-induced adverse events and treatment outcomes.
Results: We identified 69 patients that fulfill study inclusion criteria. Among them 65 patients were treated with everolimus and 4 with temsirolimus. mTOR inhibitor was given as 2nd line therapy in 50 patients, and as 3rd line in 17 patients, 1 patient received everolimus as 5th line and 1 patient as first line because of heart transplantation. We observed one patient (1.5%) who achieved partial remission and 26 patients (37.7%) had disease stabilisation. Median PFS and OS were 3.4 months and 10.2 months, respectively. There were the most frequent adverse event hyperlipidemia in 41 (59.4%) of patients (19 pts grade 1, 15 patients grade 2, 7 patients grade 3/4), presence of asymptomatic CT radiographic changes in 8 (11.6%) patients and non-infectious pneumonitis grade 3 in 6 (8.7%) patients. In patients treated with everolimus or temsirolimus, there was observed a positive association among treatment-induced plasma lipids elevation (any grade) and the significant prolongation of median PFS 6.3 vs 2.1 months [HR 0.37 95% CI(0.20–0.69); p = 0.00005] as well as median OS [13.4 vs 2.9 months (HR 0.33 95% CI(0.18–0.62); p = 0.00002]. Median time to onset hyperlipidemia was 1.1 months. The outcome of patients was not affected, when hypolipidemic therapy was administered. Similarly, significantly positive correlation was observed among patients who developed any grade of non-infectious pneumonitis with median PFS 15.0 vs 3.0 months [HR 0.42 95% CI(0.25–0.72); p = 0.0026] and median OS 17.4 vs 8.2 months [HR 0.40 95% CI(0.23–0.70); p = 0.0036]. Median onset was 3.1 months.
Conclusion: Hyperlipidemia and pneumonitis might be considered to be the meaningful clinical biomarkers of better treatment outcome in patients with metastatic renal cell cancer treated with mTOR inhibitors. This observation need to be validitate in prospective trial with larger number of patients.
No conflict of interest.

2778 POSTER

Clinico-pathological features and prognosis of patients with late-relapsing (>5 years) renal cell carcinoma after curative surgery: Results from LateR study

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Background: Late relapse of renal cell carcinoma (RCC) after radical initial nephrectomy is not a rare event. The aim of this study was to describe the late relapse of RCC, defined as 5 or more years after the primary tumour's excision in a series of RCC patients (pts).
Material and Methods: Pts who developed metastatic RCC over 5 years after curative surgery were enrolled in this retrospective analysis. Data were collected from 11 Italian centers involved in the treatment of RCC. MSKCC risk class was assessed before starting first-line treatment with sunitinib. Overall survival (OS) was estimated with the Kaplan-Meyer method with 95% CI.
Results: A total of the 2021 pts were screened and 232 pts (11%) experienced a late relapse (>5 yrs) and were included in this analysis. The median age was 66 yrs (range 29−88) and 172 pts (74%) were male. Median time to recurrence was 7.8 yrs (range 5.1–25.8). Pathological subtypes of the 232 eligible pts were clear cell RCC in 219 pts (94%) and non-clear cell RCC in 13 pts (6%), including 9 with papillary RCC (4%). At first diagnosis, Fuhrman's nuclear grade was grade (G)1 in 8 pts (3%), G2 in 153 pts (66%), G3 in 64 pts (28%), G4 in 7 pts (3%); micro-vascular and fatty infiltration were present in 28 (12%) and 29 (13%) pts, while sarcomatoid differentiation was identified in 11 pts (5%). In 16 pts (7%) the first relapse of disease was a single metastasis that was treated with surgery. The main sites for late relapse was lung (58%), followed by lymph nodes (26%), bone (19%), adrenal gland (16%), pancreas (15%), kidney (14%), liver (14%), soft tissue (9%), brain (7%), and thyroid (3%). Median OS from relapse was 38 (4.6–87.9) months. Prognostic categories using MSKCC score were good in 62%, intermediate in 32% and poor in 6% of pts. For each group median OS were 71.4, 43.5 and 16.9 months, respectively. One hundred and eight (47%) and 86 (37%) pts received a second and third-line treatment, respectively.
Conclusion: Pts with late relapsing RCC present a different metastatic spread of disease and a consistently favorable prognosis. These data should be considered in the long-term therapeutic strategy and management of these pts.
No conflict of interest.

2779 POSTER

Outcomes of unselected patients with metastatic renal cell carcinoma treated with front-line pazopanib therapy

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Background: Pazopanib is an approved tyrosine kinase inhibitor (TKI) shown to prolong progression-free survival (PFS) compared to placebo in treatment-naive and cytokine-refractory clear cell metastatic renal cell carcinoma (mRCC). Outcomes and safety data on its use in the front-line setting in unselected patients (pts) are limited. Likewise, outcome data are limited regarding subsequent therapies after front-line pazopanib therapy and in pts with non-clear-cell mRCC.
Materials and Methods: We reviewed records of consecutive pts with mRCC treated at MD Anderson Cancer Center with front-line pazopanib between 11/09−11/12. PFS and overall survival (OS) times were estimated by the Kaplan–Meier method. Univariate and multivariate Cox proportional hazards models were fitted to evaluate the association of PFS and OS with pt co-variables.
Results: 100 pts (median age 65 years, 68% male, 87% clear-cell, 78% with prior nephrectomy) met inclusion criteria. 21% had Karnofsky PS<80%. 48% had intermediate-risk and 11% had poor-risk disease by

MSKCC criteria. 42 pts have died. Median OS for all pts is 32.3 mos (95% CI: 23.3−NA). Median PFS for all pts is 11.5 mos (95% CI: 8.13–17.1) and 13.7 mos (95% CI: 8.16–18.3 m) for clear-cell pts. PFS for all pts was associated with serum LDH level >1.5xULN (HR = 5.055; 95% CI: 1.755–14.56, p value = 0.0027).
32% of pts were still receiving pazopanib at analysis. 48% discontinued pazopanib due to progressive disease. 9% discontinued due to adverse events (AEs): 7% due to increased LFTs, 1% hypertension, 1% vomiting. There were no treatment related deaths. Common AEs included fatigue (55%), diarrhea (36%), hypertension (26%), nausea/vomiting (25%), anorexia (20%), and increased LFTs (16%). 88% of AEs were grade 1/2.
66% received one or more therapies after pazopanib: 33% received everolimus, 26% sunitinib, 14% axitinib, 13% temsirolimus, 10% chemotherapy, 8% cytokines, 8% sorafenib, 4% bevacizumab, and 16% received other therapies in the second-and-subsequent-line settings.
Conclusions: In this retrospective study, pazopanib confirmed its efficacy and safety in mRCC in a real-world front-line setting. AEs were mild/moderate and manageable. Objective response rates and efficacy data on post-pazopanib sequence outcomes will be provided at meeting presentation.
No conflict of interest.

2780 POSTER

Vinflunine in routine practice for the treatment of advanced or metastatic urothelial cell carcinoma in Germany

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Background: Vinflunine is recommended by European guidelines for the treatment of advanced or metastatic urothelial cell carcinoma (UCC) after failure of platinum-based chemotherapy. In a phase III study (Bellmunt et al., JCO, 2009, 27(27):4454−61) vinflunine treated patients had a median survival of 6.9 months with moderate toxicities. The non-interventional trial investigated the effectiveness and safety of vinflunine in routine practice.
Material and Methods: Data were prospectively collected on 77 patients with advanced or metastatic UCC undergoing vinflunine treatment in 39 German hospitals or outpatient units. Dosing of vinflunine, tumor assessments and concomitant medications were performed according to physician's usual practice. The planned observation period was limited to six cycles.
Results: The patient population was representative for the specified indication (male: 82%, median age: 67 years, median Karnofsky-Index: 80, tumor location: 82% lower urinary tract, visceral metastasis: 60%). Vinflunine starting dose of 320 mg/m^2 was chosen in 48% of all patients and 280 mg/m^2 in 39%. All patients received prior systemic chemotherapy (CT), mostly cisplatin (82%) as perioperative or first line CT. Vinflunine was predominantly administered as second line CT (66%) or in subsequent treatment lines (21%). One third of the patients received more than six cycles of vinflunine and the average number of cycles was 4.7.
The frequency of treatment related hematological toxicities with minimum grade 3 was low with leukopenia 16.9%, neutropenia: 1.3%, neutropenic infections 2.6%, anemia 6.5% and thrombocytopenia 1.3%. Non-hematological toxicities with minimum grade 3 were reported with constipation 5.2%, elevated liver enzymes 5.2%, nausea 2.6%, vomiting 2.6% and fatigue 1.3%. Prophylaxis of emesis and constipation was administered in 84% and 71% of the patients, respectively.
The objective response rate was 23.4% (complete response 5.2% and partial response 18.2%) on vinflunine treatment and the median survival was 7.7 months. Patients receiving a starting dose of 320 mg/m^2 tended to benefit most of the therapy with a median survival of 10.5 months (p = 0.054).
Conclusions: This prospective non-interventional study confirmed that vinflunine is an active agent with low toxicites in an unselected population of real life experience through a large number of German centres. The treatment was manageable in daily practice with simple gastrointestinal prophylaxis.
Conflict of interest: *Other substantive relationships: AH and MR worked as consultant for Pierre Fabre Pharma GmbH within the scope of this project.*

2781 POSTER

Final results of a non-interventional study of everolimus in mRCC after exactly one previous VEGFR-TKI

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Background: Everolimus (Afinitor®) is approved for the treatment of metastatic renal cell cancer (mRCC) after failure of VEGF-targeted therapy. Despite seven approved agents for the treatment of mRCC, data beyond clinical trials is limited. In addition, data on VEGFR-TKI − mTORi sequences warrant further detailed investigation. In order to ascertain prospective data on the routine use of everolimus after a first VEGFR-TKI in patients with mRCC, a non-interventional study was conducted (NIS CHANGE, CRAD001LDE27).
Material and Methods: Patients with mRCC treated with everolimus after failure of a first VEGFR-TKI were documented in a prospective, single-armed, non-interventional study at 132 sites in Germany. Between October 2009 and December 2011, 382 patients were documented and followed until 31 December 2012, discontinuation of therapy or withdrawal of consent − whichever occurred first. Goals of the study were assessment of safety and effectiveness (as time from first everolimus intake to progression due to any cause, TTP) of everolimus in routine use.
Results: Baseline documentation had been recorded for 327 patients, with a cut-off at Dec 31st 2012. At baseline, median age of patients was 68 years and median Karnofsky Performance Status was 80%. 76% of patients were male and 92% of patients had been diagnosed with histologically proven clear-cell RCC. MSKCC risk score at start of first-line therapy was favorable in 35%, intermediate in 56%, and poor in 9% of patients. Median treatment duration with everolimus after failure of one VEGFR-TKI was 6.7 months (95% CI, 5.1−8.8 months). Median time to progression (TTP) for patients who received everolimus after failure of one VEGFR-TKI was 7.4 months (95% CI, 6.4−9.1 months). Median overall survival had not yet been reached.
Conclusions: These data represent preliminary results from a large prospective non-interventional study on the routine use of everolimus in mRCC after exactly one previous VEGFR-TKI. These data provide additional evidence for the role of everolimus in routine use after failure of one VEGFR-TKI.
Conflict of interest: *Advisory board: Novartis, GlaxoSmithKline, Roche, Astellas, Sanofi-Aventis, Pfizer, Amgen, Janssen-Cilag, Bayer. Corporate-sponsored research: Novartis. Other substantive relationships: Novartis*

2782 POSTER

Baseline peripheral blood immune cells and inflammatory molecules predict progression free survival in metastatic renal cell carcinoma patients treated with first-line sunitinib

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Background: Predicting the efficacy of tyrosine kinase inhibitors (TKI) would be of clinical value in patients with metastatic renal cell carcinoma (mRCC). We tested the hypothesis that peripheral blood immune cells and serum inflammatory markers are associated with clinical outcome in mRCC patients at favorable or intermediate prognostic risk treated with first-line sunitinib.
Material and Methods: Ninety mRCC patients were prospectively monitored at baseline (day 0) during sunitinib treatment. Serum interleukin-6 and 8 levels were determined by CLEIA and ELISA, respectively. A high-sensitivity C-reactive protein (hs-CRP) levels were measured using laser nephelometry. The immunological parameters, including proportion of

type-1 (Th1) and type-2 (Th2) cells, regulatory T cells (Treg), monocytes, mature dendritic cells and Th1/Th2 ratio, were assessed by flow cytometric analysis. Correlations between those baseline variables and progression-free survival (PFS) were examined.
Results: Median PFS was 12.6 months. Clinical benefit rate (CBR; percent complete responses+partial responses +stable disease 24 weeks) was 57.3%. In univariate analyses, baseline interleukin-8, hs-CRP and proportion of Th1 were correlated with PFS, respectively. In multivariate Cox proportional analysis, hs-CRP ($p = 0.0110$) and proportion of Th1 ($p = 0.0140$) were independent indeces to predict PFS.
Conclusion: Baseline peripheral blood immune cells and serum inflammatory markers could be of clinical interest in sunitinib-treated mRCC patiens to predict outcome. Baseline hs-CRP serum levels as well as proportion of Th1 warrant further study.
No conflict of interest.

2783 POSTER

Addition of bevacizumab as salvage treatment in patients with metastatic renal cell carcinoma

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Background: Treatment of metastatic renal cell carcinoma (mRCC) is based on VEGF inhibitors and mTOR inhibitors. However resistance occurs. A previous study showed interesting results with a bevacizumab (bev) − sunitinib combination in sunitinib-refractory patients (pts). We report on our experience on pts who were progressing on a anti-VEGF inhibitor or a m-TOR inhibitor and were given the same drug plus bevacizumab.
Population and Methods: The study population was described (pts demographics, initial tumour characteristics, treatments etc). Overall survival (OS) from the beginning of the 1st combination was estimated by Kaplan–Meier method and prognostic factors were explored using a Cox model.
Results: Twenty-nine pts were treated with such a combination: 23 men and 6 women. Twenty four pts had undergone surgery. Eleven pts (37.9%) had metastatic disease at initial diagnosis. Eighteen pts had clear cell histology, 8 had clear cell + another component (sarcomatoid or eosinophil), 2 had papillary tumours. For 1 pt the precise histology was not available.
Most patients received sunitinib as first antiangiogenic drug for metastatic RCC (93.1%). The 2 other pts were in a clinical trial and received respectively AMG-sorafenib and pazopanib+bevacizumab. Only 6 pts had received prior immunotherapy. Ten pts received the combination as 2nd line treatment, 7 as 3rd line, 8 as 4th line and 4 as 5th line.
Fifteen pts received sunitinib+ bev, 9 everolimus+ bev and 5 temsirolimus+ bev. All pts but 1 received full-dose bev (10 mg/kg). Full dose sunitinib of 50 mg 4w/6 was given to 8/15 pts. Four patients received full dose everolimus (10 mg/day) and temsirolimus (25 mg/weekly) respectively.
Main toxicities were hypertension, proteinuria, hand–foot syndrome, mucositis and haematological toxicity. Two pts had grade 3 proteinuria,3 had grade 3 hypertension and 3 grade 3 hand–foot syndrome.
More than a third of pts had improvement in their symptoms. Best radiological response was stable disease in 15 pts and partial response in 2.
With a median follow-up of 18 months (range: 1−35 mo), 2 pts are still on treatment. Fifteen pts discontinued treatment because of progression and 9 because of toxicity.
The median duration of the 1st combination was 4 months (95% IC=2−5 mo). Median OS from 1st combination was 8 months (95% IC=4−26 mo). There was no statistical difference according to the type of combination, the line of treatment and the histological subgroup.
Conclusions: Adding bevacizumab to another antiangiogenic therapy at progression can benefit some pts. Side effects should be monitored closely. However selecting which pts should receive such a treatment is not defined yet.
Conflict of interest: *Ownership: no. Advisory board: Pfizer, Bayer, Novartis, Janssens, Keocyt, Takeda, Roche. Board of directors: No. Corporate-sponsored research: Bayer, Novartis. Other substantive relationships: No*

2784 POSTER

Everolimus in clinical practice, which patients benefit?: A study of outcomes, tolerability and quality of life in an early cohort of patients

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Background: Following a phase III trial suggesting benefit, Everolimus gained approval for second line treatment for renal carcinoma. Trial data shows a PFS benefit of 3 months, and sustained quality of life. We aimed to assess outcomes in clinical practice, comparing to those expected, and investigated factors predicting increased benefit.
Methods and Materials: Patients commencing Everolimus between August 2009 and January 2012 were found via applications to the West-midlands cancer drugs fund. Data was extracted from electronic records of patient demographics and outcomes: OS and PFS, treatment length, toxicity. An adapted version of the EORTC QLQ-C30 assessed quality of life in patients on follow up.
Results: Of 47 patients identified 3 were lost to follow up. Of 44, 27 patients had died, 17 were alive. Patient characteristics were compared to trial patients: gender and age were similar, performance status was lower (0=2% vs 28%, 1=66% vs 36%), as was MSKCC risk (favourable= 18% vs 29%, poor 30% vs 15%). Median treatment time was 70 days vs 95. Discontinuation due to toxicity was higher (28% vs 10%), and increased with disease burden, $\geqslant$4 sites of metastasis (OR 2.01, $P = 0.28$). Best objective response was stable disease in 57% (vs 63%). Median PFS was 3 months (vs 4.9). PFS was reduced by poor MSKCC (0= 5, 1= 3 and 2= 2.3 months Chi-Square=1.72, $P = 0.4$), PS (0 or 1= 177 days, 2= 112, $P = 0.09$), younger age (age <60=132, $\geqslant$60= 174, $P = 0.2$) and increased disease burden (PS, 1−3 sites=194, $\geqslant$4=112, $P = 0.04$). Median OS was 8 months, and similarly reduced with poor PS, MSKCC score, increased disease burden and younger age. Of 7 patients completing the EORTC QLQ-C30, only 1 reported deterioration in QOL.
Conclusions: Poorer PS, lower MSKCC and higher disease burden were seen, and resulted in worse outcomes in Everolimus treated patients. Unexpectedly younger age was also a poor prognostic factor and disease burden appeared to reduce ability to tolerate treatment. Although benefit in PFS is lower, maintained objective response and moderate PFS advantage was seen. These factors should be considered in decisions to commence Everolimus treatment.
No conflict of interest.

2785 POSTER

Clinical significance of Ezrin and Neuropilin-2 expression in advanced renal cell carcinoma

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Background: The identification of prognostic factors in patients with renal cell carcinoma (RCC) represents an area of increasing interest. This study used a cohort of patients treated for RCC to provide information about biomarkers and prognosis. The purpose of this study was to evaluate prognostic factors in patients with RCC.
Materials and Methods: The expression of several biomarkers were measured by immunohistochemistry (IHC) in 45 patients with advanced RCC treated with second-line vascular endothelial growth factor (VEGF) targeted tyrosine kinase inhibitors (TKIs) after failure of interferon-alpha between January 2007 and June 2012. Kaplan–Meier and log-rank analyses were employed on PFS and OS and multivariate Cox proportional hazard model analyzed clinical parameters for their prognostic relevance.
Results: Age, ezrin and neuropilin-2 overexpression were statistically significant factors ($P < 0.05$) for PFS in the univariate analysis. Ezrin and neuropilin-2 overexpression, hemoglobin and albumin were statistically signifiant factors ($P < 0.05$) for OS in the univariate analysis. Multivariate analysis revealed that low expression of ezrin and neuropilin-2 were a favorable prognostic factor independent of PFS and OS. Median PFS was 4 versus 11 months in patients with overexpression neuropilin-2 versus low expression neuropilin-2 ($p = 0.033$). The median OS was 13 months versus 26 months, in patients with overexpression neuropilin-2 versus low expression neuropilin-2, respectively ($p = 0.023$). Increased expression of ezrin was related to poor prognosis with VEGF targeted TKI treatment (PFS, 3 vs. 7 months $p = 0.012$).
Conclusions: Neuropilin-2 and ezrin in particular are useful prognostic factors in patients with advanced RCC.
No conflict of interest.

2786 POSTER

A retrospective analysis of treatment efficacy of primary mediastinal germ-cell tumours

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Background: Primary germ-cell tumours of the mediastinum are rare. Treatment algorithms do not differ from those for testicular germ-cell tumours. However, extragonadal origin in the chest is an independent factor of poor prognosis.
This paper summarizes treatment results in our centre.
Material and Methods: Data of 20 patients treated in our centre in the years 1998–2012 were retrospectively analysed.
Results: Median age of the patients was 24.8 years. In 13 patients (65%), the diagnosis was established after mediastinoscopy and biopsy; 4 patients (20%) underwent partial or complete tumour resection, 1 patient had a transbronchial biopsy, 1 patient − biopsy of the supraclavicular mass; in 1 case the clinical picture (computed tomography, serum markers) was sufficient to establish the diagnosis. 19 patients received chemotherapy, 1 did not due to poor compliance. Of these, 9 (45%) had one line of chemotherapy, 8 (40%) − two lines, and 2 (10%) − three lines. Resection of residual masses was conducted in 12 (60%) patients, whereas 1 patient (5%) underwent radiotherapy to the mediastinum. The median follow-up was 16.5 months. 8 patients (40%) died of their disease; the median survival from the end of first-line chemotherapy in this subgroup was 11.3 months. 1 patient was lost to follow-up. In the subgroup of patients followed up for over 5 years, 5 of 14 (35.7%) are still alive.
Conclusions: The data confirmed a moderate efficacy of systemic treatment in primary mediastinal germ-cell tumours. The prognosis was particularly poor in patients who did not achieve remission during the first-line treatment.
No conflict of interest.

2787 POSTER

Second line treatment in metastatic patients with non-clear cell renal carcinoma (Ncc-RCC): Retrospective analysis of a 22 patients cohort

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Background: Renal cell carcinoma (RCC) more than one single disease consists of various tumor types, each one with a different histology and clinical course. Histologies include clear cell, papillary types I/II, chromophobe, collecting duct and unclassified renal carcinoma. Sarcomatoid Variant (SV) represents a phenotype of RCC that can be present in any subtype, usually showing an aggressive biological behavior. Patients with SV or Ncc-RCC have been included in RCC clinical trials, although such patients represent minority components. There is no specific recommendation for Ncc-RCC. First line prospective dedicated studies are on going. No second line data have been reported.
Material and Methods: All pts with metastatic Ncc-RCC treated in first line from 2007 to 2013 at our Institution, were retrospectively analysed. Clinical data, prognosis classifications and treatments were assessed; PFS after first and second line and OS were calculated.
Results: 22 pts with metastatic Ncc-RCC were identified. Median age at diagnosis was 62, sex ratio 16M/6F. Histological subtypes were: papillary type I/II (39%), chromophobe (18%), unclassified (13%) and sarcomatoid(30%). Nephrectomy had been performed in 18 pts (82%). Most pts presented with synchronous metastatic disease (82%). Metastatic sites were: 12 lung (55%), 17 LN (77%), 5 bone (23%), 6 liver (27%). Prognostic classification by MSKCC was good in 9, intermediate in 5 and poor in 8 pts. Median OS was 16.0 months, 9/22 pts are still alive. As first line treatment, pts received: sunitinib (9), temsirolimus (7), sorafenib (3), pazopanib (1), bevacizumab based regimen (2). Median first line PFS is 13.0 months [1−17]. Median PFS in papillary type I/II and chromophobe is 7 months and in unclassified and SV is 6 months. 11(50%) pts received a second line treatment after first line failure. Second line treatment included sunitinib (6), sorafenib (3) or mTOR inhibitor (2). Median second line PFS is 16 months [1−34]. Median PFS in papillary type I/II and chromophobe is 18 months and in unclassified and SV is 2 months.
Conclusions: This is a report of second line data in Ncc-RCC. Median second line PFS is better in papillary or chromophobe (16 months) than unclassified and SV (2 months). The optimal treatment for pts with Ncc-RCC remain to be fully explored. Definitive recommendations will require subtype specific clinical trials or, lacking that, a registry of treatment results for pts with these relatively uncommon tumors.
No conflict of interest.

2788 POSTER

Vinflunine (VFL) as second-line chemotherapy for patients with transitional cell carcinoma of the urothelium (TCCU): A multicenter retrospective study

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Background: VFL is the standard chemotherapy in second-line advanced TCCU in Europe (EMA approval 21/09/2009). We set up a multicenter retrospective study to evaluate the efficacy and toxicity of VFL in patients (pts) with advanced TCCU after platinum failure within the framework of routine practice.
Material and Methods: Descriptive and retrospective study in pts who had demonstrated prior progression to a platinum-containing chemotherapy regimen at 9 centers. VFL standard dose (280–320/m^2 every three weeks) was administered until progression or unacceptable toxicity. Objective response was evaluated according to RECIST criteria v.1.1.
Results: Between April 2010 and February 2013, a total of 66 pts with median age of 67 years (range 47−83) were analyzed. Main characteristics: ECOG 0−1−2 in 21pts (31.8%), 40pts (60.6%), 5pts (7.6%). Mean creatinine clearance was 59 ml/min. Primary sites of disease were bladder 54pts (81.78%), renal pelvis 9pts (13.16%), ureteral 2pts (3%) and prostatic urethra 1pt (1.5%). All pts had previously received platinum-based chemotherapy as a first-line treatment (cisplatin in 42.4% of pts). Metastatic locations were: 42pts (63.6%) lymph nodes, 26pts (39.3%) lung, 18pts (27.2%) bone and 17pts (25.7%) liver. The median number of cycles of VFL was 5 (1−18). All pts were assessed for response, one (1.5%) patient presented complete response (CR), 17pts (25.8%) partial response (PR), 28pts (42.4%) stable disease (SD) and 20pts (30.3%) progressive disease (PD). Median progression-free survival was 3.96 months (95% CI, 3.11−4.8). Median overall survival (OS) was 10.4 months (95% CI, 6.25–14.5). OS at 6 months was 58%. Liver metastasis ($p = 0.013$) and ECOG ($p = 0.023$) was confirmed as prognostic factors for OS. Grade 3/4 adverse events included neutropenia 6pts (9%), constipation 4pts (6%), abdominal pain 4pts (6%) and nausea/vomiting 4pts (6%).
Conclusions: This retrospective analysis confirm VFL as an active agent in pts progressing after platinum-based combination for advanced TCCU in a daily clinical practice in Spain. As ESMO (Bellmunt J, 2011) and Spanish (Castellano D, 2012) guidelines recommend vinflunine, it should be offered in this setting or alternatively, treatment within a clinical trial.
No conflict of interest.

2789 POSTER

New chemotherapeutic regimens in patients (pts) with mediastinal nonseminomatous germ cell tumors (MNSGCT): Do we still need BEP as a standard?

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Background: Pts with MNSGCT belong to the poor prognostic group by IGCCCG. BEP regimen is still a gold standard of treatment. We

retrospectively compared efficacy of different chemotherapeutic regimens which were used in our center in phase II trials.
Material and Methods: We analyzed data of 61 pts with MNSGCT, who were treated in our department during 1986–2011. Median age was 23 years (range, 18−44). Median follow-up time was 60 months (range, 4–180). Induction chemotherapy BEP was accomplished in 23/61 (37.8%), TBEP − in 17/61 (27.8%), CBOP − in 17/61 (27.8%), accelerated (dose-dense) BEP − in 4/61 (6.6%) pts. Surgery resection of residual tumor was performed in 28/61 (45.9%) pts.
Results: Based on similar efficacy of CPOB and TBEP regimens we combined pts to a single 'CPOB/TBEP' group and compared with 'BEP' group. Pts in both groups were similar according main prognostic factors, including size of the primary tumor, number metastatic sites, lungs and nonlungs metastases, age, mean levels of AFP, HCG, LDH. Marker-negative objective response obtained in 40/61 (65.6%) pts. Median OS was 24 months and 3-year OS − 46% for all pts. Marker-negative objective response rate was higher in pts in CPOB/TBEB group: 26/34 (76.5%) vs. 14/27 (51.8%), p = 0.08. Surgery resection of residual tumor was performed in 20/34 (58.8%) pts of CPOB/TBEB group vs. 8/27 (29.6%) pts of BEP group, p = 0.04. Overall survival was also higher in pts in CPOB/TBEB group: 2- and 5-years OS were 63% and 55% vs. 35% and 21% (p = 0.009, HR 2.8, 95% CI 1.30−6.1), respectively.
Conclusions: CBOP and TBEP regimens are associated with better outcome in pts with MNSGCT. These data should be confirmed in prospective trials.
No conflict of interest.

2790 POSTER

Efficacy and safety of sequential use of everolimus (EVE) in patients (pts) with metastatic renal cell carcinoma (mRCC) previously treated with bevacizumab (BEV) +/− interferon (INF) therapy − updated results from the European AVATOR retrospective study

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Background: EVE (Afinitor®) has demonstrated activity in the treatment of mRCC after failure of VEGF-targeted tyrosine kinase inhibitors. To this date, there is no published data evaluating its activity/safety after failure of first line BEV-based therapy.
Methods: Our non-interventional multicenter international study reports retrospective data on EVE in routine use. Eligible patients had mRCC; were given EVE after 1 prior first-line systemic therapy with BEV +/− INF. The data were provided by each center and centralized.
Results: Twenty sites included 43 pts between 2011 and 2012, with 42 evaluable patients. Baseline patient characteristics included median age of 69 [38−90] years old; 64.3% male; 97.5% with prior nephrectomy. First-line therapy was BEV + INF in 69% of patients, BEV only for 31%. Prognostic groups at the time of EVE initiation according to Heng [1] and to MSKCC [2] were respectively: (1) good 25%, intermediate 59.4% and poor prognosis 15.6% and (2) good 28.1%, intermediate 56.3% and poor 15.6%. Median duration of treatment with first line therapy was 7.5 months, and it was discontinuated for disease progression in 61.9% of pts.
After initiation of first line 53.3% of patients were alive at 32 months. Median OS was not reached for the second line. Median progression free survival (PFS) for EVE was 17 [5.0-not reached] months. Overall response rate was 9.5% and disease stabilization rate was 50%. At least one adverse event (AE) occurred in 73.8% of pts with 13 serious AEs. All grade common AEs were consistent with the toxicity profile of EVE with 31 % of stomatitis, 16.7% of pneumonitis, 31 % of fatigue.
Conclusions: This study provided encouraging results for the activity and safety profile of EVE in this second line mRCC setting after 1 prior first-line therapy with bevacizumab-based regimen. Further studies with larger numbers of pts are planned based on these novel findings.
Conflict of interest: *Corporate-sponsored research: Novartis − Pfizer*

2791 POSTER

Sequential assessment by FDG-PET/CT of patients with advanced renal cell carcinoma treated with tyrosine kinase inhibitors

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Background: Tyrosine kinase inhibitors (TKIs) which target vascular endothelial growth factor receptors improved the prognosis of patients with advanced renal cell carcinoma (RCC). The antitumor activity of TKIs is not cytotoxic, like classical antitumor therapeutics, but rather cytostatic, suppressing biological activity. It has been suggested that a new assessment focusing not only on the volume of the tumors, but also biological activities to evaluate the antitumor activity of TKIs is necessary. FDG PET/CT is a useful non-invasive tool to evaluate glucose metabolic status, which can be the index of biological activity of cancer. From 2008, we have been investigating the usefulness of FDG PET/CT as biological biomarker to assess the status of advanced renal cell carcinoma (RCC) as a clinical study and previously reported that the RCC which FDG accumulation decreased more or 20% on 1 month after tyrosine kinase inhibitors (TKIs) treatment started showed good prognoses (BMC Cancer 2012). In this time, we investigated the sequential FDG accumulation change during TKI treatment.
Material and Methods: Of 71 patients with advanced RCC who were enrolled in this study, we focused on the 26 patients, who were treated with TKIs (13 sunitinib and 13 sorafenib) and evaluated by FDG PET/CT (Aquiduo 16; Toshiba Medical Systems, Tokyo, Japan) before treatment, 1 month after treatment started, and following every 3 months until their RCC demonstrated progression disease (PD) defined by RECIST criteria. The standardized uptake value (SUV), which is a semiquantitative simplified measurement of the tissue FDG accumulation rate was measured sequentially during TKI treatments.
Results: The median of progression free survival (PFS) of all 26cases was 159 days. Maximum SUV (SUVmax) in 17 cases (65%) was decreased by TKI treatment and that in 9 cases (35%) were increased. The median PFS of 19 cases with decreasing SUVmax was 211 days and that of 9 cases with increasing SUVmax was 110 days. There was statistic difference (P = 0.005). In 19 cases with decreasing SUVmax, the median date when SUVmax reached to nadir was 67 days. The median decreasing ratio of SUVmax at the nadir compared with that before treatment was 30%. The SUVmax increased after nadir in 14 cases (82%) and the SUVmax in 11 cases increased before cancer showed PD defined by RECIST criteria. The time lag between SUVmax increase and PD were 0−98 days (median 63 days). Interestingly, the SUVmax at PD was higher than that before TKI treatment in 12cases (46%).
Conclusions: FDG PET/CT could evaluate the biological response of advanced RCC to TKI treatment on real time and the increase in SUVmax before RCC showed progression suggested that acceleration of glucose metabolism was one of the mechanism how RCC acquired the resistance to TKI treatments.
No conflict of interest.

2792 POSTER

Safety and efficacy of vinflunine in long-time therapy of metastatic bladder cancer

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Background: Vinflunine(VFL) has shown activity in second line metastatic bladder cancer patients. Culine et al have reported long-duration responses ranging from 4.2 to 15 months (median 9.1 months) in this setting. We performed an analysis to study clinical characteristics of long term responders to vinflunine.
Material and Methods: Patients with partial or complete response to first line treatment with platinum and gemcitabine were included. Patients had a performace status of 0 or 1, measurable disease by RECIST criteria, age >18 years, a life expectancy of a least 12 weeks, and an adequate organ function and bone marrow reserve. Patients received vinflunine 320 mg/m^2 IV day 1 every 21 days until disease progression or unacceptable toxicity.
Results: Data from 10 patients receiving an initial dose of VFL 320 mg/m^2 every 21 days show that the most frequent toxicity of vinflunine is

neutropenia (grade 1−2). Neutropenia is reversible and non-cumulative; severe anemia and thrombocytopenia were rarely observed. Constipation (any grade) was observed in 50% of patients. All patients in our serie presented site local patin related to vinflunine administration.
A total of 5 patients are still receiving vinflunine at the cut-off date; two of them have received 27 and 28 cycles of treatment. Median overall survival was not reached wtih a median follow-up of 10.5 months (range 8 to 19 months).
Conclusion: Single-agent vinflunine is safe and active as maitenance chemotherapy of patients with advanced transitional cell bladder carcinoma who have responded to a prior platinum-containing regimen, with minor toxicity and a good tolerance.
No conflict of interest.

2793 POSTER

Phase II clinical trial of sorafenib plus interferon-alfa treatment for patients with metastatic renal cell carcinoma in Japan

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Background: Much attention has been paid to molecular target-based drugs including tyrosine kinase inhibitors and mTOR inhibitors, which were approved by FDA for advanced renal cell carcinoma (RCC). Recently, however, we have already known their limitations in the treatment of patients with metastatic RCC (mRCC). To improve the antitumor effects of molecular target-based drug, sequential or combination therapy with these drugs has been advocated. In combination therapy, the additional effect of interferon (IFN)-α on sorafenib has been recently reported in mRCC patients (J Clin Oncol 25:3288, 2007) and in our murine model (J Urol 184:2549, 2010). Furthermore, the prognosis of mRCC patients in Japan was good in the cytokine era (Eur Urol 57:317, 2010). We have thus conducted a phase II clinical trial of sorafenib plus IFN-α for untreated mRCC patients in Japan (UMIN000002466).
Methods: In this multicenter, prospective study, provisionally registered patients with histologically confirmed clear cell RCC that was metastatic, measurable disease, age ⩾20 years, ECOG PS 0−1 and adequate organ function received 3 dosages of 3 million U per week of natural IFN-α treatment for 2 weeks. Then, only patients tolerable to IFN-α treatment were registered to this trial, and oral administration of sorafenib (400 mg, bid) was added to IFN-α treatment. The primary end point of the study was to evaluate response rate (CR + PR) of sorafenib plus IFN-α treatment for mRCC patients using RECIST v1.0. The secondary end point was to evaluate disease control rate (CR + PR + SD), progression free survival (PFS), overall survival (OS), and safety of the combined treatment.
Results: From July 2009 to July 2012, 53 untreated patients were provisionally registered, and 51 patients were finally registered to this trial of sorafenib plus IFN-α treatment. Nine patients were excluded because of violation of eligibility criteria. Among 42 eligible patients, 35 patients were male. Median age of patients was 64.5 years old (range 37−78). Thirty seven and 5 patients were PS 0 and 1, respectively. One patient pathologically demonstrated around 5% of spindle cell components. Response rate of the combined therapy was 26.2% (11/42) (CR 1, PR 10). Frequent adverse effects (AE) were hand–foot syndrome, fatigue, dermatitis, and diarrhea, which were well-known as common AE caused by either IFN-α or sorafenib. Neither increase of the incidence of AE nor unexpected AE due to the combined therapy was observed.
Conclusions: Our results have clearly demonstrated that sorafenib plus IFN-α treatment is safe and effective, and can be a therapeutic option for mRCC patients as a first line treatment.
Conflict of interest: *Other substantive relationships: honoraria from: Bayer Yakuhin, Ltd. and Dainippon Sumitomo Pharma Co., Ltd.*

2794 POSTER

Central and Eastern European experience with sutent from the expanded-access mRCC trial

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Background: The international, open-label, expanded-access protocol (EAP) of sunitinib including 4371 patients with mRCC between June 2005 and December 2007 reported its final results of extended follow-up in 2012. This retrospective study presents results of patients from Central and Eastern European countries (CEE) including Slovakia, Serbia, Slovenia, Bulgaria, Croatia, Hungary, Russia, Romania, Czech Republic.
Materials and Methods: We analyzed safety, overall survival (OS), progression free survival (PFS) and objective response rate (ORR) in the subgroup of patients from CEE countries. Toxicity was assessed on days 1, 14 and 28 of cycle 1 and 28 of subsequent cycles. Tumor assessments were guided by the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0) but were not scheduled in the study protocol and were performed according to local standard of care, with data on response, PFS, and OS collected when possible. (Survival data collected up to July 15, 2008.)
Results: The CEE data set comprised 401 patients (8.8% of total population). 85.3% of the patients had ECOG performance status 0 or 1 and 86.5% had a favorable or intermediate risk according to the MSKCC risk criteria. The median duration of treatment of CEE group was 9.6 months (95% CI; 8.1–11.1) and the median number of treatment cycles was 7 (range 1−57). 159 (39.6%) patients had a dose reduction. The median PFS and OS results are presented in table 1.

Table 1. The median PFS and OS results in CEE mRCC patients in general and divided by prior cytokine use

	CEE population n = 378 (PFS) n = 401 (OS)	No prior cytokines n = 161 (PFS) n = 172 (OS)	Prior cytokines n = 217 (PFS) n = 229 (OS)
Median PFS (months; 95% CI)	11.6 (10.3; 12.8)	12.2 (9.3; 16.5)	11.0 (8.8; 12.6)
Median OS (months; 95% CI)	30.7 (23.3; −)	60.8 (26.3; −)	27.5 (20.9; 36.6)

The mPFS in patients with good, intermediate or poor risk according to MSKCC was 16.2 months (95% CI; 13.3; 18.5), 9.3 months (95% CI; 8.1; 11.9) and 5.2 months (95% CI; 2.3; 6.6) with a HR for the comparison of poor vs favorable or intermediate of 3.21 ($p < 0.0001$).
46 patients (11.5%) discontinued the study due to adverse events. 143 patients (35.7%) had at least one serious adverse event. The adverse event profile was comparable to the known profile of sunitinib.
Full comparison with global data set will be disclosed.
Conclusions: Results from this subanalysis of EAP confirm the safety and efficacy of sunitinib in patients treated in CEE.
Conflict of interest: *Advisory board: Pfizer. Corporate-sponsored research: Pfizer*

2795 POSTER

Safety and efficacy of second-line axitinib versus sorafenib in metastatic renal cell carcinoma by duration of prior therapy: Subanalyses from a phase III trial

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Background: In the phase III AXIS trial (NCT00678392; sponsor: Pfizer), 723 patients with clear cell metastatic renal cell carcinoma, progressive disease after 1 systemic therapy and Eastern Cooperative Oncology Group performance status (PS) 0 or 1 were stratified by PS and prior therapy and randomised 1:1 to axitinib or sorafenib. Axitinib significantly improved

progression-free survival (PFS; primary endpoint) vs sorafenib in patients previously treated with sunitinib (n = 389) or cytokines (n = 251).
Material and Methods: In post-hoc analyses, investigator-assessed PFS, overall survival (OS), and safety of axitinib vs sorafenib by duration of 1st-line sunitinib or cytokines were evaluated.
Results: Median duration of prior sunitinib and cytokines was 9.7 and 6.5 months, respectively. Among patients with ⩾ vs <9.7 months of prior sunitinib treatment, median PFS (mPFS; 95% CI) was 6.6 (5.2−8.3) vs 6.4 (4.6−8.3) months with axitinib (*P*=.996) and 4.5 (3.0−6.5) vs 3.5 (1.9−4.7) months with sorafenib (*P*=.431); median OS (mOS; 95% CI) was 18.1 (14.8–23.0) vs 11.7 (9.3–15.2) months with axitinib (*P*=.220) and 19.0 (15.0–23.9) vs 14.9 (10.5–18.0) months with sorafenib (*P*=.018). Among patients with ⩾ vs <6.5 months of prior cytokine treatment, mPFS (95% CI) was 15.7 (12.2–22.1) vs 8.6 (6.5–13.8) months with axitinib (*P*=.002) and 8.4 (7.2–10.2) vs 6.7 (5.6−9.5) months with sorafenib (*P*=.580); mOS (95% CI) was not estimable (NE; 28.0−NE) vs 26.3 (18.8–31.6) months with axitinib (*P*=.017) and 34.5 (27.8–34.5) vs 23.1 (17.3–31.9) months with sorafenib (*P*=.014). In both arms, grade ⩾3 hypertension was more common (⩾5% difference) in patients who had received 1st-line cytokines for ⩾ vs <median duration; grade ⩾3 hand–foot syndrome was more common in patients who had received 1st-line sunitinib for < vs ⩾median duration (Table).
Conclusions: Longer prior treatment with sunitinib or cytokines was associated with longer OS with 2nd-line axitinib or sorafenib. Safety profile of 2nd-line axitinib or sorafenib differed modestly by duration of prior therapy.
Conflict of interest: *Ownership: B Rosbrook, S Kim, J Tarazi (Pfizer stock ownership). Advisory board: B Escudier (Bayer, Pfizer, and Novartis) RJ Motzer (Pfizer, Genentech, AVEO Oncology) P Zalewski (Pfizer and Novartis) E Porfiri (Astellas, Novartis, Bayer and Pfizer) G Kannourakis (Pfizer) BI Rini (Pfizer). Board of directors: None. Corporate-sponsored research: RJ Motzer (Pfizer, Novartis, GlaxoSmithKline) E Porfiri (Pfizer, GlaxoSmithKline) BI Rini (Pfizer). Other substantive relationships: B Escudier (Bayer, Roche, Pfizer, Genentech, Novartis, and Aveo) B Rosbrook, S Kim, J Tarazi (employment with Pfizer)*

Table: Common treatment-related grade ⩾3 adverse events (%)

	Axitinib				Sorafenib			
	Prior sunitinib*		Prior cytokines*		Prior sunitinib*		Prior cytokines*	
Median	<	⩾	<	⩾	<	⩾	<	⩾
n	96	94	66	60	93	96	58	65
Hypertension	10	11	23	28	11	8	12	22
Fatigue	8	11	12	13	5	3	5	2
Diarrhoea	10	17	8	12	6	10	9	8
Hand−foot syndrome	8	3	5	5	15	6	19	22
Lipase increased	0	0	2	3	1	2	3	11

*Median treatment duration subgroups.

2796 POSTER

Comprehensive activated kinase profiling to identify novel therapeutic targets in metastatic clear cell (cc)-renal cell carcinoma (RCC)

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Background: Kinase inhibitors have yielded therapeutic advances in cc-RCC. We hypothesized that determining differential kinase activity between primary and metastatic renal tumors may identify critical drivers of progression and relevant therapeutic targets in metastatic disease.
Methods: Fresh frozen RCC with a clear cell component were provided by the Cooperative Human Tissue Network (funded by U.S. National Cancer Institute). Kinomic profiling of tumor lysates was performed using the PamStation®12 high-content phospho-peptide substrate microarray system (PamGene International). The protein tyrosine kinome (PTK) and serine/threonine kinome (STK) PamChips® were used to measure global kinase activity. The degree of phosphorylation on each peptide probe was measured kinetically using Evolve software (PamGene), that measured FITC labeled anti-phosphotyrosine (or anti-phosphoserine/threonine) antibody binding to each phosphorylated peptide substrate during the 60 min assay and were further analyzed using BioNavigator software (PamGene). Advanced network modeling of altered phosphopeptides was performed using MetaCore (Thompson Reuters). All peptides in the metastatic and primary renal tumors were compared using an unpaired students t-test. Peptides were uploaded to Metacore as source-protein Uniprot ID's and a Djikstras shortest path networking algorithm with 2 steps maximum between nodes was used to generate a network model.
Results: Among 96 available tumor samples, 92 met quality control criteria for kinase activity. Frozen cc-RCC tumor was available from 79 patients from the primary site, 11 patients from the metastatic site and 1 patient from both the primary and metastatic site. When comparing the profiles of primary and metastatic tumors, 8 phosphopeptide probes were significantly altered ($p < 0.005$): 7 PTK peptides had increased phosphorylation in metastases including peptides derived from FGFR1, FAK1, MBP, EPHB4, K2C8, ACHD and EGFR; the PGYL STK peptide phosphorylation was decreased in metastases. Network modeling also identified CEBPB as a key transcription factor.
Conclusion: Comprehensive kinase profiling of fresh frozen cc-RCC tumors identified 7 tyrosine kinase substrates showing elevated phosphorylation in metastatic tumors compared to primary tumors. Further validation is warranted since these kinases may represent novel targets for the therapy of metastatic disease as well as adjuvant therapy following extirpation of localized tumors.
No conflict of interest.

2797 POSTER

Preclinical activity of CEP9722, a PARP inhibitor, in urothelial carcinoma (UC)

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Introduction: Somatic loss of DNA repair proteins ERCC1 and BRCA1 is common in UC. A rationale can be made to evaluate the preclinical activity of a PARP inhibitor, CEP9722 and its active metabolite, CEP8983, to exploit synthetic lethality.
Methods: The activity of CEP8983 alone and with cisplatin after 72 hrs was evaluated in vitro by MTT assay against human UC cell-lines: 5637, TCC-SUP, T24, and RT4. FACS for Annexin-V/PE-FITC was performed to assess apoptosis/necrosis. Alkaline COMET assay was performed post 24-hr exposure to CEP8983, cisplatin or both to assess DNA damage. Western Blot was done to examine proteins involved in DNA repair (LKB1, MRE11, BRCA1, CHK1, CHK2, RAD50, RAD51, ATM) and PAR on untreated cell-lines to identify biomarkers predictive of sensitivity. Subcutaneous RT4 xenografts were treated with placebo or CEP9722 100 mg/kg/day or 200 mg/kg/day orally for 5 days a week for 4 weeks (5 mice per group). Xenografts underwent immunohistochemistry (IHC) for apoptosis (cleaved caspase [cc]-3) and angiogenesis (CD31).
Results: CEP8983 1 μM reduced the viability of RT4 and T24 cells by 20% compared to controls (sensitive), but did not reduce viability of 5637 and TCC-SUP cells (resistant). At 10 μM, RT4 viability was reduced by 39% and 5637 viability by 18%. The combination of cisplatin and CEP8983 in vitro did not yield additive activity. FACS demonstrated apoptosis plus necrosis in 9.7 and 9.1% of RT4 and 5637 cells, respectively. RT4 cells exhibited greater DNA damage compared to 5637 by COMET assay. COMET assay also showed increased DNA damage with combination versus either CEP8983 or cisplatin alone in RT4 and 5637 cells. Western Blot did not demonstrate consistent differences for DNA damage repair proteins and PAR between resistant or sensitive cells. CEP9722 showed antitumor activity in RT4 xenografts compared to controls and dose response was observed; 200 mg/kg daily was statistically better than control ($p = 0.04$) and 100 mg/kg was not ($p = 0.26$). IHC of xenografts showed significant increase in cc-3 and decrease in CD31 with both doses ($p < 0.05$).
Conclusion: Selected UC cells are preclinically sensitive to PARP inhibition by CEP9722 and its active metabolite CEP8983. CEP8983 did not enhance the activity of cisplatin and no biomarkers predictive for activity were identified. Further investigation of PARP inhibitors as single agents and genome wide profiling to identify a signature predictive for activity may be warranted.
Conflict of interest: *Corporate-sponsored research: Research support to institution from Teva Pharmaceuticals: Sonpavde G, Jian W, Lerner SP*

2798 POSTER

Body composition as a predictor of dose limiting chemotherapy toxicity in patients with renal cell carcinoma treated with sunitinib

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Background: Predicting toxicity to chemotherapy is often difficult because of patient variation in drug metabolism and the narrow therapeutic window of most chemotherapeutic agents. Body composition is a prognostic factor in cancer patients (pts) and sarcopenia (i.e. muscle wasting) is associated with performance status, treatment toxicity and survival. Sunitinib is a standard first line oral chemotherapy for metastatic renal cell carcinoma (mRCC) that is associated with significant dose limiting toxicities. We investigated if body composition by computed tomography (CT) scan predicted dose limiting toxicity (DLT) from sunitinib in mRCC.
Methods: Pts with mRCC receiving sunitinib 50 mg as first line therapy between 2007–2012 were included. Ethical approval was obtained and prospectively maintained databases analysed. Skeletal muscle cross-sectional area at L3 was measured by CT, which had been done previously for diagnostic purposes. Sarcopenia was defined using published cut offs. Toxicity was assessed after 4 cycles of drug, according to Common Terminology Criteria for Adverse Events (CTCAE, v 4.0).
Results: 55 pts (43 male), mean age 64 yrs were included. 67% were overweight/obese (Body Mass Index [BMI] >25 kg/m^2). Sarcopenia was present in 33% (56% of normal BMI, 44% of overweight groups). Overall 40 pts (73%) experienced DLT (51% M, 100% F, p = 0.016. DLT occurred in <6 months in 53% (44% M vs 83% F, p = 0.016) and these pts who experienced DLT were older (mean 68 yrs vs 60 yrs, p = 0.01), had lower skeletal muscle mass (SMM) (51.8 cm^2/m^2 vs 59.4 cm^2/m^2, p = 0.012), and fat free mass (FFM) (51.4 kg vs 57.7 kg, p = 0.03), and received higher drug dose in mg/kg FFM (1.01 vs 0.89, p = 0.02). There was no difference in weight, BMI, fat mass or the drug dose (mg/kg). Common toxicities were gastrointestinal (65%) and fatigue (47%). 92% pts with SMM <25th centile experienced DLT compared to 57% pts with SMM >75th centile (p = 0.05). Pts <25th centile had an average of 5 toxicities vs 2 in those >75th centile (p = 0.003). All toxicities were more common in muscle wasted patients (p = 0.05). 77% (n = 10) of pts receiving a drug dose >75th centile (1.105 mg/FFM) experienced DLT in <6 months vs 44% (n = 17) receiving a dose <75th centile (<1.099 mg/FFM; p = 0.037).
Conclusions: Sarcopenia is prevalent in patients with mRCC, is an occult condition in pts with normal/high BMI, and is a significant predictor of DLT in pts receiving first line sunitinib. Our results highlight the potential use of baseline body composition to predict toxicity. There is an urgent need for validated biomarkers to help clinicians identify pts who may develop unnecessary toxicity from ineffective therapy. The role of sarcopenia in targeted therapy is evolving and its potential to predict toxicity should be further studied.
No conflict of interest.

2799 POSTER

Truly resistant patients with advanced renal cell carcinoma receiving first line sunitinib: Analysis of VEGF and VEGFR polymorphisms

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Background: Metastatic renal cell carcinoma treatment has radically changed. At present, therapeutic strongholds are TKIs directed against the angiogenetic pathway, such as sunitinib. Although in mRCC sunitinib demonstrated a huge activity profile, a large proportion of patients, ranging from 60−70%, is still refractory to such treatment approach. This latter group of patients is then exposed to potentially relevant toxicities without any hope for clinical benefit. We previously reported the predictive role of VEGF and VEGFR polymorphisms in mRCC patients treated with first-line sunitinib. The aim of our study was to evaluate the role of VEGF and VEGFR polymorphisms, in identifying a subgroup of patients truly resistant to treatment with sunitinib.
Methods: 84 formalin-fixed paraffin-embedded tissue blocks from mRCC patients receiving first-line sunitinib were tested for VEGF-A, VEGF-C and VEGFR-1,2,3 single nucleotide polymorphisms (SNPs). SNPs were correlated with PFS. Patients with a PFS under 3 months were considered truly resistant.
Results: 84 patients with metastatic renal cell carcinoma were available for our analysis, 19 of this were considered truly resistant (23%). Truly resistant patients express a TT polymorphism of rs833061 (p = 0.017), a CC polymorphism of rs699947 (p = 0.011) and a CC+CG polymorphism of rs2010963 (p = 0.009).
Conclusions: In our analysis patients with TT polymorphism of rs833061, a CC polymorphism of rs699947 and a CC+CG polymorphism of rs2010963 seemed to be truly resistant to sunitinib treatment. This subgroup of patients may, thus, be averted from unnecessary toxicities and could be considered for treatment with a different agent.
No conflict of interest.

2800 POSTER

MicroRNA profiling differentiates between urine samples from prostate cancer patients, kidney cancer patients, and patients without a cancer diagnosis

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Background: Screening biomarkers to identify asymptomatic patients with prostate or kidney cancer are not established. MicroRNAs are known to be a particularly robust species of RNA. We have performed microRNA profiling to identify biomarker candidates potentially useful as screening or recurrence biomarkers. To this end we have gathered clinical information and urine specimens from a cohort of 240 individuals: 80 patients with prostate adenocarcinoma, 80 patients with renal clear cell carcinoma, and 80 normal control individuals.
Material and Methods: Urine samples from prostate adenocarcinoma patients (no prostate massage performed; 4% Gleason score (GS) 6, 76% GS 7, 20% GS 8 or higher, 98% intermediate or high risk, 5% with N1 disease), renal clear cell carcinomas patients (63% stage I, 10% stage II, 19% stage III, 7% stage IV, 1% unknown), and normal control individuals (34% diverticulosis, 15% bariatric surgery, 14% diverticulitis, 15% hernia surgery, 10% hemorrhoids, 12% other non-cancer conditions) were collected. 10 urine samples of a single patient group were pooled. MicroRNAs from exfoliated cells and circulating microRNAs in 1 ml of urine were extracted together using the Norgen Biotek urine microRNA purification kit. The nCounter human miRNA assay kit, v2 (800 human mature miRNAs), was used according to manufacturer's guidelines with 100 ng RNA input. Data was log2 transformed, normalized using the global sum method, and analyzed using nSolver (nanoString Technologies).
Results: Here we present data of our pooled urine sample nanoString analysis representing 240 individuals. Several microRNAs were differentially expressed between prostate cancer, kidney cancer, and control patients. Consistent with previous data miR-21 was expressed higher in urine from either prostate cancer or kidney cancer patients compared to normal controls. Similarly, let-7a, miR-25, or miR-30d, all known tumor suppressors or oncomirs in various cancers, were identified in our comparisons. MiR-1268a, a microRNA not previously reported to be involved with kidney or prostate cancer biology, was found at high concentrations in urine from kidney or prostate cancer patients compared to normal controls. MicroRNA MiR-387e expression could differentiate between urine from kidney cancer patients and urine from prostate cancer patients.
Conclusions: Urine microRNA signatures are potentially useful as prostate adenocarcinoma and renal clear cell carcinoma screening biomarkers.
No conflict of interest.

2801 POSTER

Modulation of Regulatory T cells in long responsive patients with metastatic renal cell carcinoma (mRCC) treated with everolimus (EVE)

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Background: EVE has demonstrated activity in the treatment of mRCC after failure of VEGF-targeted tyrosine kinase inhibitors. mTOR inhibition

can also facilitate the induction of immunosuppressive regulatory T cells (Treg).
Methods: Our observational study reports retrospective data on EVE in routine use. Eligible patients (pts) had mRCC; were given EVE after prior first-line systemic therapies comprising anti-angiogenic agents. Blood Treg cells were evaluated by measuring CD4+CD25+Foxp3+ T cells by flow cytometry. The data were provided by each center and centralised. The focus was on immunologic assessment, the oncologic outcome and the clinical safety.
Results: Ten pts have been followed between Sept 2011 and March 2013. Baseline patient characteristics included median age of 66 [51−83] years old; 90% male; 100% with prior nephrectomy. Prognostic groups at the time of EVE initiation according to Heng classification were: good 60%, intermediate 20% and poor prognosis 20%. After initiation of EVE 75 % of patients were alive and 32 % free from disease progression at 24 months respectively. Overall response rate was 30 % and disease stabilization rate was 70%. At least one adverse event (AE) occured in 100 % of pts with 2 serious AEs. All grade common AEs were consistent with the toxicity profile of EVE. Treg cells number decreased significantly in the 3 (30%) patients who experienced the longer PFS (progression free survival). Stable Treg cells were found in 6 (60%) patients and increased in only one patient. In contrast, these cells greatly increased above 10% of total blood lymphocyte in one patient who progressed on EVE therapy.
Conclusions: These preliminary data suggest that everolimus could shape host immune responses, which in turn could contribute to the efficacy of the anti-mTOR therapy. Thus, we believe that it could be interesting to take into account the immunomodulatory effect of anti-mTOR drugs for the management of mRCC patients.
Conflict of interest: *Ownership: none. Advisory board: novartis. Board of directors: none. Corporate-sponsored research: none. Other substantive relationships: none*

2802 POSTER

Wilms' tumor gene 1 (WT1) expression in testicular germ cell tumors (TGCTs)

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Background: Wilms' tumor gene 1 (WT1) is a zinc-finger transcription factor essential for normal development of the urogenital system and male gonadal differentiation. Alterations in this gene have been found in a number of malignancies as well as in testicular dysgenesis syndromes. We studied WT1 expression and mutations to address its function in TGCT tumorigenesis and its possible clinical applications.
Material and Methods: Fresh-frozen samples of testicular germ cell tumors (TGCTs) and controls (9 seminomas, 18 non-seminomas, 2 stromal tumors, 27 non-malignant controls) were collected on a prospective basis. Expression of total WT1 and its isoforms was quantified by qPCR of our own design. Mutations in WT1 exons 7 and 9 (where the hot-spots are clustered) were detected by direct sequencing. The presence and distribution of WT1 protein was evaluated by standard immunohistochemistry (IHC) staining.
Results: The total WT1 expression was significantly lower in TGCTs than in non-malignant testicular tissues and stromal tumors − median 2 505 (range 219−32 584) WT1/ABLx10 000 in TGCTs vs. 23 200 (range 1 598−46 659) in non-malignant controls (Kruskal-Wallis, $p < 0.0001$). Of the four main WT1 isoforms, isoforms A and C missing the exon 5 (EX5[-]) were highly overexpressed in a proportion of TGCTs and both stromal tumors in comparison with controls − the mean EX5[+]/EX5[-] ratio was 2.19 (95% CI 1.88–2.50) for TGCTs vs. 4.05 (3.59–4.51) for non-malignant controls (Kruskal-Wallis, $p < 0.0001$). No WT1 mutation was found, the most common SNP (rs16754) with unknown clinical significance was present in 6/23 (26%) analyzed patients. Staining for WT1 protein was highly positive in the nuclei of Sertoli cells of control samples and undetectable in TGCT cells, corresponding well with the expression data on mRNA level.
Conclusion: Although the finding of total WT1 down-regulation in TGCTs we would interpret with caution (due to the lack of highly WT1-expressing Sertoli cells in TGCTs comparing to the control samples), the alteration of isoform expression pattern with a pronounced shift to [EX5-] variants in TGCTs and stromal tumors suggests that WT1 probably acts as a local tumor-suppressor gene in testicular tissues. Dysregulation of WT1 functions may be therefore associated with the process of malignant transformation and TGCT development.
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No conflict of interest.

2803 POSTER

Looking for predictive biomarkers for sunitinib in metastatic renal clear cell carcinoma (mRCC)

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Background: Properly validated molecular predictors of response to targeted agents are still lacking. Different molecular subtypes of clear cell RCC have been proposed by Gordan et al. It has been suggested that c-Myc may be driving proliferation in HIF2α expressing tumors in a growth factor independent manner. The predictive value of Focal Adhesion Kinase (FAK), a key signaling protein, has not been explored yet.
Material and Methods: An observational prospective study involving 9 hospitals was designed to evaluate in formalin-fixed tumor samples the predictive value of different biomarkers. We enrolled clear-cell mRCC patients (pts). Eligible pts were treated with Sunitinib in the 1st line setting following routine clinical practice.
Results: 81 pts were included, 34.5% were metastatic at diagnosis and time from diagnosis to Sunitinib was $\leqslant$1 year in 39.5%. 36% of pts had only one site of metastasis. 7%, 76.5% and 16% were ECOG PS 0, 1 and $\geqslant$2 and 18.5%, 58% and 12.5% favorable, intermediate and poor risk (MSKCC criteria). Median time of follow up was 21.02 months (m) (95% CI: 14.70–24.53). Median PFS (mPFS) was 11.5 m (95% CI: 7.2–14.8) in the favorable-intermediate risk group. Tumor samples were available for 69 pts. 10% were FAK positive (+) (any score: 1−3), 20% were PTEN+ and 27.5% were c-Myc+ (8% were c-Myc and HIF2a+). Both pts groups (+ and -) were well balanced, with the exception of differences in terms of MSKCC risk groups ($p > 0.05$) between FAK- and + pts and significant differences ($p < 0.05$) in terms of ECOG PS between PTEN- and + pts. A trend toward a lower mPFS was found in pts bearing tumours with FAK+ staining: 5.5 m vs.11.5 in -tumors (HR = 2.1275; 95% CI: 0.82–5.55; $p = 0.1136$); tumors with PTEN+ staining: 7.2 m vs. 11.5 in -tumors (HR = 1.8822; 95% CI: 0.98−3.6; $p = 0.0531$) and tumors with c-Myc+ staining: 5.9 m vs.10.9 in -tumors (HR = 1.4361; 95% CI: 0.76–2.72; $p = 0.2630$). Greater differences were found in the favourable-intermediate risk group: 5.9 m vs. 12.7 in C-Myc- tumors (HR = 1.7147; 95% CI: 0.85−3.5; $p = 0.128$) and a statistically significant worse mPFS was found in those pts with doble c-Myc/HIF2a+ staining: 4.3 m vs. 11.5 (HR = 2.6445; 95% CI: 1.027–6.8056; $p = 0.036$). A similar trend was also found in terms of overall survival.
Conclusions: These preliminary results suggest that predictive subgroups might be defined based on biomarkers such as cMyc/HIF2a, FAK and PTEN. Further validation with more pts will help to define their role in mRCC pts treated with Sunitinib.
No conflict of interest.

2804 POSTER

PI3K/AKT/mTOR and Wnt/β-catenin signaling components as a prognostic and predictor factors in patients with renal cell carcinoma treated with everolimus after anti-angiogenic therapy failure

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Background: Everolimus, an inhibitor of mTOR, has been approved for the treatment of patients with metastatic renal cell carcinoma (mRCC) The mTOR pathway can be activated by different proteins, including Wnt. The aim of this study was to search for predictive and prognostic factors in patients with mRCC treated with everolimus among the components of PI3K/AKT/mTOR and Wnt/β-catenin pathways.

Methods: Patients with mRCC after anti-angiogenic therapy failure were included in a prospective, one-arm, phase II study. Patients received everolimus 10 mg/day. A prospectively planned evaluation of potential biomarkers of PI3K/AKT/mTOR and Wnt/β-catenin pathway activation was conducted, focusing on VEGF in peripheral blood plasma, soluble E-cadherin (sE-cadherin) in serum and phosphorylated AKT 473, p70S6, Wnt-1, β-catenin, E-cadherin, cyclin D1, and p53 in the primary tumor. Additionally, 13 single nucleotide polymorphisms (SNP) of four genes were assessed, i.e. *AKT1, AKT2, PI3KCA* and *FRAP1*.
Results: The median age of the 58 patients included in the study was 60 years (range 41−78). In the univariate analysis, we found that the PIK3CA gene variant rs6443624 was significantly important [hazard ratio (HR): CC vs. AA = 2.08, 95% CI: 1.11–3.89, p = 0.0215 and HR: CC vs. AC + AA = 1.87, 95% CI 1.02–3.44, p = 0.0452). Expression of proteins involved in the PI3K/AKT/mTOR and Wnt/β-catenin pathways in primary RCC tumor tissues did not have a statistically significant association with progression free survival (PFS) and overall survival (OS). In the multivariate analysis, the independent favorable predictors for everolimus therapy were histological grade G3/4 [HR: 0.44 (95% CI 0.21–0.93, p = 0.0324)], normal LDH level before treatment [HR: 0.26 (95% CI 0.13–0.54, p = 0.0003)], a high concentration of sE-cadherin before treatment (above 66.74 pg/mL) [HR: 0.49 (95% CI 0.27–0.91, p = 0.0233)], the toxicity of the treatment regarding hypercholesterolaemia [HR: 0.40 (95% CI 0.21–0.76, p = 0.0054)] and neutropenia [HR: 0.31 (95% CI 0.14–0.67, p = 0.0032)]. In multivariate analysis, we observed that the favorable independent prognostic factors were normal LDH levels before qualifying for this treatment [HR: 0.41 (0.21–0.79, p = 0.0077)], previous therapy with sorafenib [HR: 0.36 (95% CI, 0.17–0.75, p = 0.0065)], and a neutropenia [HR: 0.19 (95% CI, 0.07–0.52, p = 0.0054)].
Conclusions: Serum sE-cadherin and LDH may be new simple tests which, together with monitoring toxicity such as neutropenia and hypercholesterolemia, could predict improved outcomes with everolimus therapy. Therapy with sorafenib and assessments of the LDH level and the incidence of neutropenia could predict the prognosis of patients with metastatic RCC. Encouraging results of our study should guarantee the need for further studies planned prospectively in patients with RCC.
No conflict of interest.

2805 POSTER

Prognostic significance of FDG-PET/CT after two cycles of first-line chemotherapy in advanced transitional cell carcinoma

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Background: A risk-adapted treatment for advanced transitional cell carcinoma (TCC) is still lacking and it may guide new trial designs with novel agents/combinations for early-recognized unresponsive patients (pts). [18F]fluorodeoxyglucose Positron Emission Tomography/computed tomography (FDG-PET/CT) is increasingly used by many centers for (re)staging in TCC. We prospectively assessed the value of FDG-PET/CT after 2 cycles of upfront chemotherapy.
Methods: In a single-center trial, pts with newly-diagnosed advanced/metastatic TCC receiving first-line MVAC underwent CT and FDG-PET/CT at baseline, a restaging with FDG-PET/CT after 2 cycles only, and a CT and/or FDG-PET/CT at the end of treatment (4−6 cycles). A CT scan every 3 months was done in the follow up (FUP) period. EORTC criteria for metabolic response were applied. The end-points were progression-free (PFS) and overall survival (OS). PFS and OS rates were estimated with the Kaplan–Meier method; univariable (UVA) and multivariable (MVA) Cox models were also fitted. Pre-specified prognostic variables were presence of visceral metastases, nodal/soft tissue disease, and early PET/CT response.
Results: 31 pts were accrued in the time-frame 05/2010−10/2012. All of them received MVAC regimen and had an ECOG-PS 0, 9 pts had an upper tract TCC, 15 had a visceral and 29 a nodal or soft-tissue disease. After 2 cycles of MVAC, 6 pts (19.3%) had a complete (CR) and 17 (54.8%) a partial metabolic response (PR), 4 pts had stable disease (SD). Median FUP was 18 months (IQR: 10−47). Those with metabolic response (CR+PR) had a median (95% CI) PFS=8.0 (7−11) mos compared to 3.0 (2−5) mos in patients without response (p = 0.024). Those with prior response had a median OS of 19.0 (9−21) mos, compared with 9.5 (6−11) mos for those without response (p = 0.813). A significant association was observed between early PET response and PFS in both UVA and MVA (p = 0.027 and p = 0.023, respectively, [Table]).
Conclusion: PET response after 2 cycles of first-line MVAC in pts with TCC seemed to confer an independent prognostic impact on PFS, similarly to the presence of visceral metastases. An international cooperation to corroborate the role of early metabolic response in advanced TCC is warranted.
No conflict of interest.

Table: Cox models for progression-free survival

	Univariable			Multivariable		
	HR	95% CI	p	HR	95% CI	p
PET response No (SD,PD) *vs* Yes (CR,PR)	2.87	(1.13, 7.31)	0.027	3.88	(1.21, 12.42)	0.023
Visceral disease Yes *vs* No	3.16	(1.29, 7.70)	0.012	3.77	(1.41, 10.04)	0.008
Nodal/soft tissue disease Yes *vs* No	3.43	(0.73, 16.08)	0.118	1.62	(0.25, 10.36)	0.611

2806 POSTER

Angiopoietin 2 (Ang-2) as prognosis biomarker in clear cell renal cell carcinoma (ccRCC) patients

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Background: Tumor progression and metastasis are critically dependent on the tumor's sustained ability to induce the growth of new blood vessels to nourish the growing tumor and to remove metabolic waste products. The angiopoietins Ang-1 and Ang-2 have critical role in tumor angiogenesis. Ang-2 acts in concert with the vascular endothelial growth factor and receptor (VEGF/VEGFR) to control vessel assembly during tumor progression.
ccRCC, the most common histological type of RCC, is a heterogeneous group of entities with variable clinical outcomes, is characterized by deregulation of angiogenic pathways. Up to now no useful prognostic biomarker has been developed in ccRCC, so our aim was to determine the value of tissular tumor Ang-2 expression in the outcome of these patients.
Material and Methods: Antigen expression was analyzed by immunohistochemistry on formalin fixed paraffin embedded ccRRC primary tumors [men: n = 22, age: Md 54 years (range 46−72); women: n = 23, age: 65 (44−82)], from patients who underwent a surgical resection as first treatment. A case was considered positive when more than 50% of the tumor cells presented specific staining. The relationships between the expression of the antigen and the known prognostic factors in ccRCC were analyzed by Chi-square test. Prognostic evaluation was analyzed with the log rank test and the multivariate Cox model.
Results: We observed that 80% of ccRCC tumors expressed Ang-2 at membrane level and more than 90% of the cases also expressed the antigen at cytoplasmic level. No association was observed between the expression of Ang-2 and other prognosis factors like ionized calcium and hemoglobin circulating levels, clinical stage and histological grade. Kaplan–Meier curves and Log rank test showed that positivity for Ang-2 was associated with a lower overall survival at five years. Multivariate analysis indicated that Ang-2 expression was not influenced by other clinico-pathological prognostic parameters.
We conclude that tumor positivity for the expression of Ang-2 in this group of ccRCC patients can be considered as an independent prognostic marker associated to a worse outcome.
Conclusions: We conclude that tumor positivity for the expression of Ang-2 in this group of ccRCC patients can be considered as an independent prognostic marker associated to a worse outcome.
No conflict of interest.

2807 POSTER

Expression of CD47 in bladder cancer

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Background: CD47, a member of immunoglobulin superfamily, is expressed by various cancers. It has been reported that CD47 expression protects tumor cells from phagocytosis by transmitting an inhibitory signal to macrophages.
Material and Methods: The present study aimed at studying CD47 expression by bladder cancer. We performed immunohistochemical analysis to eveluate CD47 expression levels in three groups; subjects undergone to transurethral bladder resection (TUR-B) outside of malignancy (tumor negative, control group), superficial bladder cancer (BC) and invazive BC.
Results: Between 2006 and 2012, 88 subjects were evaluated in superficial BC (n = 41), invazive BC (n = 14) and control groups (n = 33), retrospectively. Immunohistochemical stainning was performed on paraffin-embedded tissue sections. Median age of the patients and control were 61.5 (range, 22−91) and 55 (range, 16−77), respectively. Fourteen patients were high grade and 10 patients had lymph node positive disease. We found that CD47 expression increased significantly (Kruskal Walls test, p = 0.02,) on bladder cancer. The three groups of patients were compared according to Mann-Whitney U test. The significance of difference between each group was calculated ((the superficial BC and control (p = 0.003), invazive BC and control (p = 0.005) and superficial BC and invazive BC (p = 0.301)). Expression of CD47 was elevated significantly in BC.
Conclusions: Overexpression of CD47 may be a critical for bladder cancers in escaping from immunesurveillance.
No conflict of interest.

2808 POSTER

Prognostic significance of apoptotic marker in non muscle invasive bladder cancer treated by bacillus Calmette Guerin immunotherapy

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Background: A critical hallmark of cancer cell survival is evasion of apoptosis. This is commonly due to overexpression of anti-apoptotic proteins such as Bcl-2 which bind to the pro-apoptotic proteins and inhibit their function. It has been reported previously that Bcl-2 is overexpressed in a variety of cancers and is associated with treatment resistance. However, its impact on superficial bladder cancer recurrence after bacillus Calmette Guerin (BCG) immunotherapy has yet to be investigated. The aim of the present study was to assess the prognostic significance of Bcl-2 expression in terms of recurrence after BCG immunotherapy in superficial bladder cancer.
Material and Method: Bcl-2 positivity was detected by immunohistochemical analysis on frozen pre-treatment biopsies obtained transurethrally from 28 patients, having superficial bladder cancer. All patients were treated with BCG immunotherapy and followed up during 26 months. The prognostic significance of tumour stage, grade, loci number, tumour size, age and Bcl-2 in determining the risk for recurrence was studied with both univariate and multivariate methods of analysis.
Result: According to univariate analysis of the prognostic significance for tumour stage, grade, tumour size, loci number, age and bcl-2 expression in patients, the pT1 stage and high grade seem to be associated in a statistically significant manner with higher risk for recurrence (P = 0.004, P = 0.004, respectively). In the other hand, multivariate Cox regression's analysis selected the model involving stage, age and Bcl-2 expression as quasi-independent predictor of recurrence after BCG immunotherapy (p = 0.005, p = 0.020, p = 0.020, respectively).
Conclusion: The expression of Bcl-2 seems to offer prognostic information in predicting those patients with high risk superficial bladder cancer who may recur in a short follow-up period. These findings require further investigations on larger cohort in order to ascertain new molecular markers of the response to BCG immunotherapy.
No conflict of interest.

Proffered Papers Session (Sat, 28 Sep)
Genitourinary Malignancies − Prostate Cancer

2850 ORAL

CA184-043: A randomized, multicenter, double-blind phase 3 trial comparing overall survival (OS) in patients (pts) with post-docetaxel castration-resistant prostate cancer (CRPC) and bone metastases treated with ipilimumab (ipi) vs placebo (pbo), each following single-dose radiotherapy (RT)

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Background: Ipi boosts anticancer immunity by targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4) to deplete regulatory T cells and activate cytotoxic T cells by inhibiting negative signaling associated with CTLA-4. In metastatic melanoma, ipi demonstrated 4-year OS rates of 19−36% in phase 2 studies and significant OS prolongation in phase 3 studies. Clinical antitumor activity was also seen in phase 1/2 studies in CRPC.
Study Design: Following 1:1 randomization, pts with post-docetaxel CRPC received bone-directed RT at 8 Gy before either 10 mg/kg ipi (N = 399) or pbo (N = 400) every 3 weeks x 4, with every-3-month maintenance for eligible pts. The primary endpoint was OS.
Results: Baseline characteristics were balanced across arms and were indicative of advanced disease (48% had baseline pain of $\geqslant$4 per BPI). In the intent-to-treat analysis (N = 799), the HR for OS numerically favored ipi (HR = 0.85; 95% CI=0.72–1.00; p = 0.053). Median OS for ipi was 11.2 months (95% CI=9.5–12.7) vs 10.0 months (95% CI=8.3–11.0) for pbo. Respective 1- and 2-year OS rates for ipi vs pbo were 47% vs 40% and 26% vs 15%. Median progression-free survival (PFS) also favored ipi over pbo (HR = 0.70; 95% CI=0.61–0.82), as did prostate-specific antigen (PSA) declines of $\geqslant$50% in evaluable pts (13.1% vs 5.3%, respectively). Pre-specified subset analyses suggest that ipi may be most active in pts with no visceral disease and favorable laboratory prognostic factors (eg, decreased alkaline phosphatase, elevated hemoglobin). A post hoc analysis in pts who received treatment (N = 779; N = 387 for ipi vs N = 392 for pbo) showed an improvement in OS which favored ipi (HR = 0.84; 95% CI=0.71–1.00; p = 0.0498).
Treatment-related adverse events (AEs) were common and mostly immune-related AEs (irAEs). Grade $\geqslant$3 irAEs in the ipi vs pbo arms, respectively, were GI (18% vs 1%), liver (5% vs 1%), endocrine (2% vs 1%) and dermatologic (1% vs 0%); most were reversible using standard ipi management algorithms. Incidences of drug-related death and GI perforation were 1% and 0.6%, respectively.
Conclusions: This phase 3 study supports activity of ipi in advanced CRPC by showing a numerical improvement in OS, although statistical significance was not achieved. Drug-related AEs were similar to those reported in melanoma. Pre-specified subset analyses suggest CRPC pts with lower disease burden may experience the most benefit. An ongoing phase 3 study in chemotherapy-naive CRPC is prospectively evaluating this population.
Conflict of interest: *Ownership: McHenry: Bristol-Myers Squibb (BMS), self, Gagnier: BMS, self. Advisory board: Gerritsen: Aglaia Biomedical Ventures, Amgen, Bayer, BMS, Ipsen, Janssen, Merck, and Sanofi, Kwon: National Cancer Institute GU Steering Committee, Fizazi: BMS, self, compensated, van den Eertwegh: BMS, Astellas, Janssen-Cilag B.V., Sanofi, self, compensated, Scher: compensated: Dendreon, Endo/Orion Pharmaceuticals, Genentech, Novartis, Ortho Biotech Oncology Research and Development (compensated-donated), uncompensated: Aragon, BMS, Celgene, Exelixis, Foundation Medicine, Janssen, Johnson and Johnson Pharmaceutical & Development, LCC, Medivation, Millennium, Pfizer, Sanofi Aventis, Takeda Millennium, Ventana − Member of Roche Group. Drake CG: consultant for Amplimmune, Astellas, Bristol-Myers Squibb, Celgene, Dendreon, Janssen, and Regeneron. Corporate-sponsored research: Logothetis: Johnson & Johnson, self, Scher: Aragon, BMS,*

Exelixis, Janssen Research & Development LLC, Janssen Services, Inc, Medivation, Beer: BMS, self. Other substantive relationships: Gerritsen: speaker's honoraria from Astellas, BMS, and Janssen, Kwon: intellectual property licensed by BMS regarding unrelated B7-H1 Ligand Technologies, Fizazi: honoraria from BMS, self, van den Eertwegh: Honoraria for presentations about ipilimumab/prostate cancer, self[BMS, Sanofi, Janssen-Cilag], Logothetis: honoraria from Johnson & Johnson, self, McHenry: employed by BMS, Gagnier: consultant/advisory role, BMS, self, compensated, employed by BMS. Drake, CG: has patents/royalty with Amplimmune and Bristol-Myers Squibb.

2851 ORAL

A validated prognostic model for predicting overall survival in patients with metastatic chemotherapy naive castrate-resistant prostate cancer

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Background: Although several prognostic models for overall survival (OS) have been developed for patients (pts) with mCRPC, they are outdated and not applicable to contemporary pts. This work sought to develop and validate a contemporary prognostic model that can be used to predict OS in metastatic chemotherapy naive castrate-resistant prostate cancer (mCRPC) pts.

Materials and Methods: Data from a phase III trial of 1,050 chemotherapy naive mCRPC pts randomized to bevacizumab plus docetaxel or placebo plus docetaxel were used (CALGB 90401). The CALGB 90401 data was randomly split into training (n = 705) and testing (n = 345) sets. A separate data set from the ENTHUSE 33 phase III trial, consisting of 942 men randomly assigned to either zibotentan plus docetaxel or placebo plus docetaxel, served as a second testing set used for independent external validation. Adaptive least absolute shrinkage and selection operator (LASSO) selected eight baseline factors prognostic for OS in the training set. A predictive score was computed from the estimated regression coefficients and used to classify patients into low and high risk groups in the two testing sets. The model was assessed for its predictive accuracy using the area under the curve (AUC) on the two testing sets.

Results: The final model included: ECOG performance status, extent of disease (categorized as lymph node only; bone or bone+lymph node; or any visceral metastases), LDH (defined as > upper limit of normal), opiate use, albumin, hemoglobin, PSA, and alkaline phosphatase. The median OS values in the high and low risk groups, respectively, in the internal testing set (CALGB 90401) were 17 and 30 months with a hazard ratio (HR) = 2.2 (p-value<0.0001); and in the external testing set (ENTHUSE 33) were 14 and 26 months (HR = 2.9, p < 0.0001).

The AUC for the model with the risk score as a continuous variable was 0.73 (95% CI 0.70–0.73) and 0.76 (95% CI 0.72–0.76) on the two testing sets (CALGB 90401 and ENTHUSE 33, respectively).

Conclusions: A contemporary prognostic model for OS in chemotherapy naive mCRPC pts was developed and validated on internal and independent external data set. This model can be used to counsel pts, as well as select pts to participate in clinical trials on the basis of their prognosis.

No conflict of interest.

2851A ORAL

Evaluation of a composite biomarker panel including circulating tumor cell (CTC) enumeration as a surrogate for survival in metastatic castration-resistant prostate cancer (mCRPC)

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Background: Multiple new therapies prolong survival for mCRPC, making demonstration of a survival benefit with newer agents more difficult. Qualified surrogate biomarkers for survival benefits are a critical unmet need. CTC number is prognostic pre- and post-treatment and showed a 34% and 41% conversion rate from unfavourable (⩾5 cells/7.5 mL) to favourable (⩽4 cells/7.5 mL) in phase 2 trials of abiraterone acetate (AA) +/− prednisone (P). We explored CTC enumeration as a potential surrogate for survival in the phase 3 registration trial of AA+P in mCRPC post-chemotherapy (COU-AA-301; clinicaltrials.gov NCT00638690).

Material and Methods: Biomarkers, including CTC count (CellSearch®; Veridex, Raritan, NJ) and lactate dehydrogenase (LDH) levels, were assessed as a secondary objective in COU-AA-301 at baseline, 4, 8, and 12 weeks; prostate-specific antigen was recorded every 12 weeks. Biomarker data at each fixed time point, differences from baseline, relative differences from baseline, and conversion from unfavourable to favourable (for CTC) were analyzed. A trichotomous surrogate biomarker panel based on 12-week landmark data categorized patients as low-risk (CTC ⩽4), intermediate-risk (CTC ⩾5, LDH ⩽250 IU/L), or high-risk (CTC ⩾5, LDH >250 IU/L). Individual level surrogacy was assessed using Prentice criteria and trial level surrogacy by measuring the association between the treatment effect on the surrogate and survival within each country and randomly generated pseudo substudies.

Results: Complete biomarker data at 12 weeks were available from 711 of 1195 patients; some study sites/countries were unable to assess CTCs. All Prentice criteria were satisfied at the individual level: survival differed between the AA and placebo arms (p = 0.034); surrogate distribution differed by treatment (p < 0.001); the surrogate had strong discriminatory power to distinguish low- and high-risk patients (concordance probability estimate [CPE] = 0.79); and the treatment effect on survival was explained by the surrogate. There was only a weak association between the surrogate and survival at the trial level, potentially related to the small sample sizes of the groups studied.

Conclusions: In COU-AA-301, the 12-week CTC number and LDH level biomarker panel demonstrated survival surrogacy at the individual patient level in mCRPC progressing post chemotherapy. Individual and trial level surrogacy will be further explored in other fully accrued phase 3 trials in this patient population.

Conflict of interest: *Advisory board: Aragon, Celgene, Exelixis, Foundation Medicine, Janssen, Johnson and Johnson, Medivation, Millennium, Takeda Millennium (all uncompensated), Astellas, Bristol-Myers Squibb, Dendreon, Endo/Orion Pharmaceuticals, Genentech, Janssen, Johnson & Johnson, Medivation, Novartis, Ortho Biotech Oncology Research and Development, Sanofi Aventis, Senior Scientific LLC. Board of directors: IDDI S.A. Corporate-sponsored research: Aragon, AstraZeneca, Bristol-Myers Squibb, Exelixis, Genentech, Janssen Research & Deveopment, Janssen Services Inc, Medivation. Other substantive relationships: Astellas, IDDI S.A., Ipsen, Janssen, Janssen-Cilag, Johnson & Johnson, Medivation, Millennium, Novartis, Roche/Ventana, Takeda, The Institute of Cancer Research, Sanofi-Aventis, Veridex*

2852 ORAL

Enzalutamide (ENZA) monotherapy in hormone naive prostate cancer (HNPC): Complete analysis of a phase 2 study

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Background: Compared with castration therapy (LHRHa), monotherapy with bicalutamide (Bic) maintains quality of life (QoL) but has lower efficacy. ENZA, a US FDA-approved oral androgen receptor (AR) inhibitor with higher AR-binding affinity than Bic, increases overall survival for patients (pts) with post-docetaxel metastatic castration-resistant PC. This phase 2 open-label study assessed ENZA monotherapy in pts with HNPC and noncastrate testosterone (T; ⩾230 ng/dL).
Materials and Methods: Pts with any stage HNPC requiring hormonal therapy received ENZA 160 mg/d for 25 wks. Primary endpoint was prostate-specific antigen (PSA) response (⩾80% decline at wk 25). Other endpoints were endocrine levels, pharmacokinetics, safety, metabolic changes, and QoL. Analyses were performed after pts completed 25 wks of ENZA.
Results: 67 pts were treated. Median age was 73.0 y; 38.8% had metastatic disease, and 35.8% and 23.9% had prior prostatectomy and radiation, respectively. Plasma ENZA levels reached steady state after ~4 wks. The primary endpoint (PSA decline ⩾80%) was reached in 62 pts (92.5%; 95% CI, 86.2–98.8%); median PSA decrease was −99.6% (95% CI, −100.0 to −86.5).
Table 1 shows results in metastatic (M1) vs non-metastatic (M0) disease. Mean serum T and estradiol levels increased by 114.3% and 71.7%, respectively. Mean femoral neck bone mineral density (BMD) increased by 0.4±2.3%. Mean lean body mass decreased by 4.2±3.4%, and fat body mass index increased by 6.9±12.1%. Insulin sensitivity (measured by HOMA-IR) increased by 45.1±192.5%. Frequent treatment-emergent AEs were grade 1: gynecomastia (35.8%), fatigue (34.3%), nipple pain (19.4%), and hot flush (17.9%). There were no serious drug-related AEs. Sexual function AEs (4.5%) were grade 1 and considered possibly or not related to study drug. Per EORTC QLQ-C30, global health status was maintained from baseline to wk 25.
Conclusions: ENZA monotherapy is associated with a high PSA response rate, rapid PSA decline regardless of metastatic disease, and stable BMD and QoL. Endocrine changes and AEs were consistent with AR inhibition. Top-line results regarding 1-year persistence of PSA response will be discussed.
Funded by Astellas Pharma Global Development, Inc. and Medivation, Inc.; NCT01302041, active/not recruiting.

Table 1.

	M0 (n = 41), n (%)	M1 (n = 26), n (%)	Total (n = 67), n (%)
PSA decline ⩾80%	38(92.7)	24(92.3)	62(92.5)
PSA decline ⩾90%	37(90.2)	24(92.3)	61(91.0)
PSA ⩽4 ng/mL	38(92.7)	24(92.3)	62(92.5)
PSA ⩽0.1 ng/mL	20(48.8)	10(38.5)	30(44.8)

Conflict of interest: *Other substantive relationships: M. Smith − Consultancy for Astellas and Medivation P. Rathenborg − Consultancy for Herlev University Hospital, Denmark A. Heidenreich − Consultancy for Astellas P. Iversen − Grant for Dept of Urology, Rigshospitalet, Denmark, Support for travel and Honoraria paid by Astellas and Medivation E. Baskin-Bey − Employee of Astellas F. Perabo − Employee of Astellas D. Phung − Employee of Astellas B. Tombal − Consultancy for Astellas and Medivation*

2853 ORAL

An open-label, phase I/II safety, pharmacokinetic, and proof-of concept study of ODM-201 in patients with progressive metastatic castration-resistant prostate cancer (CRPC)

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Background: ODM-201 is a new generation androgen receptor (AR) inhibitor with higher binding affinity for the AR and a superior anti-cancer activity in prostate cancer xenograft models compared to enzalutamide. ODM-201 and its major metabolite ORM-15341 inhibit the AR nuclear translocation.
Methods: The phase I part explored six ODM-201 dose levels ranging from 200 mg to 1800 mg given orally divided in 2 daily doses, with a parallel pharmacokinetic analysis, in patients (pts) with metastatic CRPC (mCRPC). The phase II expansion part randomly explored three dose levels (200 mg, 400 mg, 1400 mg) in four cohorts of pts defined according to whether they had received chemotherapy and a CYP17 inhibitor (CYP17i) (mostly abiraterone) or not. The accrual is completed.
Results: Overall, 136 pts were recruited in the study (phase I: 24; phase II: 112). No dose-limiting toxicity was found in the phase I part. The pharmacokinetic data indicated that ODM-201 has linear kinetics up to 1400 mg with T1/2 of 5.5−8.7 h on Day 1. 78/108 (70%) currently evaluable pts experienced a PSA decline during the first 12 weeks, including a >50% PSA drop in 44/108 (41%). In chemotherapy and CYP17i naive pts, 28/43 pts (65%) experienced a >50% PSA decline, and the median PSA change was −62% during 12 weeks (200 mg −55%, 400 mg −79% and 1400 mg −85%). In chemotherapy pretreated but CYP17i naive pts, 14/33 pts (42%) experienced a >50% PSA decline, and the median PSA change was −43% during 12 weeks (200 mg −53%, 400 mg −16% and 1400 mg −51%). In the post-CYP17i group 13/32 (41%) pts experienced a PSA decrease. Median PSA change in these pts was −26%. In the meeting the radiological progression free survival, circulating tumor cell data and exploratory biomarkers will be presented. ODM-201 was well tolerated with no treatment-related SAEs. The most common AEs included grade 1−2 back pain (16 pts) (one grade 3), fatigue (14 pts), arthralgia (13 pts) (one grade 3), nausea (11 pts), constipation (10 pts), musculoskeletal pain (9 pts), pain (9 pts), diarrhea (8 pts), peripheral edema (8 pts), decreased appetite (8 pts), headache (7 pts), insomnia (7 pts) and asthenia (7pts). No seizures were observed at any of the dose levels.
Conclusion: ODM-201 is well tolerated and is associated with a high activity in pts with mCRPC, including pts with progression after docetaxel and a CYP17i.
Studies are registered as NCT01317641 and NCT01429064.
Conflict of interest: *Ownership: ARADES trial is sponsored by Orion Corporation Orion Pharma and Endo Pharmaceuticals. NCT01317641 and NCT01429064. Corporate-sponsored research: Study investigators: K.Fizazi, P.Bobo, R.Jones, V.Kataja, N.James, J.Garcia, A.Protheroe. Other substantive relationships: Orion Corporation Orion Pharma employees: A. Vuorela, L. Mattila, M.Mustonen*

2854 ORAL

The effects of enzalutamide (ENZA) in combination with abiraterone acetate (AA) in patients with bone metastatic castration resistant prostate cancer (mCRPC)

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Background: Co-targeting the androgen receptor and paracrine androgen biosynthesis in mCRPC may result in a more potent androgen signaling inhibition than either approach alone. We conducted this study to determine the safety, effects on androgen signaling and steroid metabolome and screen for efficacy of ENZA with AA (plus prednisone).
Material and Methods: Study patients (pts) had progressive mCRPC with serum testosterone (S-T) ⩽50 ng/dL, bone metastases and agreed

to serial Bone Marrow biopsy. Pts received oral ENZA 160 mg QD in combination with AA 1g QD plus prednisone 5 mg bid. Pts were monitored at 4 week intervals with liver function, electrolytes, CBC, ECG and physical examinations. Modulation of tumor microenvironment is assessed by immunohistochemistry and of the androgen metabolome by LC Mass Spectrometry (blood and bone marrow). mCRPC was assessed clinically, by serum markers (PSA, alkaline phosphatase) and by imaging (bone scan, CT scan).

Results (preliminary): Since July 2012, 41 of 60 men have been enrolled with median age 65 yrs (range 40−82), PS-ECOG 1 (range 0−2) and baseline PSA concentration 23.3 ng/ml (range 1–606.3). Gleason Score (GS) at diagnosis was ⩾8 in 28/37 (76%), [GS ⩾9 21/37 (57%)/4 pts not available]. Seventeen (41%) had ⩾20 bone lesions, 14 (34%) lesions in lymph nodes and 2 (5%) visceral metastases while 6 (15%) had received prior chemotherapy.

To date PSA changes in pts on treatment ⩾12 weeks: maximum PSA decline ⩾50% [21/29 (72%)], ⩾90% [14/29 (48%)], to PSA ⩽1ng/ml level [3/29 (10%)] and PSA rise above baseline [5/29 (17%)].

Eleven pts had Grade 3 adverse events including 4 pts with liver function test increases which normalized after AA discontinuation,1 pt with hypokalemia, 1 pt with cardiac disorders and 1 pt with femoral neck fracture. No Grade 4 adverse events.

Median baseline Serum Testosterone (S-T) was 8.5 pg/ml (range <1–47.7) and Bone Marrow T (BM-T) was 6.5 pg/ml (range <1–33.6). Following 8 weeks treatment S-T and BM-T were undetectable (<1pg/ml) in 19/23 evaluable pts.

Conclusions: ENZA+ AA combination has a favorable safety profile and depletes androgens in the blood and marrow in pts with mCRPC. Promising PSA response profile was observed: 72% of pts achieved a ⩾50% PSA decline, 48% achieved ⩾90% decline and 3 pts have undetectable PSA, following ⩾12 weeks of treatment.

Conflict of interest: *Other substantive relationships: A. de Haas-Amatsaleh − Employee of Astellas F. Perabo − Employee of Astellas D. Phung − Employee of Astellas*

2855 ORAL

Degarelix versus luteinising hormone-releasing hormone (LHRH) agonists: Safety outcomes from six comparative randomised clinical trials

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Background: LHRH agonists, used to treat men with hormone-dependent advanced prostate cancer, are associated with an increased risk of cardiovascular disease (CVD) and death. The antagonist degarelix has a distinct mechanism of action and comparative trials have shown differences in disease control between these agents. The comparative incidence of disease-related adverse events (AEs) and CVD have now been analysed.

Materials and Methods: Data were pooled from 6 prospective, comparative randomised trials (sponsored by Ferring Pharmaceuticals) of degarelix vs. LHRH agonists (n = 2328). 1686 patients received 1 year of treatment and 642 patients had 3 to 7 months of treatment. Events were analysed using Kaplan Meier plots, a log-rank test for homogeneity and adjusted for common baseline factors (Cox proportional hazard model).

Results: Baseline characteristics including age, testosterone, PSA, disease stage and CVD history were balanced between groups. 1491 patients received degarelix and 837 a LHRH agonist (goserelin, n = 458; leuprolide, n = 379). Overall probability of any urinary tract AE ($p < 0.0001$) and of a urinary tract infection ($p = 0.001$) were significantly lower in patients on degarelix. The overall probability of joint related signs and symptoms was significantly reduced in the degarelix group vs. the LHRH agonist group (5.3% vs. 8.1%, respectively; $p = 0.0116$). Overall probability of fracture (<1% vs. 2%, $p = 0.0234$) was significantly reduced in men receiving degarelix. Fracture risk in men >70 years old was also lower in the degarelix group (HR = 0.264, 95% CI 0.091–0.761; $p = 0.0137$). The risk of a CV event was significantly lower in patients receiving degarelix (HR = 0.597, 95% CI 0.380–0.938; $p = 0.0253$). In patients with CVD history the findings remained significant (HR = 0.476, 95% CI 0.260–0.871; $p = 0.0160$). The risk of a serious CV event was also significantly lower in patients with CVD history receiving degarelix (HR = 0.367, 95% CI 0.174–0.775; $p = 0.0086$).

Conclusions: This analysis of 2328 men demonstrates that, during the first year of treatment, those treated with degarelix had a reduced occurrence of disease-related side effects including urinary tract symptoms and fractures. The risk of a CV event or serious CV event was significantly lower for men receiving degarelix vs. a LHRH agonist.

Conflict of interest: *Advisory board: Amgen, Astellas, AstraZeneca, Bayer, Ferring, GlaxoSmithKline, Janssen-Cilag, Medivation, Novartis, sanofi-avenis, Teva. Other substantive relationships: Ferring employee: BE Persson*

Poster Discussion Session and Poster Session (Mon, 30 Sep)
Genitourinary Malignancies − Prostate Cancer

2856 POSTER DISCUSSION

Going beyond age for comorbidity evaluation in prostate cancer patients treated with radiation

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Introduction: Prostate cancer management involves a balance between the risks of cancer death against those from other causes. This study evaluates the potential value of several simple comorbidity indices in a large radiotherapy cohort.

Methods: 1956 men with localised prostate cancer treated with radical radiotherapy between 2000–2007 were studied. Tumour features, androgen deprivation usage, age, number of prescription medications and Adult Comorbidity Evaluation 27 Index (ACE-27) were recorded. Death from prostate cancer (DPCa) and death from other causes (DOthC) were analysed as competing causes of death using a competing risks model, with discrimination assessed using the concordance index.

Results: Patients were treated with external beam radiation only (73%) or with high-dose-rate brachytherapy boost (21%) or low-dose-rate brachytherapy (6%). Median age was 70 (95% CI 53−79). 48% had ACE-27=1, 16.5% had ACE-27=2, and 3% had ACE-27=3. ACE-27 scores correlated with patient's number of prescription medications (median number of prescriptions=2, 95% CI 0−7). Tumour features were independent of ACE-27 scores. Median follow up was 66.5 months.

Estimated cumulative incidence of DOthC at 10 years was 30.3% (95% CI 24.1–37.4%), and for DPCa was 18.0% (95% CI 13.0–24.4%). In the low/intermediate risk group (n = 1026) there was a 3.4-fold predominance of DOthC inside 10 years, with a cumulative incidence of 33.5% (95% CI 23.7–45.1%) of DOthC compared to 9.8% (95% CI 4.9%-16.1%) risk of DPCa. High risk men had approximately equal rates of DPCa and DOthC at 10 years.

Multivariable analysis showed age, ACE-27 score of one or more and number of medications to have significant associations with DOthC ($p < 0.002$ for all). No tumour related variables had an impact on DOthC. The discriminatory performance (C-Index) of univariable models of age, ACE-27 or medication number was 0.589, 0.612 and 0.608 at 10 years respectively. A multivariable model incorporating all 3 variables resulted in C-Index of 0.644. A simple prognostic score incorporating these variables facilitates usage.

Conclusion: Age, ACE-27 score and number of medications act as independent prognostic factors for DOthC in prostate cancer patients and can be considered in clinical setting to aid in predicting a patient's life expectancy and treatment decisions. Objective assessment of comorbidity can potentially reduce the rate of radiotherapy that will ultimately be futile due to comorbid deaths.

No conflict of interest.

2857 POSTER DISCUSSION

Mortality rate 60 days following radical prostatectomy in France

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Background: The increasing use of PSA testing for prostate cancer screening, in particular in ageing populations, leads to a rise in the number of overdiagnosed prostate cancers and associated overtreatment. A major element of treatment is radical prostatectomy (RP). It is of utmost importance to rely on good statistics on demographics of patients and mortality associated with this procedure.

Material and Methods: RP in men aged 40 and over conducted in France between 2007 and 2011 were retrieved from the French Technical Agency for Information on Hospitalization (ATIH) database. 637 hospitals (public and non-profit private) performing RP were included. Basic patient data such as age, place of residence, type of surgery (open/laparotomy vs. laparoscopy) and Charlson comorbidity index were available. For each patient, vital status 60 days following surgery was retrieved. Income of patients was estimated using the median income of the 'commune' of residence of patients.

Results: In the study period, 120,333 RP were performed. 68,106 were open RP and 52,227 were laparoscopic RP. The number of RP per year was stable during the study period. Patients undergoing laparoscopy were significantly younger than patients undergoing laparotomy (62.94 vs. 63.31 years, p<2.2*10−16). At 60 days following RP, a total of 183 deaths were registered, corresponding to a crude mortality rate of 0.15%. The major factor associated with mortality was age: death rate increased exponentially with age. A significant proportion of RP (18%) were conducted in patients aged over 70 years of age. In this latter group, the mortality rate was 0.36% as compared to 0.11% for patients younger than 70. Other factors associated with mortality were the type of intervention (open, ASR=0.18%; laparoscopy, ASR=0.06%), Charlson index (Charlson=0, ASR=0.10%; Charlson>0, ASR=0.59%) and socioeconomic status.
In a sensitivity analysis, the survival curve at different points in time was evaluated. Survival falls rapidly until around 60 days; afterwards death rate is more stable. This indicates that the bulk of risk following RP is within 60 days and further follow-up reflects the background risk of death.
Conclusions: In a large cohort of men, the risk of death 60 days post RP is 0.11% for men aged 40−69. RP performed after the age of 70 is associated with a tripling of risk of death. RP should be discouraged in this older population.
No conflict of interest.

2858 POSTER DISCUSSION

Which is the best radiation treatment for low risk prostate cancer? A comparison of stereotactic body radiotherapy, standard external beam radiotherapy or low dose rate brachytherapy

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Background: Stereotactic body radiotherapy (SBRT) is an emerging radiotherapy technique that appears to be efficacious, well tolerated and convenient. However, outcomes for patients treated with SBRT are unknown compared to more conventional radiation options for patients with prostate cancer. The purpose of this study is to evaluate and compare late toxicities and biochemical disease-free survival (bDFS) of low risk prostate cancer patients treated SBRT (35 Gy/5 fractions), standard external beam radiotherapy (STND; median 76 Gy/38 fractions) or low-dose brachytherapy (LDR; iodine-125, 145 Gy) at the Odette Cancer Centre.
Material and Methods: Consecutive patients with low risk prostate cancer treated with radiation from 2006–2008 were analyzed. Patients treated with SBRT were part of a phase 2 prospective clinical trial; patients treated with STND or LDR had data abstracted from medical charts retrospectively. Patients treated with neoadjuvant androgen deprivation therapy were excluded from biochemical analyses. bDFS was defined by time to Phoenix-failure (nadir + 2ng/ml). Univariate (UVA) and multivariate analyses (MVA) of Cox proportional hazard model were conducted to identify significant covariates predicting bDFS.
Results: A total of 357 low-risk prostate cancer patients were identified (84 SBRT, 81 STND and 192 LDR). The median follow-up was 57, 62, and 59 months, respectively. At baseline, 85% of patients were T1c, 15% T2a; 100% had GS 6; median PSA 5.9 ng/ml. There were more patients in the STND and LDR cohort who had T2a disease (6%, 21% and 16%, p = 0.013) and the mean PSA was higher in the STND cohort (6.08, 6.69, and 6.02, p = 0.017). Patients who received LDR experienced more late hematuria (0%, 1.23% and 11.98%, p < 0.0001); otherwise there were no significant differences in late toxicities observed. There were no significant differences in bDFS (97.4% vs 96.9% vs 97.2% at 60 months, p = 0.94). There was 79−89% power to detect a one-sided 7% difference in bDFS between cohorts. There were no covariates identified predicting bDFS on UVA or MVA, including treatment type.
Conclusions: SBRT, STND and LDR show equivalent effectiveness and both external beam techniques showed less hematuria than LDR. However, SBRT and LDR are more convenient and less costly than STND. Further prospective studies of SBRT are ongoing.
No conflict of interest.

2859 POSTER DISCUSSION

Denosumab in men with nonmetastatic castration-resistant prostate cancer (CRPC) at high risk for bone metastases

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Background: In a double-blind, placebo-controlled, multi-center, phase 3 study of men with non-metastatic CRPC at risk for bone metastasis (based on PSA ⩾8.0 ng/mL and/or PSADT ⩽10 months), denosumab significantly increased bone metastasis-free survival (BMFS) (HR 0.85, 95% CI 0.73–0.98, *P* = 0.028) (Smith et al, *Lancet*, 2012). PSA doubling time (PSADT) is a key prognostic factor for progression in men with CRPC. In this post-hoc analysis, we compare the treatment effect of denosumab in patients with PSADT ⩽6 months vs PSADT >6 months. This trial was sponsored by Amgen Inc., ClinicalTrials.gov, NCT00286091.
Material and Methods: A total of 1432 men with non-metastatic CRPC at risk for bone metastasis (PSA ⩾8.0 ng/mL and/or PSADT ⩽10 months) were randomized 1:1 to receive 120 mg subcutaneous denosumab or placebo every 4 weeks. The primary endpoint was BMFS, defined as the time to first bone metastasis (BM; symptomatic or asymptomatic) or death from any cause. Secondary endpoints included the time to first BM (symptomatic or asymptomatic, excluding death), time to symptomatic BM, and overall survival. Analyses of the primary and secondary endpoints were performed in the subset of patients with PSADT ⩽6 months who were enrolled based on aggressive PSA kinetics (short PSADT). The blinded treatment phase of the trial has been completed. The primary analysis has been reported previously.
Results: Approximately 80% of the entire study population had a baseline PSADT ⩽10 months (N = 1154). In the placebo group, men with PSADT ⩽6 months had decreased BMFS and time to BM vs men with PSADT >6 months by 17.4 months and 14.9 months, respectively. Denosumab demonstrated a greater improvement in BMFS and delay in both the time to BM (Table 1) and time to symptomatic BM in these higher risk patients. Survival was similar between treatment groups.

Table 1. PSADT ⩽10 months at baseline subset

Endpoints	Denosumab median months	Placebo median months	HR (95% CI)	p-value
BMFS				
PSADT ⩽6 months	25.9	18.7	0.77 (0.64–0.93)	0.006
PSADT >6 months	33.3	36.1	1.13 (0.81–1.57)	0.469
Treatment-by-PSADT interaction				0.054
Time to BM				
PSADT ⩽6 months	26.5	22.1	0.80 (0.65–0.97)	0.026
PSADT >6 months	33.7	37.0	1.08 (0.74–1.56)	0.698

Conclusion: Men with CRPC and aggressive PSA kinetics (PSADT ⩽6 months) are at significant risk of BM and death. The treatment effect of denosumab is greatest in these patients.
Conflict of interest: *Advisory board: Amgen (MRS KF KM BE JM TLT), Novartis (KM), Astellas (JM TLT), Ipsen (JM), GSK (TLT), Pfizer (SW). Corporate-sponsored research: Amgen (MRS BE TLT), GSK (TLT), Orion Pharma (TLT), Astellas (TLT). Other substantive relationships: Amgen (ZY AB)*

2860 POSTER DISCUSSION

A Phase 2 trial of sipuleucel-T in combination with concurrent or sequential abiraterone acetate (AA) in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC)

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Background: Sipuleucel-T and AA + prednisone (P) are FDA-approved for asymptomatic or minimally symptomatic mCRPC. Suppression of the androgen axis via AA can be immunostimulatory, suggesting AA

plus sipuleucel-T may be synergistic. However, P (used with AA) could impair sipuleucel-T production and/or immune responses if administered concurrently with sipuleucel-T. P11-3 (NCT01487863) is the first study to assess the combination of sipuleucel-T and AA + P.

Material and Methods: Pts with asymptomatic/minimally symptomatic mCRPC were co-administered sipuleucel-T (3 infusions at wks 0, 2 and 4) with concurrent or sequential AA + P (AA 1000 mg QD + P 5 mg BID for ⩽26 wks). Pts were randomised 1:1 to AA + P starting either 1 day (concurrent) or 10 wks (sequential) after the 1st sipuleucel-T infusion. The primary endpoint was antigen presenting cell (APC) activation; secondary/tertiary endpoints included APC and total nucleated cell (TNC) counts (sipuleucel-T product potency measures), immune responses, adverse events (AEs) and efficacy.

Results: As of March 2013, 64 pts have been enrolled. 30/32 pts in the concurrent arm and 31/32 pts in the sequential arm had received all 3 sipuleucel-T infusions. Median AA duration (range) was 25.4 wks (0.1–26.0) in the concurrent arm and 18.3 wks (7.9–26.0) in the sequential arm. Median cumulative APC activation and APC and TNC counts did not differ between arms (p>0.05). Indicative of a prime-boost effect, APC activation increased with the 2nd and 3rd sipuleucel-T infusions in both arms. No differences were seen between arms in the robust peripheral antibody and T cell responses observed (p>0.05). Overall AE incidence was 96.9% in the concurrent arm and 87.5% in the sequential arm; however, most AEs were infusion-related, occurring within 1 day of infusion (53.1% and 65.6% of total population, respectively). The most common AEs (incidence ⩾20% in either arm) included muscle spasms (concurrent arm, 40.6%; sequential arm, 25.0%), cough (21.9%; 15.6%), back pain (9.4%; 25.0%) and extremity pain (9.4%; 21.9%). The incidence of drug-related grade ⩾3 AEs was 3.1% (concurrent arm) and 6.3% (sequential arm). There was no difference in clinically significant laboratory toxicities between arms.

Conclusions: These data suggest sipuleucel-T can be successfully manufactured during concurrent AA + P without affecting product potency and immunological prime-boost responses. AEs were similar in both arms and generally mild to moderate in severity.

Conflict of interest: *Ownership: AS, CMC, TD − Dendreon. Advisory board: ES, TG − Dendreon. LK − Dendreon, Amgen, Bayer, Astellas, Medivation, Janssen. NS − Dendreon, Janssen. Corporate-sponsored research: ES − Dendreon. LK − Dendreon, Amgen, Janssen, Astellas Medivation, Endo, Orion, Argos, Spectrum. NS − Dendreon, Janssen. Other substantive relationships: TG − speaker for Dendreon. AS, CMC, TD − employee of Dendreon.*

2862 POSTER DISCUSSION

Assessing the impact of prior treatments on the efficacy of enzalutamide (ENZ): A subanalysis of the phase 3 AFFIRM trial

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Background: AFFIRM trial data showed a 4.8-mo survival benefit for patients (pts) with metastatic castration-resistant prostate cancer post-docetaxel (Doc) who took ENZ vs placebo (PBO; Scher et al, 2012). This posthoc analysis evaluated the correlation between ENZ response and prior therapy duration.

Material and Methods: AFFIRM randomized 1199 pts. The primary endpoint was overall survival (OS); secondary endpoints included radiographic progression-free survival (rPFS) and prostate-specific antigen (PSA) response. We assessed ENZ response by duration of exposure to A) prior Doc (time from start to end of prestudy Doc), B) any prior hormone therapy, and C) prior LHRH analogs only (calculated as the time from start of first therapy to end of last prestudy therapy or start of Doc, whichever was first; time excluded if overlapping with prestudy Doc, and continuous treatment assumed if hormone therapy changed). Data were divided into tertiles based on duration of exposure to prior therapy.

Results: All pts showed better OS, rPFS, and PSA response from ENZ vs PBO (Table).

Conclusions: In this analysis, ENZ showed consistent benefit across tertiles of exposure time for each prior therapy. Pts progressing more rapidly on previous LHRH analogs or any hormone therapy, but not on Doc, had inferior OS.

AFFIRM (NCT00974311) is sponsored by Medivation and Astellas, and is ongoing (not recruiting).

Conflict of interest: *Advisory board: K. Fizazi − Board membership for Astellas and Medivation M. Taplin − Board membership for Medivation. Other substantive relationships: J. de Bono − Consultancy for Astellas and Medivation, Support for travel of Astellas and Medivation M. Taplin − Consultancy for Advisory Board M. Hirmand − Employee of Medivation B. Franks − Employee of Astellas H. Scher − Grant, Support for travel, and Consultancy for Medivation*

	Tertile 1	Tertile 2	Tertile 3
A. Prior Doc duration (tertiles)	*⩽4.4 mo ENZ: n = 256 PBO: n = 134*	*4.4–7.2 mo ENZ: n = 286 PBO: n = 116*	*>7.2 mo ENZ: n = 258 PBO: n = 149*
OS, mo			
ENZ	18.2	18.8	18.4
PBO	9.7	15.5	14.4
HR	0.53 (0.40–0.71)	0.73 (0.53–1.02)	0.67 (0.50–0.90)
rPFS, mo			
ENZ	8.5	8.3	8.3
PBO	2.8	3.0	2.8
HR	0.39 (0.31–0.50)	0.43 (0.33–0.55)	0.40 (0.31–0.51)
PSA 50% Rate, %			
ENZ	59	54	49
PBO	3	2	0
B. Any prior hormone therapy duration (tertiles)	*⩽24.2 mo ENZ: n = 263 PBO: n = 125*	*24.2–59.3 mo ENZ: n = 266 PBO: n = 125*	*>59.3 mo ENZ: n = 257 PBO: n = 142*
OS, mo			
ENZ	15.4	NR	NR
PBO	9.4	13.9	NR
HR	0.54 (0.40–0.71)	0.68 (0.50–0.92)	0.66 (0.47–0.93)
rPFS, mo			
ENZ	5.8	8.3	10.8
PBO	2.9	2.8	3.3
HR	0.49 (0.38–0.62)	0.37 (0.29–0.47)	0.36 (0.28–0.46)
PSA 50% Rate, %			
ENZ	42	58	60
PBO	3	0	2
C. Prior LHRH analog (only) duration (tertiles)	*<12.0 mo ENZ: n = 168 PBO: n = 76*	*12.0–26.9 mo ENZ: n = 165 PBO: n = 81*	*>26.9 mo ENZ: n = 174 PBO: n = 79*
OS, mo			
ENZ	15.4	NR	NR
PBO	9.1	14.7	15.5
HR	0.49 (0.34–0.70)	0.68 (0.46–1.01)	0.56 (0.37–0.85)
rPFS, mo			
ENZ	5.7	8.3	11.0
PBO	2.8	2.8	3.0
HR	0.44 (0.33–0.60)	0.42 (0.30–0.57)	0.33 (0.23–0.45)
PSA 50% Rate, %			
ENZ	42	55	64
PBO	2	1	0

HR (95% CI) assessed by Cox regression (covariate=treatment). OS/rPFS presented as medians. NR = not reached.

2863 POSTER DISCUSSION

Prognostic index for progression-free survival in metastatic castration-resistant prostate cancer patients without previous chemotherapy: An analysis of the COU-AA-302 abiraterone acetate study

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Background: COU-AA-302 was a multinational, randomized, placebo-controlled, phase 3 trial of abiraterone acetate (AA) + prednisone (P) versus placebo + P in asymptomatic/mildly symptomatic metastatic castration-resistant prostate cancer (mCRPC) patients without prior chemotherapy and no visceral metastases (clinicalTrials.gov NCT00887198). Using readily assessable routine clinical and laboratory parameters at baseline,

we developed a prognostic index model for the primary end point of radiographic progression-free survival (rPFS) in patients treated with AA.
Material and Methods: The analyses used data from patients treated with AA in the COU-AA-302 trial. Assessment of rPFS was based on Prostate Cancer Working Group 2 criteria with required confirmatory bone scans. Baseline variables were assessed for association with rPFS through a univariate Cox proportional hazards model. Accepted values for lower (LLN) and upper (ULN) limits of normal were used to dichotomize most of the laboratory parameters; baseline median was used to dichotomize prostate-specific antigen (PSA) levels. Independent prognostic factors for rPFS were identified by multivariate Cox modeling with a stepwise procedure; internal validation was undertaken. Model accuracy was estimated by the C-index.
Results: In the model from the stepwise procedure, the following risk factors were associated with poor prognosis: presence of lymph node metastasis (HR = 1.76, p < 0.0001), lactate dehydrogenase > ULN (234 IU/L) (HR = 1.71, p = 0.0001), 10 or more bone metastases (HR = 1.71, p = 0.0015), hemoglobin < LLN (12.7 g/dL) (HR = 1.47, p = 0.0030), and PSA >39.5 ng/mL (HR = 1.42, p = 0.0078). Patients were categorized into 3 risk groups (good prognosis, n = 230; intermediate prognosis, n = 152; poor prognosis, n = 164) based on number of risk factors, and the median rPFS was calculated for each group (table). The C-index of 0.83 (95% CI, 0.73–0.91) indicated high model accuracy.

Number of risk factors	Median rPFS, months (95% CI)	HR (95% CI)[a]
0 or 1 (good)	27.6 (19.1–33.1)	–
2 (intermediate)	16.6 (13.8–21.9)	1.58 (1.17–2.12)
3–5 (poor)	8.3 (8.1–11.0)	3.08 (2.33–4.08)

[a]Versus patients with good prognosis.

Conclusions: This prognostic index associates readily available parameters to rPFS, which was positively associated with overall survival in a prior analysis of this trial. External validation is required before integrating this model into standard clinical practice and the design of future risk-stratified clinical trials.
Conflict of interest: *Advisory board: Astellas, Janssen, Johnson & Johnson, Millennium, Sanofi. Corporate-sponsored research: Astellas, Janssen. Other substantive relationships: Astellas, Janssen, Johnson & Johnson, Millennium, Sanofi*

2864 POSTER DISCUSSION

Sensitivity analyses for radiographic progression-free survival (rPFS): Results from the phase 3 AFFIRM trial comparing enzalutamide to placebo

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Background: Enzalutamide (ENZA) inhibits multiple steps in the androgen receptor signaling pathway (Tran et al, Science 2009). In the phase 3 AFFIRM trial, ENZA increased median overall survival (OS) by 4.8 months (P<0.001; HR, 0.63) vs placebo (PBO) in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC) progressing after docetaxel (Scher et al, NEJM 2012). We performed sensitivity analyses to assess the robustness of the ENZA benefit and the impact of different sources of progression on the pre-specified rPFS analysis.
Materials and Methods: AFFIRM was a phase 3 multinational, randomized, double-blind trial of 1199 post-docetaxel mCRPC pts. Randomization was 2:1 to ENZA 160 mg/day or PBO. The primary endpoint was OS; rPFS was a secondary endpoint. In the pre-specified analysis, rPFS was defined as time from randomization to the earliest objective evidence of radiographic progression or death due to any cause. Patients were assessed at regular intervals. Radiographic progression was defined by the appearance of 2 or more new bone lesions on bone scan as assessed per the PCWG2 guidelines or by RECIST 1.1 for soft tissue disease. Three sensitivity analyses (SA1–3) on rPFS assessed the impact of types of progression and other potential confounding factors. SA1 censored potential confounding factors; SA2 and SA3 added a factor (see Table) to the rPFS definition used for the primary analysis. Correlations between rPFS and OS were evaluated.
Results: As previously reported, the primary analysis for rPFS favored ENZA. The results of the 3 SA were statistically significant in favor of ENZA vs PBO treatment.

Analysis	Modifications from Primary Analysis	Total Events	Hazard Ratio* (95% CI)
Primary	None	861	0.40 (0.35–0.47)
SA1	Additional censoring criteria: • Unconfirmed bone PD • Initiation of new anti-neoplastic treatment • Incidence of SRE • Surgery/radiation for prostate cancer or bone disorders beyond first SRE	455	0.42 (0.34–0.53)
SA2	• Added: clinical progression as event	930	0.36 (0.32–0.42)
SA3	• Deleted: soft tissue PD events Added: first SRE	841	0.41 (0.36–0.48)

PD: progressive disease; SRE: skeletal-related event.
*All nominal P-values <0.0001.

Conclusions: Sensitivity analyses of rPFS, a key secondary endpoint of the AFFIRM trial, demonstrated a consistent and robust treatment benefit with ENZA. Endpoint correlations will be presented.
AFFIRM is co-sponsored by Medivation, Inc. and Astellas. The trial (NCT00974311) is ongoing, but not recruiting.
Conflict of interest: *Advisory board: K. Fizazi – Board membership at Astellas and Medivation. Other substantive relationships: H. Scher – Grant, Support for travel, and Consultancy for Medivation C. Sternberg – Consultancy for Astellas A. Armstrong – Grants/grants pending for Medivation S. Bhattacharya – Employee of Medivation, Own Medivation stock/options M. Hirmand – Employee of Medivation J. De Bono – Conultancy and Support for travel for Astellas and Medivation*

2865 POSTER DISCUSSION

New prognostic score for metastatic castration-resistant prostate cancer with incorporation of neutrophil to lymphocyte ratio

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Background: Prognostic information is important to patients, physicians, and for stratification in clinical trials. Most prognostic nomograms for men with metastatic castration-resistant prostate cancer (mCRPC) are derived from patients treated in clinical trials. Here we develop a simple prognostic score for men with mCRPC treated in daily practice. Inflammation may play an important role in cancer progression, and a high neutrophil to lymphocyte ratio (NLR) has been reported to be a poor prognostic indicator in several malignancies.
Methods: In the training cohort, NLR was added to known prognostic variables identified from published nomograms for all chemotherapy-naive patients treated with 3-weekly docetaxel at *Princess Margaret Cancer Centre* (PMCC). Cut-offs for significant variables on univariable Cox regression were evaluated by the area under the receiver operating characteristic (ROC) curves. Multivariable Cox regression with forward elimination was then used to derive a prognostic score where one risk point was assigned for each significant variable. The model was tested in an external validation cohort of patients treated at *Royal Marsden* (RM).

	PMCC (training cohort)				RM (validation cohort)			
Risk points	0	1	2	3–5	0	1	2	3–5
Prevalence, %	8	25	30	37	10	31	31	29
Median OS, months	31.5	22.5	15.7	9.8	37.6	23.7	20.2	13.6
2 year OS, %	43	37	12	3	57	39	30	15
Hazard ratio for death	1 (ref)	1.9	3.1	6.4	1 (ref)	1.7	3.0	4.6
AUC*	0.78 (95% CI 0.72–0.84)				0.66 (95% CI 0.58–0.74)			

*AUC, area under ROC curve (discriminatory accuracy for predicting 2-year survival).

Results: 357 patients from PMCC were analyzed. Median age was 71 years, 26% had ECOG performance status (PS) ⩾2, 12% had liver metastasis (LM), 12% were treated in clinical trials and median overall survival (OS) was 14.7 months. LM (HR 1.9, P = 0.03), hemoglobin <12 g/dL (HR 1.8, P<0.01), ALP >2.0 x ULN (HR 1.6, P = 0.04), LDH >1.2 x ULN (HR 2.5, P<0.01), NLR >3 (HR 1.9, P<0.01) were associated with worse OS in the multivariable model thereby leading to a score of 0 to 5

points. Four risk categories were established with 0, 1, 2, and 3−5 points. For 215 patients in the RM validation cohort, median age was 67 years, 7% had PS $\geqslant$2, 4% had LM, 16% had prior treatment with abiraterone, 64% were treated in clinical trials and median OS was 19.6 months. Prognostic and discriminatory accuracy for the training and validation sets are shown in the table.
Conclusion: This simple risk score provides good prognostic and discriminatory accuracy for men with mCRPC.
No conflict of interest.

Poster Session (Mon, 30 Sep)
Genitourinary Malignancies − Prostate Cancer

2866 POSTER

Leupaxin mediates actin cytoskeletal remodeling by regulating the phosphorylation status of the actin-binding protein caldesmon in prostate cancer cells

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Background: Prostate cancer is claiming a high number of deaths every year making prostate cancer a serious health problem. Recently, we could identify the focal adhesion protein leupaxin (LPXN) to be overexpressed in approximately 20% of prostate carcinomas (PCa) and that this overexpression leads to the progression of prostate carcinomas. In the present study, we analyzed the LPXN-mediated adhesive and cytoskeletal changes during PCa progression and report a novel mechanism for the LPXN-mediated regulation of cytoskeletal rearrangements during migration and invasion of PCa cells.
Methods: We performed siRNA studies to analyze LPXN function in the PCa cell lines PC-3 and DU 145. Yeast-Two-Hybrid-Screen, co-immunoprecipitation, and GST-pulldown assays identified interaction of LPXN and the actin-binding protein caldesmon (CaD). Relevance of interaction between LPXN and CaD during migration was examined using proximity ligation assays.
Results: Downregulation of LPXN expression resulted in a reduced adhesion of the PCa cells PC-3 and DU 145 to different substrates. To identify candidate proteins that could mediate the LPXN-induced cytoskeletal changes necessary for adhesion we performed a Yeast-two-Hybrid screen and identified CaD as a putative interaction partner of LPXN. CaD stabilizes actin structures thereby inhibiting migration and invasion. Using proximity ligation assays we could show that during migration of PCa cells LPXN interacts with CaD and more interestingly with its phosphorylated form which detaches from the actin leading to highly dynamic cytoskeletal structures. Furthermore, siRNA knockdown of CaD in these cell lines resulted in an increased migration and invasion, whereas proliferation stayed unaffected. Interestingly, we found decreased phosphorylation levels of CaD after downregulation of LPXN, whereas total CaD levels remained equal, indicating that the loss of CaD-mediated actin stabilization is the underlying cause of the observed impediments of adhesion and invasion. In addition, specific kinase inhibitors helped us to identify the extracellular signal-regulated kinase (ERK) as the kinase responsible for LPXN-induced CaD phosphorylation during migration. Moreover, we could show similar interaction patterns of LPXN and ERK during migration of PC-3 and DU 145 cells.
Conclusion: These results suggest that LPXN acts as an adapter protein that mediates the phosphorylation status of the actin-binding protein caldesmon (CaD) by interaction with the extracellular signal-regulated kinase (ERK) during migration and invasion of PCa cells.
No conflict of interest.

2867 POSTER

High lysophosphatidylcholine acyltransferase 1 expression independently predicts high risk for biochemical recurrence in prostate cancers

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Background: Lysophosphatidylcholine acyltransferase 1 (LPCAT1) has been suggested to play a role in cancer.
Material and Methods: To assess its role in prostate cancer, LPCAT1 expression was analysed on a tissue microarray containing samples from 11,152 prostate cancer patients.
Results: In benign prostate glands, LPCAT1 immunostaining was absent or weak. In prostate cancer, LPCAT1 positivity was found in 73.8% of 8,786 interpretable tumours including 29.2% with strong expression. Increased LPCAT1 expression was associated with advanced tumour stage (p <0.0001), high Gleason score (p <0.0001), positive nodal involvement (p = 0.0002), positive surgical margin (p = 0.0005), and early PSA recurrence (p <0.0001). High LPCAT1 expression was strongly linked to *ERG*-fusion type prostate cancer. Strong LPCAT1 staining was detected in 45.3% of ERG positive but in only 16.7% of ERG negative tumours (p <0.0001). Within ERG negative cancers, LPCAT1 staining was strongly increased within the subgroup of *PTEN* deleted cancers (p <0.0001). Further subgroup analyses revealed that associations of high LPCAT1 expression with PSA recurrence and unfavourable tumour phenotype were largely driven by ERG negative cancers (p <0.0001) while these effects were substantially mitigated in ERG positive cancers (p = 0.0073).
Conclusions: The prognostic impact of LPCAT1 expression was independent of histological and clinical parameters. It is concluded, that LPCAT1 measurement, either alone or in combination, may be utilised for better clinical decision-making. These data also highlight the potentially important role of lipid metabolism in prostate cancer biology.
No conflict of interest.

2868 POSTER

A role for activated leukocyte cell adhesion molecule (ALCAM) in the growth and matrix adhesion of prostate cancer cells

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Background: Prostate cancer is one of the most common cancers in men in the UK and Europe, accounting for close to a quarter of all diagnosed male cancers. Mortality and morbidity is commonly associated with the metastatic spread of the primary cancer which frequently occurs to the bone. Activated Leukocyte Cell Adhesion Molecule (ALCAM) is a glycoprotein of the immunoglobulin superfamily that has been linked to various human cancers where it frequently displays aberrant expression patterns. It has also been shown to be involved in the development of bone metastasis. The current study aimed to explore the functional role of ALCAM in human prostate cancer cells.
Materials and Methods: Human prostate cancer cell lines, PC-3 and LNCaP were used. ALCAM expression was targeted in prostate cancer cells by way of genetic manipulation, namely transfecting the cells with anti-ALCAM hammerhead ribozyme transgenes, to specifically cleave ALCAM transcripts (PC-3^{ALCAMKO}). Successful knockdown of ALCAM expression, in comparison to control PC-3 cells transfected with a closed pEF6 plasmid (PC-3^{pEF6}), was verified using quantitative PCR. The impact of targeting ALCAM on an array of biological functions were tested, including cell growth and cell-matrix adhesion, using *in vitro* functional assays.
Results: Transfection of PC-3 cells with the ALCAM ribozyme transgene brought about a substantial reduction in the levels of ALCAM transcript within this cell line. Suppression of ALCAM expression resulted in an enhanced growth rate. PC-3^{ALCAMKO} cells had a significantly increased growth rate at both three day and five day incubation periods compared to control PC-3^{pEF6} cells ($P < 0.05$). However, following ALCAM suppression, PC-3 cells displayed a reduced adhesive capacity to an artificial Matrigel basement membrane and the number of adherent PC-3^{ALCAMKO} cells was notably reduced compared to control PC-3^{pEF6}.
Conclusions: Targeting of ALCAM in PC-3 cells enhanced growth rates but reduced the capacity of the cells to adhere to an artificial matrix. The current data suggests that ALCAM may play an important role in regulating these processes in PC-3 cells and may thus be an important factor in prostate cancer progression.
No conflict of interest.

2869 POSTER

ODM-201 − new generation antiandrogen with excellent antiandrogenic and antitumor activity in nonclinical models of CRPC

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Background: Activation of androgen receptor (AR) signaling is crucial for prostate cancer growth at all stages of the disease. Also castration resistant

prostate cancer (CRPC) is still dependent on AR and is often characterized by AR overexpression and resistance to conventional antiandrogens such as bicalutamide. ODM-201 is a novel, new generation antiandrogen that has unique properties and superior efficacy in preclinical models.
Methods and Results: Receptor binding studies indicated that ODM-201 and its major metabolite bind to wild-type AR with excellent selectivity and superior affinity (9 nM) when compared to known second generation antiandrogens. In functional cell-based assays, ODM-201 and its metabolite function as full AR antagonists with improved potency over clinically tested antiandrogens. In highly AR overexpressing cells, ODM-201 functions as an antagonist unlike bicalutamide which shows significant agonism. Most importantly, ODM-201 and its metabolite were found to inhibit testosterone-induced nuclear translocation in AR overexpressing cells whereas bicalutamide fails to block testosterone-induced AR nuclear translocation. W741L (tryptophan to leucine) mutation of AR has been shown to have a role in the mechanism of bicalutamide resistance. In this mutation, both ODM-201 and its metabolite functioned as antagonists, whereas bicalutamide was a pure agonist, as previously shown. In VCaP cell line derived from a bone metastasis of a patient with CRPC and containing endogenous AR gene amplification and AR overexpression, ODM-201 dose-dependently suppressed androgen-induced cell proliferation. In a VCaP xenograft model designed to mimic the castration resistant state of prostate cancer, ODM-201 potently ($p < 0.05$ over treatment time) inhibits tumor growth with superior efficacy when compared to MDV3100.
Conclusion: In summary, ODM-201 is a new generation AR antagonist found to possess excellent antiandrogenic as well as antitumor activity both in the in vitro and in vivo models of CRPC. These results suggest that ODM-201 is a promising new therapeutic for treatment of CRPC.
Conflict of interest: *Ownership: Sponsored by Orion Corporation Orion Pharma and Endo Pharmaceuticals. Other substantive relationships: Orion Corporation Orion Pharma employees*

2870 POSTER

Association of WAVE (WASP verprolin homologous) proteins with the Arp2/3 complex in prostate cancer metastasis

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Background: Metastasis is the main cause of cancer related death in prostate cancer patients. Acquisition of an increased migratory phenotype drives metastatic potential of cancer cells. Cell locomotion is driven by actin polymerisation which is regulated by the Arp2/3 complex which itself requires activation which can be brought about by the WAVE (WASP verprolin homologous) protein family. With the discovery of elevated WAVE 1 and 3 expression in metastatic prostate cancer cell lines, this study aims to gain a better understanding of the association between WAVE expression and prostate cancer metastasis as well the relationship with the Arp 2/3 complex.
Material and Methods: The metastatic prostate cancer cell line, PC-3 was transfected with ribozyme transgenes to target WAVE 1 and 3 expression to generate knockdown sub-lines named PC-$3^{WAVE1KO}$ and PC-$3^{WAVE3KO}$, respectively. Control cell line, PC-3^{pEF6} was generated via transfection with a closed plasmid. Once expression knockdown was confirmed, a series of assays were conducted to evaluate the effects of WAVE 1 and 3 knockdown on cell growth, invasion and motility. Treatment of cells with the Arp2/3 inhibitor, 8012–5102 was also carried out in parallel.
Results: Growth of PC-$3^{WAVE1KO}$ cells was significantly reduced compared to PC-3^{pEF6} cells, whilst there was no change in cell invasion and motility. There was a significant decrease in cell growth, invasion and motility in PC-$3^{WAVE3KO}$ cells relative to PC-3^{pEF6} cells. Treatment of PC-3^{pEF6} cells with 8012–5102 saw an increase in cell growth and little change in cell invasion, whilst both PC-$3^{WAVE1KO}$ and PC-$3^{WAVE3KO}$ cells exhibited reduced cell growth and little change in invasiveness compared to untreated cells.
Conclusions: This present study demonstrates the impact of WAVE on several cell functions in the prostate cancer cell line, PC-3. Whilst knockdown of either WAVE 1 or 3 displayed a reduction in cell growth, decreased invasiveness and motility was only seen with WAVE 3 knockdown. Some aspects of cell function were affected in response to Arp2/3 inhibition in these cells and provides some insight into the relationship between WAVE and Arp2/3. It is clear expression aberrations in WAVE 1 and 3 could be a contributing factor in prostate cancer metastasis, however, functional differences between WAVE 1 and 3 highlight subtle distinctions between these proteins.
No conflict of interest.

2871 POSTER

Effects of amniotic membrane proteins on mitochondrial activity, protein synthesis, cell viability and DNA of prostate cancer cell lines: Preliminary results

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Background: Amniotic membrane (AM) is a thin tissue on the inner side of placenta. AM is already used in several clinical areas due to its attractive properties. In fact, AM has anti-inflammatory, anti-bacterial, anti-viral, anti-angiogenic, pro-apoptotic and immunological characteristics. Although these properties are already identified, little is known about AM active protein content. Due to its characteristics, AM has recently drawn attention as an upcoming therapy in oncologic disease. Regarding the strategies already implemented, nothing is known about the effect of AM proteins in cancer cells.
Material and Methods: AM tissue was obtained from healthy women (after approval by Ethics Committee) after vaginal delivery or caesarean section, washed with phosphate buffered solution and subjected to mechanical actions in order to extract proteins. Proteins were quantified using Nanodrop®. To study the effect of AM proteins in prostate cancer (PCa), studies were performed in two cell lines obtained in ATCC: LNCaP (androgen/estrogen dependent) and PC3 (androgen/estrogen independent). Cells were incubated with 1 or 3 μg/μL of AM proteins during 72 h. After this period, MTT and SRB assays were performed to assess mitochondrial activity and protein synthesis of PCa cells, respectively. Trypan blue and comet assay were used to respectively analyze cell viability and DNA damage.
Results: LNCaP mitochondrial activity decreases 31.01% and 58.13% after treatment with 1 or 3 μg/μL, respectively. Regarding PC3 mitochondrial activity, there is a decrease of 48.69% (1 μg/μL) and 95.87% (3 μg/μL) relatively to control. Through SRB assay, it was found a decrease of 17.92% and 71.03% in LNCaP protein synthesis after incubation with 1 or 3 μg/μL. AM induced a decrease of 14.19% (1 μg/μL) and 34.25% (3 μg/μL) of protein synthesis ability in PC3. Through trypan blue we found that LNCaP viability is reduced after treatment, being this response dose-dependent in both cell lines. Preliminary results of comet assay allowed to verify DNA damage in LNCaP, being these most evident when cells were exposed to 3 μg/μL. When exposed to 1 μg/μL, PC3 DNA does not seem to be affected. However, the DNA damage is apparent after 3 μg/μL treatment.
Conclusion: Our preliminary results indicate that AM proteins have a promising role in the PCa therapy. Mitochondrial activity, protein synthesis, cell viability and DNA of PCa cell lines under study appear to be affected by AM treatment, being the effects in hormone dependent PCa cell line more evidenced.
No conflict of interest.

2872 POSTER

Paxillin in the prostate cancer cell models

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Introduction: Prostate cancer is characterised by its unique but not entirely understood prevalence of osteoblastic metastasis. Cells migration and adhesion are involved in cancer metastasis and the direct result of the dynamic changes in the extracellular matrix environment, i.e. stimulation with growth factors or bone matrix proteins. Paxillin, being one of the proteins involved in integrin-dependent cell attachment may aid the colonisation of bone marrow.
Objectives: The present study uses a variety of prostate cancer cell lines (generating osteolytic, mixed osteolytic/osteoblastic and osteoblastic metastasis) with significantly down-regulated expression of *PAXILLIN* gene and investigates their response to hepatocyte growth factor (HGF) or/and bone matrix extract (BME) stimulation. An aggressive human breast cancer cell line (MDA-MB-231) was used to establish any organ-related differences.
Methods: Three prostate cancer cell lines PC-3, LNCaP, MDA-PCa-2b and a breast cancer cell line MDA-MB-231 were transfected with specifically generated anti-paxillin ribozymes to obtain the *PAXILLIN* gene knock-down. Knock-down cell lines were treated with 40 ng/ml HGF and/or 50 μg/ml BME and growth, migration, adhesion and invasion assays were performed.
Results: Up to date 2 knock-downs of PC-3 (Rib1 Col3 and Rib2 Col6) were confirmed using PCR and Real-Time RT PCR (with GAPDH gene expression as a normalization factor throughout the experiments) as well

as by Western blotting. Low level of paxillin exhibited by both cell lines seems to contribute not only to their morphology changes but also to the significant decrease in their adhesion and invasion abilities comparing to the control PC-3 pEF6 cell line. Migration abilities of PC-3 Rib2 Col6 cell line are impaired when untreated or non existing upon HGF stimulation while migration of untreated PC-3 Rib1 Col3 cells remains on the level of the control, is slightly slower when stimulated with HGF or slightly faster upon BME treatment. The lack of any viable MDA-PCa-2b cells with *PAXILLIN* knock-down may suggest that its lack is fatal hence necessary for their adhesion and survival.
Conclusions: Our preliminary results into the role of paxillin in the metastasis of prostate cancer suggest that the environment of HGF or bone matrix influences its expression which might contribute to metastasis in prostate cancer.
No conflict of interest.

2873 POSTER

Continued excess mortality for long-term prostate cancer survivors

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Background: Many cancer patients want to know their actualized prognosis after having survived cancer for some time. We estimated population-based conditional 5-year relative survival rates for prostate cancer patients.
Material and Methods: All 98,672 patients diagnosed in the Netherlands with prostate cancer stage I−III in 1989–2008 aged 45−89 years were selected from the Netherlands Cancer Registry and followed until 2010. Conditional 5-year relative survival was estimated for every subsequent year of survival up to 15 years after diagnosis.
Results: Conditional 5-year relative survival decreased with time of survival since diagnosis. Excess mortality (conditional 5-year relative survival <95%) for patients with clinical T1 stage started 5 years after diagnosis and increased to almost 10% after 10 years. Patients with more advanced disease (cT2-cT4) exhibited an excess mortality of 6−12% at diagnosis which increased up to 15−22% after 10 years. Excess mortality occurred earlier for the older age groups. Five-year relative survival at diagnosis was <90% for all age groups of patients with cT3/cT4 and excess mortality for this group increased to over 20% for those who had already survived for 5 years since diagnosis.
Conclusions: Excess mortality was found for prostate cancer patients at some point within 10 years after diagnosis, being earlier for more advanced stage and older age groups. Quantitative insight into conditional survival is useful for caregivers to help planning optimal cancer treatment and surveillance and to inform patients about their actual prognosis during follow-up, taking the current condition of the patient into account.
No conflict of interest.

2874 POSTER

Feasibility of assessing quality of prostate cancer care by means of Patient Reported Outcome Measures (PROMS): Results from the population-based PROFILES registry

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Background: In the past years attention has increasingly been paid to Patient Reported Outcomes Measures (PROMs) for measuring and benchmarking the performance of oncological health care providers. Our aim was to investigate the feasibility of using the EORTC QLQ-C30 and QLQ-PR25 as measures of health related quality of life (HRQoL) and prostate cancer specific symptoms to assess potential variation in health care performance on hospital level among patients treated for localized prostate cancer.
Methods: We estimated to minimally need 65 patients with localized prostate cancer (cT1/cT2) per hospital to be able to find clinically meaningful differences in HRQoL between hospitals. We therefore randomly selected 150 patients per hospital diagnosed with prostate cancer between 2006 and 2009. In total, 1050 prostate cancer patients from 7 hospitals as registered in the Eindhoven Cancer Registry were asked to complete a questionnaire 2−6 years after diagnosis. The questionnaire included a survey on HRQoL (EORTC QLQ-C30) and prostate cancer specific symptoms (EORTC QLQ-PR25). Analyses of covariance were conducted, correcting for differences in case mix, to investigate the variation in HRQoL and symptoms between hospitals.
Results: A total of 698 patients (66%) responded to the invitation. For this analysis we selected 532 (76%) patients with cT1 or cT2 disease. Despite similar age, stage and comorbidity distribution of participating patients in the different hospitals, treatment at diagnosis varied between hospitals. Overall, 34% was treated with prostatectomy (varying between hospitals from 23% to 51%), 17% was treated with external radiotherapy (11%-24%), 18% received brachytherapy (3%-33%), and 30% was treated with hormonal therapy only (20%-41%).
As expected, patients treated with prostatectomy reported clinically meaningful higher incontinence scores compared to other treatment groups (20 vs. 6−15), but also best physical functioning (89 vs. 80−87) and most sexual activity (33 vs. 22−30), whereas patients treated with external radiotherapy reported most bowel symptoms (9 vs. 2−4). When comparing HRQoL or prostate cancer symptoms between hospitals we only observed a statistically significant and clinically meaningful difference regarding incontinence scores, ranging from 8−23 points. No significant differences were observed regarding all other symptoms.
Conclusions: Despite the strong association between prostate cancer treatment and outcomes and the large treatment variation between hospitals, we did not observe clinically meaningful differences in PROMS (HRQOL and symptoms) between hospitals, except for urinary incontinence. This might imply that although variation in treatment is large the ultimate hospital outcome performance is almost similar. Or, using PROMS to measure and benchmark hospital performance is less sensitive than we thought.
No conflict of interest.

2875 POSTER

Tolerability and reproducibility of a novel rectal obturator to localise the prostate and spare the rectum during radical prostate radiotherapy

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Background: ProSpare® is a daily disposable rectal obturator designed to localise the anterior rectal wall on X-Ray image-guidance radiotherapy (IGRT) and increase sparing of rectal tissue during radical prostate radiotherapy. A previous clinical trial documented inadequate reproducibility of the device in the superior-inferior (SI) direction which led to design modifications. We have re-assessed the modified ProSpare® device.
Materials and Methods: We designed a clinical trial (ProSpare II, UKCRNID 11814) in two parts. Part I assessed feasibility, patient tolerance and accuracy. The primary endpoint had to be met to continue to part II: 80% of measured displacements were required to be 6 mm or less in the superior-inferior direction in at least 6 out of 9 patients (66.7%). Part II will subsequently assess treatment accuracy using an intra-patient randomised design treating men sequentially with and without ProSpare®. Patients planned for radical radiotherapy to the prostate and seminal vesicles were eligible for the study. Three intra-prostatic gold seed fiducial markers (FMs) were implanted in each patient. ProSpare® was inserted by the patient before patient set-up to skin marks. Daily cone-beam CT (CBCT) scans were obtained and the patient shifts were determined online using co-registration of the intra-prostatic FMs and the planning CT. ProSpare® displacements were analysed offline. Reproducibility was assessed by calculating the ProSpare® displacement after bony alignment. Planning target volume (PTV) margins were calculated using the Van Herk equation. Tolerability was assessed using an in-house questionnaire.
Results: Eleven men were enrolled into the study between September 2012 and November 2012. All patients successfully completed treatment using ProSpare® for all fractions. A total of 365 treatment fractions were analysed with 3285 displacements measured. Eight out of the 11 patients (83%) had more than 80% of SI displacements of 6 mm or less.

Table 1. Reproducibility displacement errors, systematic and random errors and consequent PTV margins required using ProSpare for prostate IGRT.

	Right–Left (n = 365)	Superior–Inferior (n = 365)	Anterior–Posterior (n = 365)
Total no. of reproducibility errors >6 mm	0	66	23
% of fractions with reproducibility errors ⩽6 mm	100%	82%	94%
Systematic Error (Σ) Prospare IGRT (mm)	1.28	3.15	0.83
Random Error (σ) Prospare IGRT (mm)	1.05	2.94	1.21
Prostatic PTV margin required for online Prospare IGRT (mm)	3.9	9.9	2.9

Conclusions: The device was tolerable in 100% of patients. The primary endpoint was met. The localising ability of ProSpare is promising in the lateral and vertical axes although certain limitations remain in the longitudinal direction. Hybrid CBCT co-registration techniques will allow maximal benefit to be gained from ProSpare IGRT.

Conflict of interest: *Ownership: David Dearnaley and the Institute of Cancer Research own some intellectual property rights to ProSPare. Advisory board: Nil. Board of directors: Not on board of directors. Corporate-sponsored research: Device manufacting cost only supplied by Neerveen Healthcare. Academic sposor is Institute of Cancer Research. Other substantive relationships: No other conflicts of interest or relationships*

2876 POSTER

Time to first skeletal-related event (SRE) with radium-223 dichloride (Ra-223) in patients with castration-resistant prostate cancer (CRPC) and bone metastases: ALSYMPCA trial stratification factors analysis

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Background: Ra-223, a novel alpha-emitting pharmaceutical, targets bone metastases (mets) with high-energy, short-range (<100 μm) alpha-particles. In the phase 3 ALSYMPCA trial, Ra-223 significantly improved overall survival in CRPC patients (pts) with bone mets by 3.6 months vs placebo (pbo) (median OS: 14.9 vs 11.3 mo; HR = 0.695; 95% CI, 0.581–0.832; $P = 0.00007$) with a highly favorable safety profile. Analyses of time to first SRE with and without Ra-223, and impact of trial stratification factors on Ra-223 effects on time to first SRE are presented.

Methods: SREs were a key secondary endpoint, including use of external beam radiation therapy to relieve skeletal symptoms, new clinically detected pathologic bone fractures, spinal cord compression, and tumor-related orthopedic surgical intervention. Time to first SRE was assessed for the entire ITT population (n = 921) and by trial stratification factors (baseline alkaline phosphatase levels [ALP: <220 or ⩾220 U/L], current bisphosphonate use [yes/no], and prior docetaxel [yes/no]).

Results: Ra-223 significantly prolonged time to first SRE vs pbo (median time to first SRE: 15.6 vs 9.8 mo; HR = 0.658; 95% CI, 0.522–0.830; $P = 0.00037$). Treatment effect on time to first SRE favored Ra-223 over pbo regardless of current bisphosphonate use, with a trend toward even greater Ra-223 effect in pts given bisphosphonates. Similarly, time to first SRE was significantly prolonged vs pbo regardless of baseline ALP level (<220 or ⩾220 U/L). Pts with prior docetaxel had a significantly longer time to first SRE with Ra-223; there is a trend toward risk reduction for time to first SRE with Ra-223 vs pbo (HR = 0.74) in pts with no prior docetaxel (Table).

Conclusions: Ra-223 prolonged time to first SRE in pts with CRPC and bone mets, irrespective of baseline stratification factors. Time to first SRE may be prolonged for pts given Ra-223 who had concurrent bisphosphonate use.

Group	n	Time to 1st SRE (median, mo)	Hazard Ratio (95% CI)	*P* Value*
Overall				
Ra-223	614	15.6	0.66 (0.52, 0.83)	0.00037
Pbo	307	9.8		
Total ALP <220 U/L				
Ra-223	348	16.5	0.64 (0.48, 0.86)	0.00297
Pbo	169	10.2		
Total ALP ⩾220 U/L				
Ra-223	266	14.1	0.69 (0.47, 1.0)	0.04562
Pbo	138	7.9		
Current bisphosphonate use				
Ra-223	250	19.6	0.49 (0.33, 0.74)	0.00048
Pbo	124	10.2		
No current bisphosphonate use				
Ra-223	364	11.8	0.77 (0.58, 1.0)	0.06835
Pbo	183	8.4		
Prior docetaxel therapy				
Ra-223	352	13.5	0.61 (0.46, 0.82)	0.00087
Pbo	174	7.8		
No prior docetaxel therapy				
Ra-223	262	17.0	0.74 (0.50, 1.0)	0.11950
Pbo	133	19.5		

*Not adjusted for multiplicity.

Conflict of interest: *Ownership: OB: Minor stockholder, Algeta ASA − KS: Algeta ASA. Advisory board: REC: Consultant, Bayer − OB: Algeta ASA − OS: Consultant and investigator for Algeta and Bayer. Other substantive relationships: REC: Honoraria from Bayer and Amgen, Paid Expert Testimony for Novartis − OB: Paid Expert Testimony (to institution) for Bayer − KS: Employed at Algeta ASA − JGV: Employed as Senior Medical Director Oncology at Bayer*

2877 POSTER

Hematologic safety of radium-223 dichloride (Ra-223) in the phase 3 ALSYMPCA trial in castration-resistant prostate cancer (CRPC) patients with bone metastases: Baseline prognostic factor subgroup analysis

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Background: Ra-223 is a targeted alpha-emitter that selectively binds to bone metastases (mets) and emits ionizing radiation as high-energy, short-range (<100 μm) alpha-particles. In ALSYMPCA, Ra-223 significantly prolonged overall survival compared to placebo (pbo) in patients (pts) with CRPC and bone mets with a highly favorable safety profile. Incidence of grade 3 and 4 hematologic adverse events (AEs) was low in both Ra-223 and pbo groups: anemia in 13% of both groups; neutropenia (NP) in 2% and 1% and thrombocytopenia (TCP) in 6% and 2% of Ra-223 and pbo groups, respectively. Here we report a post hoc analysis of hematologic AEs in both treatment (tx) arms based on ALSYMPCA baseline prognostic factors. Since the incidence of grade 3 and 4 events was low, this analysis included grade 2−4 hematologic AEs.

Methods: Pts with progressive, symptomatic CRPC with ⩾2 bone mets were randomized 2:1 to Ra-223 (50 kBq/kg IV) q4wk (n = 600) or matching pbo (n = 301). The relationships of hematologic toxicity and 6 baseline factors (study tx, current bisphosphonate use, prior docetaxel use [pDoc], extent of disease >6 mets including superscan, prior external beam radiotherapy [EBRT] for bone pain, and total alkaline phosphatase [ALP]) were assessed at baseline, week 24, and follow-up (40 weeks after the first study drug dose) using multivariate Cox regression analysis.

Results: In the regression analysis of grade 2−4 hematologic AEs, tx with Ra-223 (vs pbo) and pDoc (vs no pDoc) were associated with a greater risk for NP (Ra-223: HR = 4.10, $P = 0.0207$; pDoc: HR = 2.81, $P = 0.0254$) and TCP (Ra-223: HR = 2.17, $P = 0.0118$; pDoc: HR = 2.31, $P = 0.0035$). Risk of anemia was significantly increased with pDoc (HR = 1.41, $P = 0.0087$) and more extensive disease (>6 mets) (HR = 4.50, $P < 0.0001$). Pts with lower baseline ALP levels (<220 U/L) had a significantly lower risk of TCP (HR = 0.56, $P = 0.0166$) and anemia (HR = 0.36, $P < 0.0001$) independent of tx group. No differences were seen in risk of hematologic AEs with bisphosphonate use or prior EBRT for bone pain. Blood transfusions were required for 137/614 (22%) and 69/307 (22%) of Ra-223 and pbo pts, respectively. Each tx group had 1 case of sepsis.

Conclusions: Ra-223 tx is associated with a low incidence of myelosuppression. Both Ra-223 and pDoc treatment are strong prognostic factors for grade 2−4 NP and TCP. Lower baseline ALP <220 U/L is a strong prognostic factor for lower risk of TCP and anemia.

Conflict of interest: *Ownership: IH: Stock options, Algeta ASA. Advisory board: AW: Astellas, Q-med − NJ: Algeta and Bayer − NV: Consultant for Algeta/Bayer. Board of directors: MD: Intituto do Cancer do Estado de São Paulo (ICESP). Corporate-sponsored research: NJ: Algeta ASA − MD: 2 clinical trials in follow-up − NV: Algeta ASA and Bayer HealthCare. Other substantive relationships: AW: Employment as Medical Advisor (50%), Sanofi Oncology − MD: Employment as Surgical Oncology Medical Director, ICESP − IH: Employment as Drug Safety Officer, Algeta ASA − AC: Employment, Pharmanet/i3 − JGV: Employment as Senior Medical Director Oncology, Bayer Healthcare*

2878 POSTER

Effects of radium-223 dichloride (Ra-223) on health-related quality of life (QOL) outcomes in the phase 3 ALSYMPCA study in patients with castration-resistant prostate cancer (CRPC) and bone metastases

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Background: Ra-223, a first-in-class alpha-emitter, significantly improved overall survival (OS) by 3.6 mo vs placebo (HR = 0.695; 95% CI, 0.581–0.832; $P = 0.00007$) in CRPC patients (pts) with bone metastases and was well tolerated (Parker et al, ASCO 2012). Ra-223 was also shown to have a positive impact on pain; it significantly delayed time to external beam radiation therapy and reduced pain and opioid use (Nilsson et al, ASCO GU 2013). Reported here is a post hoc analysis assessing treatment effect on QOL including pain-related score and time to deterioration in QOL over the entire treatment and follow-up phases.
Methods: QOL was assessed at weeks 16, 24, and follow-up visit 2 (week 44) using the Functional Assessment of Cancer Therapy for Patients with Prostate Cancer (FACT-P) questionnaire. Mixed-effect linear regression models were used to assess the average treatment effect in terms of change from baseline in FACT-P total score and subscales. The time to deterioration in QOL analysis defined deterioration as a $\geqslant$10-point reduction in FACT-P total score.
Results: For the entire trial period (weeks 16, 24, and 44), deterioration in mean FACT-P total score from baseline was significantly greater in the placebo group compared to the Ra-223 group (mean: −8.7 vs −4.8; $P = 0.004$). The results for 4 of the 5 FACT-P subscales indicate that Ra-223 pts had significantly higher QOL than placebo pts, the exception being the Social/Family Well-being Subscale (interactions with friends and family), which was not affected by treatment. Within the Prostate Cancer Subscale, the mean pain-related score improved with Ra-223 but declined with placebo; the treatment difference was statistically significant (mean: 0.6 vs −0.2; $P < 0.001$). In addition, Ra-223 was associated with significantly longer time to deterioration in QOL vs placebo (median: 6.3 vs 5.6 mo; HR = 0.75; 95% CI: 0.59–0.95; $P = 0.016$).
Conclusions: Ra-223 was associated with a significantly longer time to deterioration in QOL than placebo, with better preservation of QOL on most FACT-P subscales. Ra-223 is a well-tolerated agent that not only has a proven survival benefit, but also has a positive impact on QOL in patients with CRPC and bone metastases.
Conflict of interest: *Ownership: CGOT − Algeta ASA. Advisory board: CP: Consultant or advisory relationship, Algeta, Bayer, BNIT − DH: Speakers bureau or advisory committee, Bayer − SN: Advisory board, Algeta. Other substantive relationships: CP: Honoraria, Amgen, Astellas, Bayer, Janssen, Sanofi-Aventis, Takeda − DH: Honoraria, Bayer − VP: Employment, Bayer HealthCare − JRS: Employed as statistical consultant by Bayer Pharma AG − CGOT: Employed as Chief Medical Officer with Algeta ASA − SN: Travel costs and accommodations for study and writing meetings from Bayer*

2879 POSTER

Acute toxicity of hypofractionated IMRT with simultaneous integrated boost in high-risk prostate cancer patients

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Background: McGill has over 10 years of successful experience with hypofractionation in favorable risk prostate cancer (PCa) where only the prostate has been irradiated. We have now expanded the use of this regimen to a phase II study involving high-risk PCa patients where the prostate and the pelvic nodes receive hypofractionated intensity-modulated radiotherapy (IMRT) with a simultaneous integrated boost. We report the acute toxicity found with this new approach.
Material and Methods: 69 high-risk PCa patients (stage T3, or PSA $\geqslant$20 ng/ml, or Gleason score of 8−10) entered in the study. Patients received androgen suppression before, during and after radiotherapy. IMRT plans were designed to deliver 60 Gy in 20 fractions of 3 Gy over 4 weeks to the prostate and base of seminal vesicle (PTV60), while simultaneously delivering 44 Gy in 20 fractions of 2.2 Gy to the pelvic lymph nodes (PTV44). All patients had daily image guidance with ultrasound and/or cone-beam. PTVs were CTVs with a 7 mm margin. Whole bladder and rectum constraints were as follows: V56 Gy<25%; V48 Gy<50% for the rectum and V60 Gy<25%; V52 Gy<50% for the bladder. Acute gastro-intestinal (GI) and genito-urinary (GU) toxicity were recorded prospectively, weekly during treatment and every 2−6 months post IMRT, using the NCI-CTCv3 scoring system. Correlation between acute toxicities and various dosimetric parameters including mean and maximum doses to the target volumes and to organs at risk (bladder and rectum) was performed, using the Wilcoxon test.
Results: Median age is 73 years (54−85). All patients, except one, completed IMRT without interruption, and were followed for more than 3 months. The exception was an 80 year-old patient who interrupted treatment at 54 Gy due to medical reasons diagnosed prior to IMRT. Acute toxicity is summarized in the table below and compared to the only phase III study (Pollack et al. 2006) comparing standard fractionation (arm I with 76 Gy in 38 fractions) to hypofractionation (arm II with 70.2 Gy in 26 fractions) for high-risk PCa patients treated with IMRT to the prostate and pelvic nodes. There was no grade $\geqslant$4 acute toxicity. in our study, acute toxicity did not correlate with any of the dosimetric parameters examined, and this analysis will be presented in details.
Conclusions: Hypofractionated IMRT to the pelvis with simultaneous integrated boost to the prostate is feasible with acute GI and GU toxicity rates similar to standard fractionation. The trial is continuing to accrue. Longer follow-up is critical to accurately assess long term toxicity and disease control.
No conflict of interest.

Grade	McGill		Pollack arm 1		Pollack arm 2	
	GU (%)	GI (%)	GU (%)	GI (%)	GU (%)	GI (%)
0	28	41	16	52	8	42
1	59	43	28	40	44	40
2	10	13	54	8	40	18
3	3	3	2	0	8	0

2880 POSTER

Association between VEGF-A gene variants and clinical outcome in prostate cancer patients treated with definitive radiotherapy

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Purpose: Vascular endothelial growth factor-A (VEGF-A), a key regulator of tumor-induced angiogenesis, is a critical factor in tumor growth and metastatic tumor spread. The present study was aimed to analyze the role of VEGF-A polymorphisms and haplotypes for the development of biochemical recurrence and distant metastases in prostate cancer patients treated with definitive radiotherapy.
Methods and Materials: The association of VEGF-A genetic variants was analyzed in a prospective study including 496 prostate cancer patients recruited from 2004 to 2007. Seven polymorphisms were selected for analysis and determined by 5′-nuclease (TaqMan) assays. Haplotypes and linkage disequilibrium were analyzed using the Haploview program.
Results: Within a median follow-up time of 80 months, 118 patients (23.8%) developed biochemical recurrences (defined according to the 'Phoenix Definition') and 41 patients (8.3%) distant metastases, respectively. In univariate analysis, the ATTGC haplotype formed by the −2578A, −2489T, −1498T, −634G, −7C alleles was significantly associated with distant metastases-free survival (hazard ratio (HR)=2.035; 95% CI 1.165–3.556; p = 0.013). In multivariate analysis, the HR for the development of distant metastases was 2.143 for carriers of the ATTGC haplotype (95% CI 1.161–3.956; p = 0.015). Furthermore, univariate analysis revealed a trend toward decreased biochemical recurrence-free survival for carriers of the CG haplotype formed by the 936C and 1612G alleles (HR = 1.292, 95% CI 1.101–1.669, p = 0.05). In multivariate analysis, the HR for the development of biochemical recurrence was 1.329 for carriers of the CG haplotype (95% CI 1.014–1.743; p = 0.04).
Conclusions: We conclude that VEGF-A gene polymorphisms and haplotypes may influence clinical outcome in prostate cancer patients undergoing definitive radiotherapy.
No conflict of interest.

2881 POSTER

Impact of high dose to the prostate in IGRT on patient outcome

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Background: The clinical benefit of prostate IGRT is not yet fully demonstrated. The objective of the study was to compare the biochemical failure and the late urinary and rectal toxicity risks in high dose prostate cancer 3DCRT, with or without IGRT.
Material and Methods: A total of 302 patients (pts) received a 3DCRT for localized prostate cancer. Median age was 69 years (52−81). History of abdominal or pelvic surgery, anticoagulant therapy (ACT) and diabetes were observed in 29%, 24% and 8% of pts, respectively. D'Amico risk groups were: good (10%), intermediate (64%) and bad (26%). Total dose in the prostate was: 78 Gy (13%) or 80 Gy (87%), 2 Gy/fraction, without any pelvis lymph nodes irradiation. The RT technique did not include any IGRT for 66% of pts (58% receiving 'standard' 3DCRT and 8% IMRT). IGRT (fiducials or CBCT) was combined with IMRT in 34% of pts. The data were prospectively collected for all the pts. Digestive and urinary toxicities were analyzed according to the SOMALENT classification (⩾ Grade 2). The impact of pts characteristics and RT techniques on pts outcome were assessed by univariate and multivariate analysis.
Results: The median follow-up was 60 months (range: 6 to 152). The 5 year grade ⩾2 rectal and urinary toxicity rates were: 17% (95% CI: 12−22%) and 22% (95% CI: 17−27%), respectively. The 5 year biochemical failure rates by risk group were: good: 0%, intermediate: 21% (95% CI: 14−28%) and bad: 38% (95% CI: 26−50%) (RR = 2.5; p < 0.0001).
IGRT combined with IMRT decreased the risk of grade ⩾2 rectal toxicity:
– compared to 'standard' 3DCRT without IGRT (RR:0.54; p = 0.02)
– compared to IMRT without IGRT (RR = 0.26; p = 0.05).
IGRT was not associated with a significant decrease of the risk of GU toxicity or biochemical failure.
Conclusion: Prostate IGRT is associated with a significant decrease of the risk of late rectal toxicity, without any obvious benefit on late urinary toxicity and biochemical failure.
No conflict of interest.

2882 POSTER

Salvage stereotactic body radiotherapy in radio-recurrent prostate cancer − what dose is feasible?

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Background: Although the last decade has seen great improvements in radiotherapy techniques in prostate cancer, 10−20% of patients with organ-confined prostate cancer will experience PSA failure. For a subset of these patients, disease recurrence occurs exclusively within the prostate, most commonly at the site of dominant disease nodule at original presentation. The optimum treatment in this scenario is unknown but with stereotactic radiotherapy techniques we can dose-paint to target solely the area of recurrence.
Methods: This planning study selected 16 patients with dominant nodules at presentation, as a surrogate for intraprostatic recurrence. Planning target volume was defined as dominant tumour nodule plus 5 mm, except where this volume extended posteriorly towards the rectum when it was clipped at 3 mm posteriorly.
Planning objectives were to deliver 30 Gy in 5 fractions to cover 95% of the PTV whilst respecting a rectal constraint of D1% <22.5 Gy, based on published HDR re-irradiation constraints. The plans were calculated using Multiplan ®, the planning system for Cyberknife®.
Results: 30 Gy in 5 fractions could be delivered within rectal D1% constraint in 9/16 cases despite the PTV overlapping with the rectum in 9/16 cases. Keeping within this constraint a mean dose of 28.6 Gy was deliverable (range 22.9–30.3 Gy).
To deliver 30 Gy, mean dose to 1% of the rectum was 21.4 Gy but ranged from 5.1 to 30.9 Gy. Mean dose to 50% of the rectum was 2.8 Gy (range 0.85−8.1 Gy) and mean dose to 40% of the bladder was 2.4 Gy (0.9 to 6.0 Gy).
Ability to deliver 30 Gy within constraints was strongly correlated with distance from the anterior rectal wall to the GTV (p < 0.0001) If the distance from the GTV to the rectum was <2 mm 8/9 plans exceeded the rectal constraint, compared to 1/7 if this distance was ⩾2 mm.
The relationship between GTV volume (which ranged from 0.46 cc to 12.35 cc) and dose to 1% rectum was also significant (p = 0.04).
Conclusion: 30 Gy in 5 fractions (which delivers a BED of 150 Gy if a/b ratio = 1.5 Gy) can be delivered within rectal constraints likely to be safe in 56% of cases. The ability to achieve this is strongly correlated with distance between GTV and the anterior rectal wall and is also significantly related to GTV size. This study will aid case selection for future clinical trials examining the role of SBRT in radio-recurrent prostate cancer.
Conflict of interest: *Corporate-sponsored research: Accuray are sponsoring the PACE trial for which Dr van As is the principal investigator and all authors are recruiting patients to. Other substantive relationships: Authors have received unrestricted educational grants from Accuray to facilitate attendance at international conferences. The Royal Marsden NHS Foundation trust is in receipt of an unrestricted grant to support a research fellow.*

2883 POSTER

Radium-223 dichloride (Ra-223) efficacy and safety in patients with castration-resistant prostate cancer (CRPC) with bone metastases: Phase 3 ALSYMPCA study findings stratified by age group

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Objective: Ra-223, a novel alpha-emitting pharmaceutical, targets bone metastases (mets) with high-energy, short-range (<100 μm) alpha-particles. In ALSYMPCA, Ra-223 significantly improved overall survival (OS) in CRPC patients (pts) with bone mets (median OS: 14.9 vs 11.3 mo; HR = 0.695; 95% CI, 0.581–0.832; *P* = 0.00007) compared to placebo, and had a highly favorable safety profile. Here we present age group analyses of efficacy and safety.
Methods: Eligible pts had progressive, symptomatic CRPC with ⩾2 bone mets and no known visceral mets; were receiving best standard of care; and were post-docetaxel, or were unfit for or declined docetaxel. Pts were randomized 2:1 to 6 injections of Ra-223 (50 kBq/kg IV, n = 614) q4wk or matching placebo (n = 307). Primary endpoint was OS; secondary endpoints included skeletal-related events, time to ALP progression, and safety. OS, secondary efficacy endpoints, and safety were analyzed for age groups <65 y and ⩾65 y.
Results: Baseline characteristics are shown in the Table. Ra-223 significantly prolonged median OS versus placebo in both age groups. Median times to first SRE and ALP progression were significantly prolonged with Ra-223 versus placebo regardless of age. As observed in the overall population, grade $\frac{3}{4}$ neutropenia and thrombocytopenia were reported more frequently with Ra-223 versus placebo in both age groups. However, the incidence of grade $\frac{3}{4}$ hematological adverse events was lower in the ⩾65 years age group than in the <65 years age group.

Age group	<65 years		⩾65 years	
Treatment	Ra-223	Placebo	Ra-223	Placebo
Baseline Characteristics (%)				
n	158	73	456	234
ECOG ⩾2	10	15	14	13
Prior docetaxel	75	69	51	53
Extent of disease (>20 mets/superscan)	48	33	38	42
Primary Endpoint				
n	158	73	456	234
OS, Median (mo)	16.9	11.4	14.1	11.3
HR (95% CI)	0.53 (0.36–0.78)		0.77 (0.62–0.94)	
P value	<0.01		<0.01	
Secondary Endpoints				
n	158	73	456	234
Time to 1st SRE, Median (mo)	12.1	6.6	17.1	11.2
HR (95% CI)	0.58 (0.38–0.90)		0.67 (0.51–0.89)	
P value	<0.05		<0.01	
Time to ALP progression, Median (mo)	7.4	4.0	NE	3.7
HR (95% CI)	0.21 (0.13–0.35)		0.16 (0.12–0.22)	
P value	<0.00001		<0.00001	
Grade 3/4 Adverse Event Incidence (%)				
n	153	71	447	230
Anemia	14	20	12	11
Neutropenia	3	0	2	1
Thrombocytopenia	10	3	5	2

Conclusions: Regardless of pt age, Ra-223 prolonged survival and showed consistent efficacy with a favorable safety profile in CRPC with

bone mets. Older pts (⩾65 y) can benefit from and tolerate Ra-223 as well as younger pts.

Conflict of interest: *Ownership: FF: Stock options, Bayer. Advisory board: SN: Algeta − OS: Consultant and investigator for Algeta and Bayer − REC: Consultant for Bayer − CP: Consultant or advisory relationship with Algeta, Bayer, and BNIT. Other substantive relationships: SN: Travel costs and accommodations for study and writing meetings from Bayer − REC: Honoraria from Bayer and Amgen, Paid Expert Testimony for Novartis − FF: Employed by Bayer − CP: Honoraria from Amgen, Astellas, Bayer, Janssen, Sanofi-Aventis, and Takeda*

2884 POSTER

Up-to-date results of a clinical trial of carbon-ion radiotherapy for prostate cancer: Analysis of 1,144 patients

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Background: The carbon ion radiotherapy (C-ion RT) for the prostate cancer was started in 1995 using the Heavy-Ion Medical Accelerator in Chiba (HIMAC) at the National Institute of Radiological Sciences (NIRS), Japan. After preceding phase I/II dose escalation studies of 20 fractions over 5 weeks, a phase II study was initiated in April 2000 using the treatment techniques and the recommended dose fractionation established by the phase I/II studies. This study was also successfully completed in October 2003 when the C-ion RT for the solid tumors including the prostate cancer was approved as 'Advanced Medicine' from the Ministry of Health, Labor, and Welfare.

Materials and Methods: A phase II study of C-ion RT (9904[1]−[3]) for localized prostate cancer (T1b–T3bN0M0) was started from April 2000. A C-ion RT schedule of 66.0 GyE/20fr./5 weeks, 63.0 GyE/20fr./5w and 57.6 GyE/16fr./4w were used in 9904[1], 9904[2] and 9904[3] trials, respectively. The patients with low-risk prostate cancer were treated with C-ion RT alone, and the patients with intermediate-risk and high-risk prostate cancer were treated with C-ion RT combined with hormonal therapy of 6 months and ⩾24 months, respectively. Biochemical failure was defined as PSA increase of 2.0ng/ml above nadir after the treatment.

Results: A total of 1,144 patients were enrolled to the clinical study. Out of 1,144 patients, more than 50% patients were categorized as high-risk group with T3 clinical stage, Gleason's score of 8 or higher, or PSA of 20 or higher. The 5-year overall survival rate and biochemical relapse free rate of the entire group was 95.7% and 91.0%, respectively. Biochemical relapse free rates of low-, intermediate- and high-risk patients were 90.1%, 94.2% and 89.7%, respectively. T-stage, Gleason score was significant prognostic factors for both the biochemical control and patient survival and initial PSA was also a predictive factor for survival. Regarding the late radiation toxicity, incidence of rectal toxicity of grade 2 or worse was 1.1% and that of genitourinary toxicity was 6.5%, respectively. In addition, incidence of the toxicity in the patients treated with more hypofractionated C-ion RT of 16 fractions over 4 weeks were lower than those of 20 fraction-treatment.

Conclusions: These favorable outcomes can be thought as apparent evidence of physical and biological advantages of the hypofractionated C-ion RT.

No conflict of interest.

2885 POSTER

Prostate cancer stem cells are involved in radioresistance

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Background: Prostate cancer is one of the leading death causes among men and its relapse is driven by a small population of malignant cells resistant to conventional therapies. Preclinical and clinical findings suggest that a higher proportion of cancer stem cells (CSC), or tumour progenitor cells, which are responsible for tumour initiation and growth, correlate with higher cancer radioresistance. Therefore, the identification and validation of novel biomarkers for the early CSC detection and CSC-targeted therapy is essential for the optimisation of treatment strategies.

Material and Methods: We used global gene expression and proteomics analysis to identify novel biomarkers indicative of CSC population radioresistance and the signalling pathways involved in its maintenance. The morphological and functional changes in radioresistant prostate cancer cell populations were compared to bulk tumour cells and analysed using Western blot analysis, immunofluorescence microscopy, proliferation and migration assays. To measure the efficiency of DNA-double strand break (DSB) repair and the level of reactive oxygen species (ROS) in CSCs and non-CSCs populations after irradiation, γ-H2A.X foci formation assay and flow cytometry analysis were applied. To verify the results and to assess the role of the identified biomarkers in prediction and regulation of prostate cancer radiosensitivity, we used NMRI nu/nu murine models.

Results: Our work showed that aldehyde dehydrogenase (ALDH) activity is indicative of tumorigenic cells with increased radioresistance. Purified ALDH-positive prostate cancer cells possess higher tumour stem cell properties *in vitro*, including high clonogenic potential and sphere forming ability, and high tumorigenic potential in nude mice. ALDH- positive cancer progenitor cells are more resistant to irradiation and conventional chemotherapeutic drugs as compared to ALDH- cell population. Our data suggest that high ALDH activity could define a chemo- and radioresistant cancer cell progenitor population.

Furthermore, we established the radioresistant prostate cancer cell lines, which showed more efficient DSB repair, lower ROS level and enhanced expression of stem cell markers, including CD133, ABCG2, CXCR4, Oct-4 and NANOG, as compared to their parental cell lines. Moreover, they showed an increased activation of survival signalling pathways, elevated expression of EMT signatures and enhanced migratory potential.

Conclusions: Taken together, our results suggest that CSC markers can be used for the identification and isolation of radioresistant prostate cancer cell populations. Further validation of the clinical relevance of CSC based biomarkers and their characterisation as potential therapeutic targets will be beneficial in the development of individualized chemo- and radiotherapy.

No conflict of interest.

2886 POSTER

Stereotactic body radiation therapy (SBRT) for prostate cancer in men with large prostates (>50 cm^3)

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Background: Patients with large prostate volumes have been shown to have higher rates of genitourinary and gastrointestinal toxicities after definitive IMRT treatment for prostate cancer. Stereotactic body radiation therapy (SBRT) delivers fewer high-dose fractions of radiation which may be radiobiologically favorable to the conventional low-dose IMRT fractions commonly used for prostate cancer radiotherapy. However, the efficacy and toxicity of SBRT treatment for prostate cancer in patients with large prostate volumes remain unclear. We report our early experience using SBRT for localized prostate cancer in patients with prostate volumes greater than or equal to 50 cm^3.

Methods: Patients treated with SBRT from February 2008 to February 2013 at Georgetown University Hospital for localized prostate carcinoma were included in this retrospective review of data that was prospectively collected in an institutional database. 57 patients were identified as having prostate volumes ⩾50 cm^3 prior to treatment with a minimum follow up of two years. Treatment was delivered using Cyberknife with doses of 35–36.25 in 5 fractions. Biochemical control was assessed using the Phoenix definition. Toxicities were recorded and scored using the CTCAE v.4. Quality of life was assessed before and after treatment using the American Urological Association Symptom Score (AUA) and the Expanded Prostate Cancer Index Composite (EPIC)-26. Late urinary symptom flare was defined as having both an AUA score ⩾15 with an increase of ⩾5 points above baseline six months after the completion of SBRT.

Results: 57 patients (23 low-, 25 intermediate- and 9 high-risk according to the D'Amico classification) at a median age of 69 years (range 54−83) received SBRT with a median follow up of 2.9 years. The median prostate size was 62.9 cm^3 (range 50–138.7 cm^3). 33.3% patients received ADT. The median pre-treatment prostate-specific antigen (PSA) was 6.5 ng/ml, and, at 2 years, the median PSA decreased to 0.4 ng/ml (p<0.0001). A median baseline AUA symptom score of 7.5 significantly increased to 13 at 1 month (p = 0.001) and returned to baseline at 3 months (p = 0.21). 23% of patients experienced a late transient urinary symptom flare in the first two years following treatment. Mean baseline EPIC bowel scores of 95.8 significantly decreased to 78.1 at 1 month (p <0.0001), but subsequently improved to 93.5 at three months (p = 0.08) and 94.7 two years (p = 0.32). The 2-year actuarial incidence rates of GU and GI toxicity ⩾ grade 2 were 49.1% and 1.8%, respectively. 2 patients (3.5%) experienced a grade 3 urinary toxicity, and no patient experienced grade 3 gastrointestinal toxicity.

Conclusions: SBRT for clinically localized prostate cancer was well tolerated in men with large prostates. Late GI and GU toxicity rates were comparable to conventionally fractionated radiation therapy. Late symptom flares were observed but the majority resolved with conservative management.

Conflict of interest: *Corporate-sponsored research: S Collins and B Collins serve as clinical consultants to Accuray Inc. The Department of Radiation Medicine at Georgetown University Hospital receives a grant from Accuray to support a research coordinator.*

2887 POSTER

Low PSA values by hormonal intervention do not guarantee biochemical control in the salvage radiotherapy for prostate cancer after radical prostatectomy

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Background: To identify the influence of preferential hormone use in the postoperative salvage radiotherapy for prostate cancer after radical prostatectomy by analyzing radiotherapeutical survival (RTS), which was defined as 2nd biochemical failure (BCF)-free survival after radiotherapy.
Material and Methods: A total of consecutive 34 prostate cancer patients were treated with postoperative salvage radiotherapy after radical prostatectomy between July 2004 and March 2011. On retrospective review, median age at diagnosis was 65.5 years and 19 patients (55.9%) had PSA level of more than 10 ng/mL. After radical prostatectomy, the patient number of T3-T4 stage, Gleason score 8−10, and positive resection margin was 11 (32.4%), 10 (29.4%), and 17 (50.0%), respectively. PSA reached below 0.2 ng/mL within 2 months without hormonal intervention in 19 patients (55.9%), which rose above 0.2 ng/mL again afterwards. For the other 15 patients (44.1%), PSA fell below 0.2 ng/mL not by surgery alone but by additional hormone use due to initial high PSA level or poor surgical pathology findings. No gross loco-regional or metastatic lesion was detected after surgery and radiotherapy was performed by median dose 64.8 Gy (range, 52.9–70.0 Gy) with 1.8−2.3 Gy fractionations. 2nd BCF was defined as a PSA level of >0.4 ng/mL or hormonal intervention due to steep PSA increase after radiotherapy. The timing of hormone and radiation was decided at physician's discretion and the median follow-up period after radiotherapy was 32.5 months (range, 10–118 months).
Results: All patients had their PSA values reached below 0.2 ng/mL median 4 months (range, 0−25 months) after radiotherapy and it was done within 1 month in 13 patients (38.2%). The 3-year rates of RTS were 60.3%. On univariate analysis, preferential hormone use ($p = 0.022$), persistent PSA after surgery ($p = 0.047$), higher PSA at radiotherapy ($p = 0.005$), shorter surgery to 1st BCF interval ($p = 0.033$), and higher PSA at 2 months after surgery ($p = 0.003$) were related to shorter RTS. High PSA at diagnosis ($p = 0.070$) and less radiation dose ($p = 0.062$) showed a tendency to poor RTS. On multivariate analysis, RTS benefit was associated with lower PSA at radiotherapy ($p = 0.016$), higher radiation dose ($p = 0.007$), and non-preferential hormone use ($p = 0.046$).
Conclusions: Fundamentally, lower PSA value is correlated with better prognosis in postoperative salvage radiotherapy. However, PSA decreased by hormonal intervention is not always reliable and should not be underestimated in radiotherapy planning. Therefore, this aspect should be considered in randomized trials together with proper radiotherapy timing as a salvage treatment.
No conflict of interest.

2888 POSTER

Interfractional variability in patients with prostate cancer treated with intensity-modulated radiotherapy with or without pelvic thermoplastic immobilization

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Background: To determine the variability of patient positioning errors associated with intensity-modulated radiotherapy (IMRT) for prostate cancer, and to assess the impact of pelvic thermoplastic immobilization on these errors using kilovoltage (KV) cone-beam computed tomography (CBCT).
Materials and Methods: From February 2012 to June 2012, the records of 314 sessions of 19 patients with prostate cancer treated with IMRT with or without immobilization at two different facilities of Korea University Hospital were analyzed. The KV CBCT images were matched with simulation computed tomography (CT) images to determine simulation-to-treatment variability. The shifts along x-(lateral), y- (longitudinal), z- (vertical) axes and the 3D vector were measured.
Results: The measured systematic errors of immobilized group during the treatment were 0.46±1.75 mm along the x-axis, −0.35± 3.83 mm along the y-axis, 0.20±2.75 mm along the z-axis, and 4.05± 3.02 mm in 3D vector. Those of non-immobilized group were −1.45± 7.50 mm along the x, 1.89±5.07 mm along the y, 0.28± 3.81 mm along the z, and 8.90± 4.79 mm in 3D vector. The immobilized group with pelvic thermoplastics showed lesser interfractional variability in x- axis, y-axis, and 3D vector compared to non-immobilized group($p<0.05$).
Conclusions: IMRT with pelvic thermoplastic immobilization in patients with prostate cancer appears to be useful in stabilizing interfractional variability during the planned treatment course.
No conflict of interest.

2889 POSTER

Urinary toxicity in high risk prostate cancer patients treated with whole pelvis intensity modulated radiotherapy (WP-IMRT) with cone beam ct (CBCT) for image guidance

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Background: In India, the incidence of prostate cancer is low & patients are usually diagnosed in the advanced stages of the disease. Patients with localized high risk prostate cancer undergo androgen deprivation therapy (ADT) and whole pelvic radiation. This study aimed to assess the impact of radiation dose escalation on urinary toxicity in Indian men undergoing treatment for prostate cancer with WP-IMRT utilizing CBCT image guidance.
Material and Methods: In 2010, radiation dose escalation with WP-IMRT was initiated in our centre following the acquisition of a linear accelerator with CBCT. Between 2010 and 2013, patients with localized high risk prostate cancer were treated with ADT and WP-IMRT. WP-IMRT (4680 cGy) was followed by an IMRT boost (2520 to 2880 cGy) to the prostate, based on the tolerance of organs at risk. Image guidance was done by Daily CBCT. Urinary symptoms of the patients were assessed by the International Prostate Symptom Score (IPSS) prior to starting radiation and during each follow up. The initial scores were analyzed and compared with the scores on follow up.
Results: Twelve patients with localized high risk prostate cancer were treated with WP-IMRT with CBCT image guidance. The median prescription radiation dose was 7380 cGy. The planned radiation dose to the urinary bladder was within the accepted tolerance limits. The median follow up time after completion of radiation was 9.5 months with a range of 3 to 23 months. IPSS scores improved in 5 patients at the time of the first follow up and in 9 by the second follow up. Only one patient had a 10 point increase in his IPSS at his first follow up, but the score improved to below his baseline by the second follow up. There was no clinically significant worsening of urinary symptoms in the patients by the second follow up. No patient suffered urinary incontinence or obstruction.
Conclusion: IMRT delivered with image guidance is a relatively new treatment modality in India. Patients undergoing WP-IMRT experience urinary toxicity.However, this resolves within a year and the majority of patients do not experience any significant long term urinary toxicity.
No conflict of interest.

2890 POSTER

Preliminary results of combining external beam radiotherapy with Cs-131 brachytherapy implantation in patients with prostate cancer

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Background: Combining external beam radiation therapy (EBRT) with brachytherapy to treat prostate cancer offers several therapeutic advantages compared to the use of either treatment modality alone. Utilizing a prostate 'boost' with brachytherapy allows increased intraprostatic dose that cannot be achieved with EBRT alone. Further, EBRT can deliver dose to the periprostatic region that would otherwise not be reached with brachytherapy. Prior studies have reported excellent biochemical control rates with combination therapy using I-125 or Pd-103 as the brachytherapy source. However, using Cs-131, a source with higher energy, shorter half-life, and a lower total dose of radiation has also gained attention. Here, we report the initial results of prostate cancer patients treated at our institution with 45 Gy EBRT and Cs-131 brachytherapy implant.
Materials and Methods: We retrospectively analyzed prostate cancer patients treated with combination therapy of EBRT plus Cs-131 brachytherapy from 2006–2011. EBRT was delivered with the intensity modulated radiotherapy (IMRT) technique to a total dose of 45 Gy in 1.8 Gy fractions. The prescribed dose of the Cs-131 implant was 90 Gy. Acute and late gastrointestinal (GI) and genitourinary (GU) toxicity was determined using the Common Terminology Criteria for Adverse Events (CTCAE) 4.0 scale. Biochemical failure was defined both by the ASTRO consensus guidelines and the ASTRO-Phoenix criteria.
Results: A total of 34 patients were included in the final analysis; 19 of whom received EBRT prior to Cs-131 implant. The median age of the patients included was 67 years old with a median follow-up of 31 months. Patients had a median tumor stage of T1, Gleason score of 7 and pre-treatment PSA of 7.14ng/mL. To date, only 1 patient experienced acute

grade 2 GI toxicity with no grade 3−4 toxicity reported. No patient suffered late grade 2−4 GI toxicity. Twelve patients experienced acute grade 2 GU toxicity, mainly consisting of increased frequency and nocturia. There was no acute grade 3−4 GU toxicity noted. Eight patients reported late grade 2 GU toxicity, but no late grade 3−4 toxicity. Only one patient has suffered biochemical failure based on the ASTRO consensus guidelines (but did meet the ASTRO-Phoenix criterion for failure) 36 months after completion of therapy.
Conclusions: Combining EBRT with brachytherapy affords the possibility of dose escalation to the prostate while treating the periprostatic region. We show here that using a source with a short half-life and high energy, such as Cs-131, is well-tolerated with acceptable rates of acute GI and GU toxicity. Albeit short follow-up, no patient has experienced late grade 3−4 GI or GU toxicity with a current biochemical control rate of 97%.
No conflict of interest.

2891 POSTER

Salvage dose escalated prostate fossa radiotherapy for eMRI detected recurrence

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Background: Radiation therapy is effective treatment for rising PSA following prostatectomy. Patients that present with undetectable disease have potentially curable disease, however reported outcomes for patients with gross recurrence are poor. Imaging of the prostate fossa with eMRI can identify patients with macroscopic disease who may benefit from targeted dose escalation. This series reports outcomes for men with rising PSA and eMRI detected recurrent disease treated with prostate fossa radiation and dose escalation.
Patients and Methods: Data of 270 men treated between 2009–2012 with salvage RT following radical prostatectomy was reviewed using an IRB approved database. Twelve men who had eMRI detected recurrences were identified for analysis of outcomes and treatment parameters were extracted from the TPS.
Positive surgical margins were reported in four (33%) patients. Pathological Gleason scores were 6 in two pts, 7 in six pts and $\geqslant$8 in four pts. The median PSA level before radiotherapy was 1.2 ng/ml (range 0.13−6.5).
The GTV was contoured using eMRI recurrence and the CTV was defined using the EORTC guidelines for post prostatectomy radiation. Radiotherapy was delivered using IMRT technique with rapid arc (n = 9) or stationary beams (n = 3). Since radiation was delivered in either 2 Gy (n = 10) or 2.3 Gy (n = 2) fractions, dose will be reported as EQD2 Gy.
Results: The mean dose to the GTV was 73.2 Gy (range 70−80). The mean dose delivered to the prostatic bed CTV was 70.2 Gy (range 66−76). Radiotherapy to the pelvic lymph nodes (46 Gy) was delivered to four (33%) patients. Six months of concomitant androgen deprivation therapy was administrated to 10 (83%) of the patients.
At median follow up of 30 months (12−65) biochemical freedom from failure survival was 75%. The mean post treatment PSA nadir was 0.157ng/ml (0.01−0.8). The treatment was well tolerated with grade I gastrointestinal toxicity in four pts. (33%), grade 1−2 urinary toxicity in 6 (50%) of the patients, and one patient with grade 3 urinary toxicity (stricture).
Conclusions: Radiation treatment using IMRT/IGRT and eMRI to define gross prostatic fossa recurrence is associated with minimal toxicity and can safely allow for dose escalation in selected patients. This approach when combined with short term androgen deprivation is associated with excellent outcomes in this small series.
No conflict of interest.

2892 POSTER

Genetic variants in DNA repair genes and radiation-induced late toxicity in prostate cancer patients

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Background: Homologous recombination (HR) is one of the two major mechanisms to repair DNA double-strand breaks (DSB), the most deleterious form of radiation-induced DNA damage, and the polymerization of RAD51 onto single-stranded DNA ends of a DSB is a limiting factor in HR. BRCA1 and 2 interact and co-localize with RAD51 in the process of double-strand break repair. A down-regulation of RAD51, BRCA1 and 2 has been associated with increased radiosensitivity. The purpose of the present prospective study was to analyze the role of RAD51, BRCA1 and 2 in the development of severe side effects after radiotherapy for prostate cancer.
Material and Methods: A total of 607 patients from the Austrian PROCAGENE study were included for further analysis. All eligible patients received a three dimensional conformal radiotherapy with high energy photons (18MV) five times a week to a total dose of 66–70.4 Gy. Late genitourinary and rectal toxicity was graded according to standard RTOG criteria. 38 SNPs located in important regulatory regions (promoter region, 5′UTR) of the RAD51, BRCA1 or BRCA2 genes, as well as functional polymorphisms, haplotype-tagging SNPs and intronic SNPs if their minor allele frequency was >0.05 were selected for further analysis and genotyped with the Applied Biosystem's 'TaqMan OpenArray'System.
Results: After a median follow-up time of 82 months, radiation induced severe urinary or rectal toxicity, classified as EORTC/RTOG grade$\geqslant$2 was observed in 133 (22%) and 73 (12%) patients. After correction for multiple testing, none of the investigated polymorphisms was significantly associated with late rectal or urinary toxicity grade $\geqslant$2.
Conclusion: We conclude that the presence of the analyzed single nucleotide polymorphisms is not associated with a higher risk of radiation-induced severe urinary or rectal late toxicity in prostate cancer patients.
No conflict of interest.

2893 POSTER

PTV margins in prostate cancer

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Background: It is Known that radiotherapy is affected by geometrical accuracy: target delineation error, intrafraction and interfraction target movement or calibration errors. In prostate treatments the most important one is interfraction movement, to manage it one possible solution is the implantation of fiducial gold markers within the prostate. With them, daily set-up error, which comprises a random and a systematic component, is solved. The first one would lead to a blurring of the dose distribution around the CTV whereas the second would shift the dose distribution, what could lead to underdose the CTV. Analyzing daily set-up displacements of patients with gold markers allow as to calculate CTV to PTV margins for prostate patients with no fiducial markers.
Material and Method: Thirty seven patients with prostate cancer were treated in a Siemens Oncor LINAC equipped with a Megavoltage Cone Beam Imaging system based on Si detectors. Immobilization during radiotherapy was made with alpha cradle molds. We get two orthogonal images in all sessions to override systematic and random set-up errors. Shift between treatment isocenter an simulation isocenter is automatically calculated by Siemens Syngo Therapyst system, comparing fiducial markers between planning system DRRs and Portal Imanging.
We calculated the population systematic error (Σ) and the population random error (σ), and finally we composed the PTV margin using Van Herk formula:
Margin = $2.5\,\Sigma + 0.7\,\sigma$
Results: Table 1 presents a summary of random (σ), systematic (Σ) error and CTV to PTV margins. The largest value of error and margin is seem in the vertical direction and can be correlated to rectum and bladder filling. Moreover, this margin should be taken carefully because involve rectal toxicity.
Conclusion: Systematic and random set-up errors are now known for our prostate cancer patients. Further, this has allowed us to obtain 'Ad hoc' CTV to PTV margins to treat with the required accuracy patients with no fiducial markers.
No conflict of interest.

Table 1.

	Vertical (mm)	Lateral (mm)	Longitudinal (mm)
Random error (σ)	3.8	2.4	2.4
Systematic error (Σ)	4.4	3.8	3.1
Van Herk margins (M)	13.7	11.2	9.4

2894 POSTER

A pathology verified, innovative method to predict nodal (N) status using an artificial intelligence (AI) approach in prostate cancer (PC) patients (pts): Beyond the Roach formula?

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Aim: We already presented an innovative AI-based method to predict N status in PC, integrating several pre-treatment variables (Gleason Score/sum, age, initial PSA, neoadjuvant hormonal therapy vs no hormonal therapy − HT). We now present an independent test of the predictor in a population of 204 operated pts, classified as cN0 preoperatively and with a well-defined pN status (187 pN0 and 17 pN1).
Material and Methods: 1804 pts from a National Italian multicentre database with a known cN0−1 status were analyzed. Cases (N = 55) with node-positive pelvic MRI and/or CT scan and/or showing a nodal only relapse after RT (none received pelvic RT), were considered N+. Using Roach formula with a cut-off of >15%, >10% and >5%, the individual risk of N involvement was calculated. 3 AI methods, based on decision trees (J48, Forrest Tree and Random Tree) combined with 3 techniques of manipulation of imbalanced samples (oversampling, undersampling and combined under/oversampling) were created to predict the N status. Accuracy of the classical and of the AI based approaches was calculated. Finally, the results of the AI metodhs were tested on an independent population of 204 operated Brescia patients, not treated with HT, submitted to postoperative RT, classified as cN0 preoperatively, with a known pN status (187 pN0 and 17 pN1 pts. To that end, new algorithms without HT as input variable were generated.
Results: The AI methods perform better than the Roach formula. The classic approach showed an accuracy rate (i.e. true positives + true negatives/whole population) ranging, depending on the cut-off, between 19% and 42% in the test sample of 204 pts and between 34% and 52% in the whole series of 1804 pts. The accuracy of the 3 AI methods ranged between 19% and 86% in the test sample of 204 pts and between 56% and 98% in the whole series of 1804 pts. Concerning the specificity, the Roach Formula showed rates ranging, depending on the cut-off, between 12% and 32% in the test sample of 204 pts and between 32% and 51% in the whole series of 1804 pts. The specificity of the 3 AI methods ranged between 12% and 91% in the test sample of 204 pts and between 61% and 96% in the whole series of 1804 pts.
Conclusions: Non-linear relationships with more than two variables influence the N status of the patients and the Roach formula has suboptimal predictive performances. New approaches considering more variables could possibly improve these performances.
No conflict of interest.

2895 POSTER

Cabazitaxel for metastatic castration-resistant prostate cancer: Safety data from the Spanish Early Access Programme

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Background: Based on the results observed in the TROPIC trial, cabazitaxel (Cbz) has been recently approved for the management of metastatic castration-resistant prostate cancer (mCRPC) in patients who have progressed during or after treatment with a docetaxel-containing regimen. This single arm multicentre, open-label study (NCT01254279) provided early access to Cbz for use in patients similar to those evaluated in the TROPIC trial to further evaluate the Cbz safety profile in clinical practice. Results in Spain are reported here.
Patients and Methods: Eligible patients received Cbz 25 mg/m^2 iv every 3 weeks, in combination with oral prednisone or prednisolone 10 mg daily until disease progression, death, unacceptable toxicity, Investigator's decision, or up to 10 cycles and until it was commercially available. Safety assessments were performed before each cycle. A descriptive safety analysis was performed.
Results: A total of 153 patients were included. Median age was 70 (IQR: 65−75) years; 26.8% were aged over 75 years; 94% (n = 144) had bone metastasis and 51% had visceral (n = 78) metastasis. Most patients (136 [88.9%]) had an ECOG PS $\leqslant$1. Patients had previously received a median of 8.0 (IQR: 6.0–10.0) cycles of docetaxel and 59.5% (n = 91) had experienced disease progression $\geqslant$3 months from last docetaxel dose. Patients received a mean number of 6.2$\pm$2.9 cycles of Cbz and a mean cumulative dose of 149.2$\pm$72.1 mg/m^2. Adverse events (AEs) considered related to the study drug were experienced by 143 (93.5%) patients. The most common clinically significant grade 3 or higher AEs were neutropenia (25 [16.3%] patients) and asthenia (11 [11.1%] patients). Febrile neutropenia was reported in 5.2% of the patients. Grade 3 or 4 diarrhoea was identified in 5.2% of the patients. Incidence of grade $\geqslant$3 peripheral neuropathy (1 [0.7%]) was low. There were 5 (3.3%) treatment-related deaths, mainly infection-related. Granulocyte colony-stimulating growth factors were used in 114 (74.5%) patients mostly as preventive treatment (n = 107; 69.9%).
Conclusions: In clinical practice the treatment of mCRPC with Cbz is tolerable with manageable AEs, especially in a real-world Spanish population with poor prognostic factors (aged >70; with visceral metastasis). Proactive management of AEs, especially in >65 and ECOG>2 patients, might have a role for minimisation of haematological AEs.
Funding: Sanofi.
No conflict of interest.

2896 POSTER

Anti-angiogenic and Immuno-modulatory effects of metronomic cyclophosphamide treatment in prostate cancer patients with PSA failure

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Background: After curative local therapy, patients (pts) will experience rising PSA as an early indicator of recurrent prostate cancer and no standard of care exists. Previous studies demonstrated the clinical interest of cyclophosphamide metronomic chemotherapy (CMC) in several cancers. Multifactorial modes of action including immunological and anti-angiogenic effects have been well described by Kerbel *et al* and Ghiringhelli *et al* (Cancer Research 2006 and European Journal of immunology 2004, respectively). In the current study, we investigated the safety and immuno-modulatory effects of CMC in prostate cancer patients with PSA failure (biochemical relapse).
Methods: We conducted a prospective phase II study to characterize the clinical and immunological interest of CMC in histologically proven prostate cancer patients previously treated by prostatectomy and with biochemical relapse (defined as PSA >1 and <20ng/mL and progressive PSA level on 3 different measures). CMC was administered *per os,* at daily dose of 50 mg during 6 months. PSA level, serum VEGF and immune parameters were monitored every month in blood samples.
Results: Thirty-four consecutive pts were enrolled in this study and all received CMC. The median age was 68.3 (range, 56.9−82.1) and all pts had good performance status (ECOG-PS = 0). Gleason Score was 7 in 58%, $\leqslant$6 in 13%, and $\geqslant$8 in 13%. No serious adverse events (grade 3−5) were observed. The most common drug-related adverse event was grade 1 lymphopenia. Baseline PSA was 2.92 ng/mL (range, 1.1–9.35). Twenty-two pts presented stable PSA (64.7%), one patient had partial response defined by >50% decline in the serum PSA (3%), and 11 pts (32%) had PSA progression before 6 months. The immuno-monitoring performed in all pts who completed 6 months of CMC. A decrease of immunosuppressive regulatory T cells (Treg) was observed in 56% (12/23). In addition, high rate of activated HLA-DR+ cytotoxic CD8 T cells was also detected in these cohort. Furthermore, serum VEGF level decreased at month 1 but it returned to baseline level at the end of treatment in 9/17 pts evaluated (52%). In some patients the correlation was observed between the control of PSA level, the decrease of Treg and VEGF parameters.
Conclusions: This study demonstrated the clinical benefit and the ability of CMC to promote the blockage of angiogenesis and immuno-modulatory effect in prostate cancer patients treated for a biochemical relapse. It will be of interest to combine CMC to vaccination in these patients.
No conflict of interest.

2897 POSTER

Impact of prior antiandrogen exposure on clinical outcomes in patients (pts) receiving abiraterone acetate (AA): Results from a randomized study (COU-AA-301) in metastatic castration-resistant prostate cancer (mCRPC) post-docetaxel (D)

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Background: AA is a potent androgen biosynthesis inhibitor approved for treatment of mCRPC. Since AA is not a potent antiandrogen, minimal cross-resistance would be expected after prior antiandrogen exposure. A post hoc exploratory analysis was conducted to determine whether prior first-generation antiandrogens would have an impact on overall survival (OS), radiographic progression-free survival (rPFS), and prostate-specific antigen (PSA) response in mCRPC pts post-D.

Material and Methods: COU-AA-301 is a randomized double-blind study of AA (1 g) + prednisone (P) (5 mg po BID) vs P only in mCRPC post-D (N = 1195) with biochemical/surgical castration. The primary end point was OS. Pts who received prior antiandrogens bicalutamide (BIC), nilutamide (NIL), and flutamide (FLT) were examined here. Secondary end points included rPFS (based on modified RECIST [target lesion $\geqslant$2 cm] or bone scan [$\geqslant$2 new lesions not consistent with bone flare]) and PSA response ($\geqslant$50% decrease from baseline). Cox model was used to obtain the hazard ratio (HR) and associated 95% CI, with statistical inference by logrank statistic.

Results: 65%, 15%, and 2% of pts received 1, 2, or 3 antiandrogens, respectively. Pts received prior BIC (893 [74.7%]), NIL (84 [7.0%]), FLT (202 [16.9%]) for a median duration of 12.5 m, 6.0 m, or 9.3 m, respectively (any prior antiandrogen combination, AA+P: 15.3 m [95% CI: 0.2–192]; P: 12.2 m [0.3–166]). Baseline disease characteristics in pts with and without prior BIC, NIL, and FLT were similar. Pts receiving AA+P with prior BIC or FLT had a statistically significant reduction in risk of death and radiographic progression vs P as in pts without prior use (Table). Statistically significant benefit to AA+P was not observed for pts with prior NIL; this may be related to the low n's. PSA response was observed in all pts with prior antiandrogens (AA+P vs P: BIC: 30% vs 6%; NIL: 25% vs 3%; FLT: 31% vs 13%).

	BIC		NIL		FLT	
	+	−	+	−	+	−
AA+P/P	(n = 606/299)	(n = 191/99)	(n = 52/32)	(n = 745/366)	(n = 131/71)	(n = 666/327)
OS (AA+P vs P)						
HR	0.66	0.68	0.64	0.67	0.56	0.69
95% CI	(0.54–0.81)	(0.48–0.96)	(0.34–1.21)	(0.56–0.79)	(0.37–0.85)	(0.57–0.83)
p value*	<0.0001	0.0275	0.1688	<0.0001	0.0065	<0.0001
rPFS (AA+P vs P)						
HR	0.67	0.74	0.64	0.69	0.53	0.72
95% CI	(0.57–0.79)	(0.56–0.97)	(0.38–1.07)	(0.60–0.80)	(0.38–0.75)	(0.62–0.84)
p value*	<0.0001	0.0315	0.0886	<0.0001	0.0003	<0.0001

+/− = with or without antiandrogen exposure; *AA+P vs P.

Conclusions: As shown in this exploratory analysis of COU-AA-301, prior antiandrogen exposure does not appear to impact clinical benefit of AA+P vs P in mCRPC pts post-D. This suggests little cross-resistance to AA after prior BIC and FLT.

Conflict of interest: *Advisory board: Aragon, Astellas, Bayer, BMS, Celgene, Dendreon, Exelixis, Foundation Medicine, GSK, Janssen, Johnson and Johnson, Medivation, Millennium, Novartis, Pfizer, Sanofi, Takeda Millennium (all uncompensated), Astellas, Bristol-Myers Squibb, Cougar, Dendreon, Endo/Orion Pharmaceuticals, Genentech, Janssen, Johnson & Johnson, Medivation, Novartis, Ortho Biotech Oncology Research and Development, Sanofi-Aventis, Senior Scientific LLC, Tokai. Corporate-sponsored research: Aragon, Bristol-Myers Squibb, Exelixis, Janssen Research & Deveopment, Janssen Services Inc, Johnson & Johnson, Medivation. Other substantive relationships: Astellas, Cougar, Dendreon, Janssen, Janssen R&D, Johnson & Johnson, Medivation, Sanofi-Aventis, The Institute of Cancer Research, Tokai*

2898 POSTER

ARN-509 in men with high risk non-metastatic castration-resistant prostate cancer

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Background: ARN-509 is a novel second-generation anti-androgen that binds directly to the ligand-binding domain of the androgen receptor, impairing nuclear translocation and DNA binding. In the Phase II portion of a multicenter Phase I/II study, we evaluated the activity of ARN-509 in 3 distinct patient populations of men with castration-resistant prostate cancer (CRPC): high risk non-metastatic CRPC, metastatic treatment-naive CRPC, and progressive disease after abiraterone acetate. Here we present updated results for the high risk non-metastatic CRPC cohort.

Methods: All patients had CRPC, no radiographic evidence of metastases (pelvic lymph nodes <3 cm below the iliac bifurcation were allowed), and high risk for disease progression based on PSA value $\geqslant$8 ng/mL within 3 months of enrollment and/or PSA doubling time $\leqslant$10 months. Patients received ARN-509 at the recommended Phase II dose of 240 mg/day, previously established in Phase I (Rathkopf et al, ASCO GU 2012). The primary endpoint was PSA response rate at 12 weeks according to the Prostate Cancer Working Group 2 Criteria. Secondary endpoints included safety, time to PSA progression and 1-year metastasis-free survival. PSA assessments were collected every 4 weeks and tumor scans were performed every 16 weeks.

Results: Forty-seven patients were enrolled between November 2011 and June 2012. The median age was 71 years (range 51 to 88) and at baseline, patients presented with ECOG performance status 0 (77%), Gleason Score 8−10 (32%), and median PSA of 12.2 ng/mL. Twenty-six (55%) patients had PSA doubling time $\leqslant$10 months at baseline. All patients received prior treatment with a LHRH analog with or without a first-generation anti-androgen. At a median follow-up of 13.4 months, 10 (21%) patients discontinued the study. The most common treatment-related adverse events (AE) were fatigue (40%), diarrhea (34%), nausea (21%), abdominal pain (17%), and rash (11%). No seizures have been observed to date. As previously reported (Smith et al, ASCO GU 2013), the PSA response rates at 12 and 24 weeks were 91% and 91%, respectively. Median metastasis-free survival has not been reached, however among 34 patients with 1-year follow-up, 3 have developed metastases.

Conclusion: In men with high risk non-metastatic CRPC, ARN-509 is safe and well tolerated with promising preliminary activity based on durable PSA response and disease control.

Conflict of interest: *Ownership: Aragon Pharmaceuticals (ECM)*

2899 POSTER

Docetaxel and curcuminoids combination in patients with castration-resistant prostate cancer: A phase II study

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Background: Prostate cancer is a major problem in the aging male population. Docetaxel, the first-line reference treatment in castration-resistant prostate cancer (CRPC) induces a prostate-specific antigen (PSA) response in 45% of patients and an objective tumor response in 12%. Preclinical studies suggested that curcuminoids inhibit tumor metastasis, invasion and angiogenesis and reverse drug resistance. We wanted to potentiate docetaxel by curcuminoids (CCM) in CRPC first line. Our previous phase I study showed the safety and the tolerability of CCM associated to docetaxel for advanced breast cancers. We have conducted in 2009–2010 a phase II study to assess the response of CRPC to this combination.
Methods: Patients (n = 30) with progressing CRPC and rising PSA were enrolled to receive the experimental treatment. Docetaxel was given in standard conditions (75 mg/m^2, 1 h i.v infusion every 3 weeks for 6 cycles + prednisolone) with CCM orally at the dose of 6gr/day (7 days by cycle: d-4 to d+2). The primary endpoint was response rate assessed by biological and paraclinical examinations. The secondary endpoints included safety, time to progression and compliance. Twenty nine patients were evaluable on PSA assessment and 15 on RECIST criteria.
Results: 26 patients received the treatment totality and 4 withdrew prematurely. No patient withdrew for toxicity (2 deaths and 2 PSA progressions). A PSA response was observed in 17/29 patients (59%) (4 complete and 13 partial) observed rapidly (before the 3rd cycle) for 15 patients. The median time to subsequent PSA progression (TTP) was 5.8 months. Six patients (40%) had a partial objective response and 9 (60%) a stable disease. The median TTP on targets was 7.85 months (n = 13/15). The regimen was well tolerated, with uncommon grade 3/4 toxicity; no adverse event was attributed to CCM. Of 169 cycles, 150 (89%) were completed with perfect compliance. Overall survival was 19 months (mean) and 24 months (median) with 17 events as of december 2012.
Conclusions: These results are promising in improving the response rate to docetaxel in terms of both PSA decrease and objective response, with good tolerability and acceptability of CCM. A randomized trial is necessary to confirm this results.
No conflict of interest.

2900 POSTER

Preliminary product parameters from P11-1, a Phase 2, open-label trial of sipuleucel-T in European men with metastatic castrate-resistant prostate cancer (mCRPC)

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Background: Sipuleucel-T is an autologous cellular immunotherapy approved in 2010 by the FDA for the treatment of asymptomatic or minimally symptomatic mCRPC. Sipuleucel-T is designed to stimulate an immune response against prostate cancer. In the pivotal Phase 3 IMPACT trial, sipuleucel-T showed a 22.5% reduction in risk of death (HR = 0.775 [95% CI: 0.614–0.979]; p = 0.032), and a 4.1-month improvement in median overall survival (25.8 months vs. 21.7 months). P11-1 (NCT01477749) is a Phase 2, open-label, multicentre trial enrolling in Europe. The main aim of the study is to demonstrate that sipuleucel-T can be successfully manufactured for patients (pts) with mCRPC at a European manufacturing facility.
Materials and Methods: Pts enrolled into the study receive sipuleucel-T at approximately 2-week intervals for a total of 3 infusions. Sipuleucel-T is manufactured from autologous PBMCs isolated by leukapheresis prior to each infusion, and activated with PA2024 (a recombinant fusion protein composed of prostatic acid phosphatase [PAP] linked to GM-CSF). The primary endpoint is summarisation of the product parameters and product viability. The product parameters include antigen presenting cell (APC) activation as measured by CD54 upregulation and APC (large CD54$^+$ cells) and total nucleated cell (TNC) counts (x10^9).
Results: As of March 2013, 11 pts have been enrolled into the study across three sites in Austria, the Netherlands and the United Kingdom. APC activation was elevated at infusion 2 (median 16.20; range 6.00–23.50) and infusion 3 (median 14.90; range 7.80–21.20) compared with infusion 1 (median 8.90; range 5.40–16.60), indicative of an immunological prime-boost effect. APC counts did not differ between infusion 1 (median 0.62; range 0.18–1.32), infusion 2 (median 0.49; range 0.16–1.03) or infusion 3 (median 0.61; range 0.19–0.93). In addition, TNC counts remained stable between infusions: infusion 1 (median 4.74; range 1.40–9.80), infusion 2 (median 4.31; range 0.97–12.11) and infusion 3 (median 4.37; range 1.61–7.98).
Conclusions: These preliminary data from the P11-1 trial show that sipuleucel-T can be successfully manufactured by a European manufacturing facility that services multiple nations within the EU. The product parameter profiles are similar to those observed when sipuleucel-T is manufactured for mCRPC pts in the US, and provide evidence of an immunological prime-boost effect.
Conflict of interest: *Ownership: JW, NS, CMC, AS − Dendreon. Advisory board: PM − AstraZeneca, Johnson & Johnson, Dendreon, Wilex. MDS − Amgen, Astellas, Bayer, Dendreon, Eli Lilly, Ferring, GSK, Janssen, Pfizer, Novartis, Pierre-Fabre Oncology, Roche, Sanofi Aventis, Teval Oncogenex. KF, TP − Dendreon. Corporate-sponsored research: PM − Bayer, Astellas. MDS − Pierre-Fabre Medicament. TP − Dendreon. Other substantive relationships: JW, NS, CMC, AS − employee of Dendreon.*

2901 POSTER

Evaluation of continuous abiraterone acetate (AA) plus prednisone (P) dosing in fasting and fed states in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC)

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Background: AA plus P is approved for treatment of pts with mCRPC. A single oral dose of AA in healthy subjects in fed vs an overnight fasted state resulted in a 5- to 10-fold increase in abiraterone exposure. Prescribing guidelines recommend that AA+P is taken orally on an empty stomach with no food consumed at least 2 h before and 1 h after dosing (modified fasting). Pharmacokinetic (PK) exposure and food effect may differ in pts with mCRPC. Here we examined the short-term safety and PK profile of pts with mCRPC treated with AA+P in modified fasting and fed states.
Material and Methods: In this open-label, multi-centre study (NCT01424930), mCRPC pts received oral AA 1 g daily + P 5 mg bid. On Days 1−7, all pts (N = 25) received AA+P in the modified fasting state. On Days 8−14, AA+P was administered within 0.5 h after a standardized low-fat (Group 1, n = 6) or high-fat meal (Group 2, n = 18). Pts then continued AA+P therapy in the modified fasting state until disease progression. Serial 24 h PK sampling was done on Days 7 and 14 (to allow for intrasubject comparison under modified fasting vs fed state), and on Days 8 and 11 at 2 h post dose. Safety was assessed via clinical evaluations and laboratory testing.
Results: Geometric mean (GM) area under the plasma concentration–time curve (AUC) of abiraterone was ~2-fold higher when dosing occurred after high-fat meals compared with the modified fasting state (GM [SD]: 1992 [720] vs 973 [667] ng*h/mL). There was minimal difference in AUC between dosing after low-fat meals vs the modified fasting state (GM [SD]: 1264 [963] vs 1271 [1279] ng*h/mL). Subgroup analysis of modified fasting data revealed that pts who took AA at $\geqslant$2 h after food intake appeared to have higher AUCs compared to those who took AA at $\geqslant$1 h before a meal (GM [SD]: 1466 [1145] vs 843 [541] ng*h/mL). During cycle 1, treatment-emergent adverse events(TEAE) were all grade $\leqslant$3 and similar across pt groups 1 and 2 or AA dosed in a modified fasting or fed state. Grade

3 TEAEs: hypertension, hypokalaemia, hypocalcaemia, vomiting; 1 each occurring in 3 pts.
Conclusions: In pts with mCRPC, repeated dosing of AA+P with high-fat meals resulted in ~2-fold higher mean exposure to abiraterone compared with the modified fasting state. There was negligible change in abiraterone exposure after repeated dosing with low-fat meals. The short-term dosing of AA with food does not alter the safety profile of abiraterone. Taken together, abiraterone exposure associated with food intake does not appear to be clinically relevant.
Conflict of interest: *Advisory board: Janssen. Corporate-sponsored research: Janssen. Other substantive relationships: Janssen, Janssen R&D, Johnson & Johnson*

2902 POSTER

Updated safety results from a cohort compassionate-use programme (CUP) and early access programme (EAP) with cabazitaxel (Cbz) plus prednisone (P; Cbz + P) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel (D)

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Background: Cbz + P significantly improved survival versus mitoxantrone + P in pts with mCRPC previously treated with D in the TROPIC trial (NCT00417079; de Bono, et al. Lancet 2010). A Sanofi-sponsored CUP and EAP were established to provide access to Cbz + P ahead of commercial availability and to document safety in a real-world population.
Materials and Methods: The CUP and EAP are expected to enrol 1600 pts at 250 centres worldwide. Pts receive Cbz 25 mg/m^2 IV Q3W + P 10 mg QD until disease progression, death, unacceptable toxicity or physician/pt decision. In some countries, commercial availability also requires discontinuation. Pts are followed for 30 days after treatment. Granulocyte colony-stimulating factor (G-CSF) use in pts with factors predisposing to neutropenic complications is recommended per ASCO guidelines (Smith, et al. J Clin Oncol 2006).
Results: We report data from 1301 pts in 37 countries. Pts (mean age: 68 years) had received a median of 1 prior line of therapy with D (range: 1−5). Most pts (90.8%) had an ECOG PS of $\leqslant$1, and 60.4% had $\geqslant$2 metastatic sites. Median time from last D dose to first Cbz + P dose was 5.3 months. In 16.6% of pts, disease progression had occurred during the last D line. A total of 697 pts (53.6%) received $\geqslant$6 cycles of Cbz + P. Disease progression was the most common reason for discontinuation (44.0%). The most frequent Grade 3−4 adverse events (AEs; NCI-CTCAE v4.03) possibly related to Cbz + P (total: 42.8%) were neutropenia (18.2%), febrile neutropenia (6.9%), leukopenia (6.8%), anaemia (4.9%), fatigue (4.3%) and diarrhoea (3.9%). In pts with prophylactic G-CSF use at Cycle 1 (n = 571, 44.0%), clinical neutropenia (all Grades) and febrile neutropenia occurred in 11.4% and 2.3% of pts, respectively. These values were similar to those observed in pts not receiving G-CSF at Cycle 1 (11.2% and 2.7%, respectively).
Conclusions: Data from CUP/EAP programmes with Cbz + P show a manageable tolerability profile consistent with results from the TROPIC trial. The similar incidence of neutropenic complications in pts with prophylactic G-CSF use and in pts without G-CSF use at baseline suggests that adequate risk mitigation of such haematological AEs can be achieved with G-CSF in pts at risk of developing neutropenia.
Conflict of interest: *Ownership: S. Hitier has stock ownership in Sanofi. Advisory board: Z. I. Malik has participated in advisory boards for Sanofi, Astellas, Janssen, GSK, Pfizer, Novartis and AstraZeneca. P. Parente has participated in advisory boards for Sanofi. Corporate-sponsored research: F. Saad has conducted research sponsored by Sanofi. A. Heidenreich has conducted research sponsored by Sanofi and Astellas. Other substantive relationships: F. Saad has held a consultant or advisory role with and received honoraria from Sanofi. I. van Oort has received honoraria from Sanofi. S. Hitier holds an employment position at Sanofi. A. Heidenreich has held a consultant or advisory role with Astellas, Amgen, Pfizer, Janssen, Sanofi and Takeda and has received honoraria from Sanofi, Astellas, Janssen, Ipsen, Takeda and Bayer. A. Ardavanis has received honoraria from Sanofi and Novartis.*

2903 POSTER

Metastatic disease detection is an important cause of screen failures in a phase II trial evaluating the optimal sequence of androgen deprivation therapy and sipuleucel-T in hormone-naive patients with biochemically-recurrent prostate cancer (BRPC)

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Background: The management of biochemical failure after definitive local therapy is controversial. Androgen deprivation therapy (ADT) is a standard treatment for this patient (pt) population. An ongoing, randomized phase 2 trial (NCT01431391; P10−2) explores the role of sipuleucel-T in combination with ADT in pts with biochemical failure in order to improve outcomes. It is commonly believed that radiographically-detected metastatic disease is rare in this population. However, a high frequency of metastatic disease (32%) has recently been reported in men with presumed non-metastatic castration resistant prostate cancer screened for the phase 3 ENTHUSE M0 trial (Yu et al., J Urol 2012). Here, we report the rate and characteristics of screen failures for hormone-naive pts who attempted to enroll on the P10−2 study.
Methods: Inclusion criteria are: prior primary therapy (radical prostatectomy [RP], radiation [XRT], or both) for prostate cancer, non-metastatic disease, rising prostate-specific antigen (PSA; $\geqslant$0.5ng/mL for RP, nadir plus 2ng/mL for XRT), PSA doubling time $\leqslant$12 months, testosterone $\geqslant$200ng/dL, and total prior ADT $\leqslant$6 months. We describe the characteristics of pts who did not meet the protocol-specified eligibility criteria (i.e., screen failures).
Results: A total of 99 pts were screened over a 9-month period, with 68 pts randomized into the study and 31 who failed screening (31.3%). Radiographic metastatic disease was detected in 11.1% (11/99 pts) of the total screened population, and was one of the leading reasons for screening failure (35.5%; 11/31 pts). Other reasons for screening failure included PSA doubling time >12 months (35.5%), testosterone levels <200ng/dL (16.1%), no rising PSA (9.7%), and ADT for >6 months prior to registration (3.2%). Compared to enrolled study pts, those with radiographic metastatic disease demonstrated a trend towards higher baseline median PSA (4.3 ng/mL [range: 1.7–141.7; n = 7] versus 2.4 ng/mL [range: 0.3–47.8; n = 68]) and median lactate dehydrogenase (174 U/L [range: 147–599; n = 7] versus 161 U/L [range: 103–248; n = 65]), and shorter median PSA doubling times (3.5 months [range: 1.1−7.6; n = 10] versus 5.1 months [range: 1.0–16.4; n = 68]).
Conclusions: We report a high frequency of radiographic metastatic disease in the earlier setting of hormone-naive BRPC. Pts at high risk for metastatic disease generally had worse prognostic factors. These results highlight the importance of screening for metastases in this population.
Conflict of interest: *Ownership: BMS-patents license: Drake. Advisory board: Dendreon: Kibel, Antonarakis, Yu. Corporate-sponsored research: Dendreon: Antonarakis, Karsh, Yu, Vogelzang The Urology Center of Colorado: Karsh. Other substantive relationships: Denderon consultant: Shore, Drake, Karsh Dendreon honoraria: Karsh Dendreon speaker: Karsh, Vogelzang Dendreon employee ands stock holder: Tyler*

Table (abstract 2905): Outcomes

Outcome	DCA (n = 77)	DAC (n = 36)	Multivariable analysis	
			Significant covariates	(HR)*(95% CI)
Median OS*	18.2	11.8	Sequence (DCA vs. DAC)	0.12 (0.022–0.733)
(95% CI) (mos)	(16, 22)	(9.8, 14.4)	CCI	1.33 (1.060–1.674)
			2nd line duration	0.99 (0.992–0.998)
			PSA/100 ng/ml	1.02 (1.006–1.041)
Median TTF1	5.2	4.3	Narcotic use	1.85 (1.012–3.408)
(95% CI) (mos)	(4.3, 7)	(2.4, 5.1)		
Median TTF2*	10.4	7.1	Sequence (DCA vs. DAC)	0.18 (0.050–0.644)
(95% CI) (mos)	(9.2, 12.1)	(5.6, 8.1)		
C	195.1	88.9		
Median duration* (days)	17 (22)	23 (63.8)		
Treatment <3 months* n (%)				
A	126.4	122.7		
Median duration (days)	32 (41.5)	14 (38.8)		
Treatment <3 months n (%)				

*p-value <0.05.

2904 POSTER

A retrospective study on cabazitaxel and abiraterone acetate sequential treatment (CAST) in docetaxel treated metastatic castrate-resistant prostate cancer patients

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Background: The European Association of Urology considers both cabazitaxel and abiraterone acetate first-choice options for patients with metastatic castrate-resistant prostate cancer (mCRPC) progressing during or after docetaxel. No scientific evidence exists for the preferred second-line therapy. In the CAST-study, the outcome in mCRPC patients treated with cabazitaxel and abiraterone is evaluated retrospectively, with the objective to establish a first scientific indication to the preferred second-line therapy in patients whose condition allows treatment with both compounds.
Patients and Methods: Twelve Dutch hospitals participated in the CAST-study. mCRPC patients were included when having disease progression during or after docetaxel therapy, and when cabazitaxel or abiraterone therapy was initiated before November 3rd, 2012. Patients received standard abiraterone (oral 1000 mg daily) and cabazitaxel treatment (intravenous 25 or 20 mg/m^2 q3w) plus prednisone (10 mg daily). Patients' characteristics were compared between the group that received cabazitaxel first (CA) to patients who received abiraterone first (AC). Primary outcome was median overall survival (OS). Secondary outcomes were progression-free survival (PFS) and biochemical PFS. All data were collected retrospectively; this study did not have any influence on the treatment of mCRPC patients. Therefore these results depict the outcome of cabazitaxel and abiraterone treatment in a representative clinical setting.
Results: In this interim analysis, 48 and 42 patients treated with CA or AC have been included; their median age was 65 and 69 years, respectively. Both treatment groups had on average 2 metastatic sites. Median treatment duration of cabazitaxel plus abiraterone was 10.0 months in the CA-treated group and 7.8 months in the AC-treated group. Median follow-up was 21.2 and 21.0 months; 45.8% and 59.5% of CA- and AC-treated patients had died, respectively. Median OS was 1.48 and 1.19 years in CA- and AC-treated patients, respectively. In CA-treated patients, total PFS was 7.7 and total biochemical PFS was 9.6 months, whereas total PFS and biochemical PFS were 5.5 and 6.4 months in patients treated with AC.
Conclusion: In this interim analysis of the CAST-study, there was a slight survival advantage for patients treated with CA. Further studying is needed to ensure that the results are not biased. At ECCO 2013, an updated analysis will be presented.
Conflict of interest: *Advisory board: Sanofi (Coenen, Gerritsen, Van Oort)*

2905 POSTER

Outcomes with different sequences of cabazitaxel and abiraterone acetate following docetaxel in metastatic castration-resistant prostate cancer (mCRPC)

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Background: The feasibility and outcomes with different sequencing of cabazitaxel (C) and abiraterone acetate (A), following docetaxel (D) in a real world setting in men with mCRPC is unclear. To better understand this research question, we evaluated treatment patterns overall survival (OS), and time to treatment failure (TTF) among post-D mCRPC patients receiving both A and C.
Methods: A retrospective analysis of the US Oncology network iKnowMed electronic health records (EHR) was conducted. with post-D mCRPC patients received both C and A: C followed by A (DCA) and A followed by C (DAC) from April 2011 to May 2012 with $\geqslant$2 visits, excluding clinical trial patients. Median time to OS and TTF were analyzed by Kaplan–Meier method from the start of 2nd line therapy post-D to the end of 2nd line (TTF1) and for the combined 2nd and 3rd line therapy (TTF2). Cox proportional hazard models were used to evaluate impact of age, PCWG2 subtype, Charlson comorbidity index (CCI), PSA/100 ng/ml, hemoglobin (Hb), narcotic use, and 2nd and 3rd line treatment duration on OS and TTF.
Results: 113 evaluable patients were identified (DCA n = 77, DAC n = 36). Baseline characteristics were similar. The median OS and TTF2 were significantly better in the DCA group vs. DAC group (Table). The median number of cycles of C therapy in DCA was greater than in DAC (6 vs. 4) while the duration of A was similar in both DCA and DAC.
Conclusions: In men with mCRPC receiving both C and A post-D, more men received the sequence of DCA compared to DAC and longer exposure to C was observed in the DCA sequence. Given the favorable impact of DCA on OS, we hypothesize that DCA may be a more optimal sequence due to better feasibility of C preceding A. Results from this study are exploratory and a randomized trial may provide definitive results.
Conflict of interest: *Corporate-sponsored research: Research support to institution: Guru Sonpavde, Menaka Bhor, Debajyoti Bhowmik, Debra Rembert, Mark Yap, Rahul Dhanda, Ian Schnadig. Other substantive relationships: Employment by Sanofi-Aventis: Daniel Hennessy, Liji Shen, Leonardo Nicacio*

2906 POSTER

Enzalutamide (ENZA) in heavily pretreated patients with bone metastatic castration resistant prostate cancer (mCRPC) resistant to androgen biosynthesis inhibitor (ABI) treatment − the Hellenic experience of the Name Patient Access Program (NPAP)

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Background: The novel antiandrogen Enzalutamide following its FDA approval for docetaxel treated mCRPC patients (pts) was made available in the European Union through a Name Patient Program. This is a preliminary report of the Hellenic Experience in far advanced mCRPC patients focusing on those resistant to ABIs in an effort to identify and target 'androgen signaling addicted' disease.
Material and Methods: Patients have progressive mCRPC with serum testosterone⩽50 ng/dL. Pts receive oral ENZA 160 mg QD. Pts are monitored at 4 week intervals with liver function, electrolytes, CBC, and physical examinations and agreed to serial Bone Marrow biopsy and use of archived tissue for molecular characterization by immunohistochemistry [Androgen Receptor (AR)- N, AR-C19, ARV7,CYP17, ERG, Glucorticoid receptor, pSrc, pmet,Ki67] and qPCR for AR copy number assessment. Disease is assessed clinically, by serum markers (PSA, alkaline phosphatase) and by imaging (bone scan, CT scan).
Results (preliminary): Since July 2012, 25/35 men who have initiated ENZA treatment within the NPAP had received prior ABIs [Abiraterone Acetate 20, Orterenol 7, (Both 2)]. Median age is 77 yrs (range 66−90), PS-ECOG 2 (range 0−3), baseline PSA concentration 120 ng/ml (range 3.6–649) and LDH > normal limit in 8/25 (32%). Gleason Score (GS) at diagnosis was ⩾8 in 15/20 (75%), [5 pts not evaluable]. Twenty (75%) had ⩾20 bone lesions, 16/25 (64%) lesions in lymph nodes, 4/25 (16%) visceral metastases and 6/15 (40%) had confirmed bone marrow infiltration. All but one pts have received prior chemotherapy [14 (56%) ⩾2 lines]. To date maximum PSA decline ⩾50% is observed in 6/15 (40%) evaluable pts (on treatment ⩾12 weeks and primarily refractory if discontinued earlier. Self-reported PS improvement 4/12 (33%) evaluable pts. No Grade ⩾3 adverse events are reported.
Conclusions: ENZA is well tolerated in a cohort of heavily pretreated far advanced m-CRPC patients and appears in this preliminary report to benefit a subset of pts resistant to prior ABI treatment. Further follow up and a planned molecular characterization of archived bone marrow infiltrating tumors will help guide selection of this population.
Conflict of interest: *Advisory board: advisory boards sc and speakers bureau jnj, Sanofi, astellas, millennium, Bayer*

2907 POSTER

NeuACT, a Phase 2 randomised, open-label trial of DN24-02 in patients (pts) with surgically resected HER2+ urothelial cancer (UC) at high risk for recurrence: updated analysis of product parameters and safety

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Background: DN24-02 is a HER2-targeted autologous cellular immunotherapy (ACI) consisting of antigen presenting cells (APC) cultured with BA7072, a recombinant HER2-derived antigen (HER500) linked to GM-CSF. DN24-02 is based on the same manufacturing platform as sipuleucel-T, an ACI approved for asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer. NeuACT (N10−1; NCT01353222) is an open-label, randomised Phase 2 trial comparing adjuvant DN24-02 to surveillance in HER2+ UC pts at high risk of relapse following cystectomy or nephroureterectomy. The primary endpoint is overall survival. Enrolment is ongoing. Here we report a preliminary analysis of product potency and safety.
Methods: Pts randomised to DN24-02 underwent leukapheresis followed by infusion of DN24-02 for a total of 3 infusions at 2 week intervals. Product potency was assessed by measuring CD54 molecules on APCs; APC activation was defined as the ratio of the average number of CD54 molecules on post-culture cells compared with the number observed on pre-culture cells. Adverse events (AEs) were assessed using CTCAE v4.03.
Results: As of March 2013, 16 pts finished their DN24-02 infusions and were assessed for product potency. APC activation was observed on all 3 infusions but was typically greater at infusions 2 (median 15.25; range 10.19–23.97) and 3 (median 14.63; range 9.70–21.80) compared with infusion 1 (median 7.67; range 4.73–14.34). Of the 22 pts who had received ⩾1 leukapheresis, the most commonly reported AEs in >15% of pts were chills (45.5%), nausea (40.9%), fatigue (36.4%), vomiting (27.3%) and headache (18.2%). Most of these AEs were considered infusion-related, occurring within 1 day of infusion: chills, 40.9%; nausea, 27.3%; fatigue, 22.7%; vomiting, 18.2%; headache, 13.6%. No grade ⩾3 DN24-02-related AEs have been reported. One serious AE (grade 2 pyrexia) was considered treatment-related. No clinically significant left ventricular ejection fraction (LVEF; defined as an LVEF <40% or an absolute reduction in LVEF of ⩾20%) findings have been reported.
Conclusions: This preliminary analysis suggests that DN24-02 product potency (APC activation) is indicative of an immunological prime-boost effect comparable to that observed with sipuleucel-T. The majority of AEs were infusion-related and mild to moderate in severity. Preliminary assessment of safety suggests DN24-02 is well tolerated in UC pts.
Conflict of interest: *Ownership: PS − Jounce. RS, TD, NS − Dendreon. Advisory board: DB − Dendreon, Pfizer, Eli Lilly, Novartis. LG − Dendreon, Astellas, Bayer, Abbott, Janssen. Corporate-sponsored research: DB − Dendreon, Genentech, Pfizer, Novartis, Amgen, Genta. LG − Dendreon, Astellas, Janssen. Other substantive relationships: DB − honoraria from Eli Lilly. PS − consultant for Dendreon, BMS, Jounce, MedImmune, Helsinn Therapeutics. RS, TD, NS − employee of Dendreon. POD, LG − honoraria from Dendreon.*

2908 POSTER

Clinical outcomes (CO) evaluation of very old (⩾80 years) castration resistant prostate cancer (CRPC) patients (pts) treated with docetaxel (DOC): Updated results of an Italian multicenter retrospective study (cooperative group for DELPHI study)

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Background: Since prostate cancer is mainly diagnosed in pts over 65 yrs of age, castration resistance is usually observed in older pts. In the case of very old pts (⩾80 years), fear of high toxicity degree limit chemotherapy use due to both pts frailty and several comorbidities occurrence. Moreover, if treated these pts usually receive an adapted chemotherapy, often with a weekly schedule, which in TAX327 trial failed to show survival advantage compared to mitoxantrone. The present retrospective study is aimed to assess CO in this very elderly CRPC population.
Methods: In this multicentric retrospective study, after Ethical Committee approval, we have reviewed the clinical records of all ⩾80 yrs CRPC pts from participating institutions, treated with DOC in clinical practice, recording the pre and post-DOC clinical history, the DOC treatment details and outcomes.
Results: To date we collected a consecutive series of 95 pts from 22 Italian hospitals. The median age was 83 yrs (range 80−90). The median baseline PSA was 124 ng/ml (range 3–1597); 83% of the pts had bone metastases, while nodal, lung and liver metastases were observed in 38%, 5%, and 6% of the pts, respectively. Median Cumulative Illness Rating Scale score was 3 (range 0−11), median Activity Daily Living index score was 0 (range 0−5), median Instrumental Activities of Daily Living score was 0 (range 0−5). The DOC was administered on 3-week or weekly schedule basis (40%/60%). A PSA reduction >50% and an objective response were observed in 76% and 10% of the pts, respectively. Grade 3−4 toxicities were: neutropenia (11%), fatigue (9%), diarrhea (1%), renal (2%), and febrile neutropenia (1%). The median PFS and OS were 7.5 mos and 21.5 mos, while the 1-year PFS and OS rates were 18.6% and 44.2%, respectively.
Conclusions: This data suggests that DOC treatment, both on 3-week or weekly schedule, is able to produce good survival outcomes, comparable to pivotal trials (18 mos), also in highly selected very older (⩾80 yrs) CRPC pts. Data collection is ongoing from other Hospitals.
No conflict of interest.

2909 POSTER

P10−1, an open-label, multicenter study of sipuleucel-T in men with metastatic castrate-resistant prostate cancer (mCRPC) previously treated with sipuleucel-T: Analysis of immunological data

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Background: Sipuleucel-T is an autologous cellular immunotherapy shown to improve survival in men with asymptomatic or minimally symptomatic mCRPC. P10−1 (NCT01338012) is an open-label, multicenter study of sipuleucel-T in men with mCRPC who previously received sipuleucel-T in the androgen-dependent setting in the Phase 3 PROTECT study (NCT00779402). This analysis of P10−1 evaluates antigen presenting cell (APC) activation, cellular immune responses and cytokine responses in patients (pts) retreated with sipuleucel-T.
Materials and Methods: Pts who had previously received at least one infusion of sipuleucel-T in PROTECT and had progressed to mCRPC will be retreated with up to three infusions of sipuleucel-T in P10−1. APC activation was assessed by CD54 upregulation (expressed as the ratio of the average number of CD54 molecules on post- vs pre-culture cells). Cellular immune responses were assessed before retreatment and at weeks 2, 4 and 6 by enzyme-linked immunospot (ELISPOT) assays. Serum cytokine levels were measured at baseline, after each sipuleucel-T infusion, and at week 6.
Results: As of March 2013, 7 pts have been enrolled and have received at least one infusion of sipuleucel-T. The median years from the last treatment on PROTECT was 8.6 years (range 5.5–10.0). APC activation was higher with the 1st sipuleucel-T infusion in P10−1 (median 19.8; range 11.7–26.2) compared with the 3rd infusion in PROTECT (median 13.2; range 6.4–19.0). Antigen-specific ELISPOT responses were detected at baseline, and elevated after the 1st infusion. IL-2 was the only cytokine significantly increased following the 1st sipuleucel-T infusion compared with baseline ($p = 0.005$). T cell activation-associated cytokines (IL-4, IL-5, IL-10 and IFN-γ) were significantly elevated after either 2nd or 3rd sipuleucel-T infusions vs baseline ($p < 0.05$).
Conclusions: P10−1 is the first study of pts retreated with sipuleucel-T after treatment in an earlier disease setting. Higher APC activation in the 1st treatment in P10−1 and detection of antigen-specific ELISPOT responses before retreatment indicate an underlying immunological memory response several years after initial treatment. Elevation of antigen-specific ELISPOT responses after the 1st infusion is a hallmark of memory immune response. Further studies are required to determine whether increased serum IL-2 levels following the 1st infusion of retreatment with sipuleucel-T is unique to pts previously treated with sipuleucel-T.
Conflict of interest: *Ownership: HH, RS, YW, NS − Dendreon. Advisory board: TB − Dendreon. MG − Dendreon, Bayer. Corporate-sponsored research: TB, MG, RG, JC − Dendreon. Other substantive relationships: HH, RS, YW, NS − employee of Dendreon.*

2910 POSTER

Impact of news drugs in the median overall survival of patients with metastatic castration resistant prostate cancer (mCRPC)

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In the past 3 years new therapies, such as cabazitaxel (C): a novel taxane, enzulatamide (E): a new androgen receptor signaling inhibitor and abiraterone acetate (A): an inhibitor of androgen synthesis, have been developed in the treatment of post-docetaxel métastatic castration resistant prostate cancer (mCRPC) patients. This study assessed the clinical impact of these new drugs, comparing the outcomes of two historical cohorts of patients with mCRPC.
Methods: We retrospectively reviewed the data of all patients with mCRPC treated by first line chemotherapy with docetaxel (D) at the Centre Léon Bérard. Based on the timing of the development of new drugs, we defined two cohorts based on two time periods depending on drugs available on the market: group 1: 2006–2009 corresponding to the period when only conventional drugs (D, mitoxantrone) were available; group 2: 2009–2012 corresponding to the period when new drugs like C, E, A could be used post docetaxel.
Outcome evaluated was overall survival (OS). OS was defined as the time from date of D introduction to date of death or date of last follow-up for patients alive at last contact. Survival distributions were estimated by the Kaplan–Meier method and compared between groups using Log-Rank test.
Results: One-hundred and thirty five patients were included: 66 patients in group 1 and 69 patients in group 2. Median age was 64 years in both groups. Karnofsky score was $\geqslant$80% for 67.7% of patients in group 1 and 81.8% in group 2. Gleason score was $\geqslant$9 for 38.7% and 31.4% of patients, respectively. In group 1, 47% of patients had node metastases when started on chemotherapy *vs* 40.6% in group 2. The weekly schedule of D (25 mg/m^2) was significantly more frequently used in group 1 than in group 2 (53% *vs* 15%, $p < 0.001$). Median cumulative doses of D as first line treatment were significantly higher in group 2: 643 mg/m^2 *vs* 454 mg/m^2 ($p < 0.001$).
Median overall survival was 10.6 months (95% CI 7.8–15.7) in group 1 *vs* 32.5 months (95% CI 25–42.4) in. group 2 ($p<0.0001$).
Conclusions: This study reflects how the management of mCRPC patients has evolved over the last 7 years. Survival has improved especially through an earlier management, a more intensive schedule of D and the impact of these new drugs.
Conflict of interest: *Other substantive relationships: Pfizer, Sanofi, Janssen, Novartis, Roche*

2911 POSTER

Quality of life (QoL) in patients with metastatic castration resistant prostate cancer (mCRPC) treated with cabazitaxel: Interim analysis of a prospective non-interventional trial (QoLiTime)

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Background: Cabazitaxel (Caba) combined with Prednisone or Prednisolone is approved for second-line treatment of mCRPC after Docetaxel. Potential toxicity of chemotherapy may impact on patients' QoL and counterbalance treatment benefits. Thus QoL data are becoming more important from patients and regulatory perspective.
Material and Methods: Patients with mCRPC receiving Caba are asked to fill in EORTC QLQ C30 QoL questionnaires every three weeks. Here we describe QoL results of the first 131 patients of 480 planned in total.
Results: 131 patients who had finished 4 cycles of Caba treatment are evaluated. Median age was 72 years with generally good performance status (ECOG 0, n = 51; ECOG 1, n = 70). Bone metastases (n = 106 (82%)) and lymph node metastases (n = 66 patients (51%)) are most common. 114 patients have been pretreated with Docetaxel (6 cycles mean). Mean baseline functioning scales were (n = 119 patients): cognitive 80, emotional 65, physical 64, social 63, role 53. QoL questionnaire compliance was excellent: 114 patients (96%) reporting QoL data in cycle 4. Mean functioning values and global health status remained unchanged during the first 12 weeks of treatment. Mean baseline values for symptom scales are: fatigue 50, pain 42, sleep disturbance 39, appetite loss 32, dyspnea 31, constipation 24, financial difficulties 15, diarrhea 13, nausea/vomiting 9. A significant improvement of pain between baseline and cycle 4 (mean 35) ($p = 0.03$) and a trend regarding improvement of sleeping disturbance (cycle 4 mean 33) ($p = 0.15$) were noticed, while diarrhea significantly increased (cycle 4 mean 21; $p < 0.01$). Other parameters remained unchanged.
Conclusions: This interim analysis is the largest prospective non-interventional analysis of QoL in patients receiving Cabazitaxel for mCRPC. QoL questionnaire compliance was excellent. A significant improvement of pain and a trend for improved sleep quality were shown, for the price of increased diarrhea. Importantly, mean global health status was maintained during the 12-week observation period. Results need to be confirmed by final analysis.
Conflict of interest: *Advisory board: Sanofi-Aventis Germany. Other substantive relationships: Sanofi-Aventis Germany*

2912 POSTER

Does testosterone breakthrough impact biochemical failure in prostate cancer patients?

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Background: Androgen deprivation therapy (ADT) has been shown to play an important role in earlier stages of prostate cancer. Indeed, in patients with locally advanced or high-risk localized disease, the addition of neoadjuvant and adjuvant hormone therapy is now considered the

standard of care for those men treated with radical radiotherapy. Although luteinizing hormone-releasing hormone (LHRH) agonists have been used for many years as ADT, they may be associated with clinical testosterone breakthroughs. The question, however, remains if these testosterone breakthroughs impacts disease progression. This study will analyzed the breakthrough rates above castrate levels of testosterone, in a population-based series of men undergoing LHRH agonist therapy with curative radiation therapy and further correlated this with the rate of biochemical failure at 5 years.
Methods: Prostate cancer patients treated between 2000 and 2011 with curative radiation therapy were potentially eligible (n = 1442). Of these, 542 patients fulfilled the eligibility criteria with at least 3 months of LHRH agonist therapy and serial testosterone and PSA measurements during and after continuous LHRH therapy. Breakthrough rates of 0.7−1.1 nmol/L, 1.1−1.7 nmol/L and >1.7 nmol/L were calculated for each patient course. Various factors influencing the PSA failure and testosterone suppression were identified, and early surrogates of oncological outcome (clinical stage, Gleason score and pretreatment PSA) were determined for multivariate analysis.
Results: The risk of any breakthrough >0.7 nmol/L was 25%. Breakthrough 1.1−1.7 nmol/L occurred in 4.5% of the patients and >1.7 nmol/L in 5.6%. During 2334 person-years of follow-up, 92 patients experienced a biochemical relapse, yielding an overall rate of 3.94% per year. In multivariate analysis (adjusting for clinical stage, pretreatment PSA, Gleason score, age and smoking) neither overall biochemical failure (bNED = Nadir + 2) nor survival were compromised, although subgroup analysis showed a trend towards inferior 5-year bNED in those with breakthroughs of >1.7 nmol/L vs those without, with an adjusted HR: 1.74 (0.98–3.10). Furthermore, there were no differences in testosterone breakthrough amongst the commonly prescribed LHRH agonists (Goserelin, Leuprolide i.m, Leuprolide s.c and triptorelin).
Conclusion: Testosterone breakthrough above 0.7 nmol/L occurs in, at least, one quarter of these patients treated with curative radiation therapy and LHRH agonist. Breakthrough levels above 1.7 nmol/L appear to be associated with higher rates of biochemical failure. As such, it is imperative to monitor testosterone levels and PSA during LHRH agonist therapy.
No conflict of interest.

2913 POSTER

Predictors of outcome to post-docetaxel abiraterone acetate (AA) in metastatic castration-resistant prostate cancer (mCRPC) patients (p)

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Background: AA is a standard treatment in mCRPC p both pre- and post-docetaxel treatment, but there is no recognized predictive marker of outcome. We have performed a retrospective analysis of mCRPC p treated with AA after progressing to docetaxel at the three hospitals of the Catalan Institute of Oncology.
Material and Methods: Data on p characteristics, upfront therapy, treatment outcomes and toxicity were collected. Multivariate analyses were performed using cox regression with stepwise algorithm to identify markers of progression-free survival (PFS) and overall survival (OS).
Results: From August 2011 to March 2013, 49 mCRPC p who had progressed to docetaxel were treated with AA. Median age, 74 years (y) (49−86); performance status (PS) 0, 1, 2 in 11 (22%), 25 (51%) and 13 (26%) p, respectively; Gleason score, 6−7/10 in 14 (29%) p and 8−10/10 in 27 (55%). Bone, nodal and visceral metastases were present in 39 (80%), 25 (51%) and 3 (6%) p, respectively. Median time on hormonal treatment (LHRH analogues) before starting docetaxel was 3 y. Before starting AA treatment, 30 (61%) p had received only docetaxel, and 19 (39%) had received docetaxel followed by $\geqslant$1 other chemotherapy regimens. Median number of cycles of docetaxel was 8. 4 (8%) p progressed during docetaxel treatment or within 3 months (m) after receiving their last dose; the remaining p progressed later. Median time on AA treatment was 7.5 m (0.5−12). Median PSA doubling-time at AA start was 1.5 m. On AA treatment, 21 (43%) p had $\geqslant$50% PSA decline, and 16 (33%) p had no PSA decline. 5 (10%) p attained partial response (RECIST), and 9 (18%) had stable disease. 17 (35%) p had clinical improvement. Median follow-up was 7 m (1−18). Median PFS was 7.5 m. Median OS was not reached. Only grade 1 toxicity was observed in 11 (22%) p. In the multivariate analyses, time on hormonal treatment (HR, 1.0; P = 0.007), PS (HR, 7.6; P = 0.036) and PSA nadir on AA treatment (HR, 2.9; P = 0.013) were markers of PFS, and time on hormonal treatment (HR, 0.995; P = 0.03) and PSA nadir (HR, 3.98; P = 0.01) were markers of OS.
Conclusions: This is the largest cohort of mCRPC p treated with AA post-doc outside a clinical trial setting in Spain. Treatment outcomes are in line with results of clinical trials and confirm the effectiveness of AA in an unselected population. Time on hormonal treatment, PS and PSA nadir have emerged as potential predictors of outcome to AA.
No conflict of interest.

2914 POSTER

Temsirolimus (TEM) maintenance therapy benefits patients with castration-resistant prostate cancer (CRPC) after response to docetaxel (TAX)

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Background: There is no standard therapy for men with CRPC who have responded to TAX and have not yet progressed. Aside from androgen receptor signaling, the mTOR pathway is amongst the most relevant contributors to CRPC progression. Given significant preclinical anti-CRPC activity of mTOR inhibitors, we designed a single-arm, multicenter phase II trial to explore whether therapy with TEM has the potential to maintain the response to TAX without compromising quality of life.
Methods: From 2009 until 2012 we recruited 21 CRPC pts with documented response to 6 to 10 cycles of TAX (75 mg/m^2 q3wks) by PSA (>50% decline from baseline) or RECIST (1.0) criteria. Pts received weekly TEM (25 mg iv x 4/cycle). The primary endpoint was time to treatment failure (TTF; RECIST or symptomatic progression). Secondary endpoints included safety (NCI-CTCAE v3.0), quality of life (FACT-P, PPI), PSA parameters, tumor response rate, and overall survival (OS). We also collected serum, plasma and peripheral blood mononuclear cells at baseline and 3-monthly thereafter for correlative studies such as the measurement of angiogenic factors.
Results: The mean ($\pm$SD) age of pts was 68 ($\pm$7.7) years. 8 pts had undergone prostatectomies, 17 pts had received local radiation therapy. After a median of 7 cycles of TAX (range 6−10) pts presented with a median baseline PSA of 17.3 μg/L (0.02–380.7). 18 pts had bone, 9 visceral and 10 nodal metastases. Pts received a median of 7 cycles of TEM (2−28), resulting in a median TTF of 6 months (95% CI 4.2−9.2), considered meaningful based on shorter treatment-free intervals observed during intermittent TAX therapy. 11 pts achieved SD and 1 patient a PR by RECIST, but no PSA responses were seen (median time to PSA progression 2.8 months). While the median OS is not yet reached, the 6, 12 and 24 month survival rate was 100%, 94% and 75%, respectively. TEM-associated grade 3 events were infrequent, and quality of life was not adversely affected by TEM. 13 pts discontinued treatment because of treatment failure (symptomatic 9, RECIST 3, combined 1); 4 pts for other reasons, including TEM-associated lymphedema in 1 pt; and 4 pts remain on TEM. Biological samples are currently being analyzed.
Conclusions: TEM maintenance therapy in CRPC pts that have responded to TAX is feasible, does not adversely affect their quality of life, and it results in meaningful prolonged TTF. Further study of TEM may be warranted in the rapidly changing post-TAX treatment space.
No conflict of interest.

2915 POSTER

Phase I trial of fractionated-dose 177Lutetium radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody J591 (177Lu-J591) for metastatic castration-resistant prostate cancer (CRPC)

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Background: A phase II trial of single-dose ^{177}Lu-J591 in men with metastatic (met)CRPC demonstrated efficacy with acceptable toxicity and a dose-response relationship. Dose fractionation may decrease toxicity while maintaining or increasing efficacy.
Methods: In the dose-escalation phase, cohorts of 3−6 men with progressive metCRPC received 2 fractionated doses of ^{177}Lu -J591 2 weeks apart: Cohort 1 (20 mCi/m^2 x2), dose escalation 5 mCi/m^2 per dose per cohort up to 45 mCi/m^2 x2 to determine dose limiting toxicity

and cumulative maximum tolerated dose (MTD) of fractionated ^{177}Lu -J591. Expansion of recommended phase II dose (RP2D) cohorts was performed for preliminary efficacy data. ^{177}Lu -J591 planar imaging with semi-quantitative scoring was performed.

Results: 28 men in the dose-escalation phase received up to 45 mCi/m^2 x2; 12 additional in expansion cohorts (total n = 40). Median age 75.4 years (range 55−95), median baseline PSA 44.7 (2–766.5). 85% had bone mets, 65% LN mets and 47.5% lung/liver mets. All had progressed after 1−4 hormonal therapies and 40% after 1−4 lines of chemotherapy including docetaxel. Despite cumulative doses exceeding the single-dose MTD (70 mCi/m^2, a dose at which 41% receive platelet transfusions), during the dose-escalation phase only 6 men receiving up to 90 mCi/m^2 experienced Gr 4 thrombocytopenia (plts); 2 received transfusion. 3 experienced Gr 4 neutropenia (ANC) without fever or growth factors. Gr >1 non-hematologic toxicity was rare. 24 men were treated at RP2Ds (40 mCi/m^2 x2 or 45 mCi/m^2 x2 with allowable WBC growth factor); 12 (50%) had Gr 4 plts (10 with transfusion), 8 (33%) had Gr 4 ANC without fevers (2 received growth factor). By planar imaging, accurate targeting of known sites of PC mets was seen in 87%. Including all cohorts, 50% had any PSA decline, 30% with ⩾30% decline, 20% with ⩾50% decline. At RP2Ds, 58.3% had any PSA decline, 41.7% with ⩾30% decline, 29.2% with ⩾50% decline. Those with stronger PSMA expression by semi-quantitative imaging had more PSA declines (53% vs 20%, p = 0.18) and PSA responses (34% vs 0%; p = 0.29). 10 of 13 with baseline elevated circulating tumor cell counts (CTCs, CellSearch methodology) decreased by 6 weeks and 3 additional with 0 CTCs at baseline remained 0. Median survival is 25.3 mo [95% CI 17.3, 33.4] for all, 43.5 mo [95% CI, 26.5, 60.5] at RP2D. Survival was longer for those with PSA decline (32.7 vs 23.0 mo, p = 0.03).

Conclusions: Fractionated dose ^{177}Lu-J591 is well tolerated, with reversible myelosuppression and better tolerance of higher cumulative doses than single-dose ^{177}Lu-J591. Non-invasive assessment of PSMA expression might be a predictive biomarker.

Sponsors: Department of Defense, National Institutes of Health, Prostate Cancer Foundation, Weill Cornell Medical College [clinicaltrials.gov NCT00538668]

Conflict of interest: *Ownership: BZL Biologics. Advisory board: BZL Biologics*

2916 POSTER

Testosterone defining prognosis and predicting response in castration-resistant prostate cancer (CRPC)

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Background: New second line treatments in CRPC have emerged in the last 3 years. Lack of prognostic and predictive factors has arised the question of who benefits most from a chemotherapy (CT) or a salvage hormonal treatment (HT) after docetaxel failure. We analyzed the role of testosterone in this setting.

Material and Methods: We retrospectively analyzed 101 patients with CPRC included in 9 different first line CT phase II−III trials in two single institutions in Spain, since August 2006 until October 2012. Inclusion criteria required castration levels of testosterone(<50 ng/dL). Baseline testosterone level (TL) was determined by automated immunoassay. We also analyzed patients who received a hormonal maneuver after first line CT. Response was measured by PSA (PSAR). Survival times were analyzed using a Kaplan–Meier model. A Cox regression model was used to analyze prognostic factors for survival. Multivariate analysis was performed on those variables that were significant on the univariate analysis.

Results: Median TL was 11.53 ng/dL. First line CT was docetaxel in 70% of the patients. Testosterone baseline levels had impact in overall survival (OS), Disease Free Survival (DFS) and time to death since 1st line CT progression (TTD) (table 1). Other prognostic factors shown to be significant were: Baseline PSA (Lower vs Higher, HR 0.48, p = 0.0062), age (<65 vs ⩾65 years old, HR 0.48, p = 0.0259) and anemia (No vs Yes, HR 0.40, p = 0.0015).

After first line CT failure, 41/101 patients were treated with hormonal treatment. There were more responders in the High TL group than in the Low TL group (56% vs 21%, p = 0.0196). Responders to HT had a higher OS when testosterone was high (60.9 vs 20.6 months, p = 0.0092).

Conclusions: Lower than median testosterone levels, higher than median PSA levels, >65 years and anemia were significant prognostic factors for a worse survival in patients with metastatic CRPC. Higher baseline testosterone levels predicted a better response to salvage hormonal therapy after CT failure. This response translated into a better survival. Baseline testosterone could help us in treatment decision after first line chemotherapy failure.

No conflict of interest.

Table 1. Survival times depending on testosterone levels

Survival (months)	All patients (N = 101)	TL < median value (N = 49)	TL > median value (N = 52)	P log-rank	Cox-Prop HRR
OS	24.5	22.4	32.7	0.0162	HR 0.52 p = 0.018
DFS	5.1	4.9	5.7	0.0010	HR 0.484 p = 0.0014
TTD	19.3	16.4	23.7	0.0456	HR 0.58 P = 0.0482

2917 POSTER

Impact on abiraterone pharmacokinetics (PK) and safety: Open-label drug–drug interaction (DDI) studies with ketoconazole and rifampicin

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Background: Abiraterone acetate (AA) is a prodrug of abiraterone, an androgen biosynthesis blocker, which specifically inhibits CYP17. AA + prednisone or prednisolone therapy improves overall survival or radiographic progression-free survival in patients with metastatic castration-resistant prostate cancer with and without prior chemotherapy. In vitro, abiraterone is a substrate of CYP3A4, a key enzyme involved in metabolism of many prescribed drugs. These DDI studies evaluate the impact of a strong CYP3A4 inhibitor, ketoconazole (K), and a strong inducer, rifampicin (R), at steady state on the PK exposure and safety of abiraterone.

Material and Methods: Data from 2 (NCT01588782, NCT01655147) single-center, open-label DDI studies conducted in healthy men to evaluate the effects of K (Group A) and R (Group B) are presented. Subjects in both groups received 1000 mg of AA on Days 1 and 14. Group A (n = 20) received 400 mg K on Days 11−16. Group B (n = 19) received 600 mg R on Days 8−13. Serial PK sampling was done on Days 1 and 14 and safety was assessed via clinical and laboratory test and adverse event (AE) reporting.

Results: Based on geometric mean ratios (GMR), abiraterone exposure was increased by 9% for C_{max} (90% CI, 90.0–131.1) and 15% each for AUC_{last} (90% CI, 97.9–134.3) and AUC_{∞} (90% CI, 98.3–134.4) for AA+K vs AA alone. Mean (SD) values of abiraterone PK parameters for AA+K vs AA alone: C_{max} (137 [48] vs 131 [60] ng/mL), AUC_{last} (739 [274] vs 672 [332] h*ng/mL) and AUC_{∞} (753 [277] vs 682 [335] h*ng/mL).

Based on GMR, abiraterone exposure was reduced to 45% each for C_{max} (90% CI, 35.0–57.0) and AUC_{∞} (90% CI, 38.0–53.9) and to 42% for AUC_{last} (90% CI, 35.2–50.6) for AA+R vs AA alone. Mean (SD) values of abiraterone PK parameters for AA+R vs AA alone: C_{max} (61 [43] vs 138 [72] ng/mL), AUC_{last} (294 [169] vs 727 [433] h*ng/mL) and AUC_{∞} (332 [170] vs 747 [438] h*ng/mL).

Treatment-emergent AEs were reported in 8 (40%) patients in Group A and 13 (68%) in Group B; most were grades 1−2. No serious AEs, deaths, or discontinuations due to AEs were reported.

Conclusions: Ketoconazole had no clinically meaningful impact on abiraterone exposure. Rifampicin, however, decreased abiraterone exposure by half. Hence, clinical efficacy should be carefully evaluated when administering AA with known strong CYP3A4 inducers. The safety profile of adult men who received a single dose of AA was similar to previous studies of healthy adult men.

Conflict of interest: *Other substantive relationships: Janssen, Janssen R&D, Johnson & Johnson*

Table 1 (abstract 2918). Characteristics of patients with a ⩾50% PSA response.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at steroid switch (yr)	73.1	81.8	62.5	69.2	66.5
Metastatic disease at start of AA	Bone	Bone, LN	Bone, LN	LN	Bone
Baseline PSA before steroid switch (ng/mL)	1084	2689	210	41	1458
Max.PSA decline on switch (%)	95.6%	84.5%	78.6%	77.2%	55.5%
Duration of treatment Abi-Dex (m)	5.4 (Ongoing)	5.7	8.2 (Ongoing)	5.4 (Ongoing)	0.8
Time to PSA nadir on Abi-Dex (m)	3.6	1.8	6.2	2.9	0.4
Duration of treatment Abi-Prednisolone (m)	4.8	4.8	14.9	29.9	28.7
Max. PSA decline on Abi-Pred	78%	27%	38%	99%	99%
Previous Single Agent Dexamethasone treatment (duration, m)	Yes (59.9)	Yes (15.3)	Yes (3.5)	No	No
Previous chemotherapy lines	1	1	1	0	2
Baseline variables at steroid switch					
ECOG PS	1	0	1	0	2
Hemoglobin (g/dL)	10	12.4	13.7	10.6	7.9
Alk Phos (IU/L)	2238	100	85	44	277
LDH (IU/L)	418	214	169	150	208
Albumin (g/dL)	36	42	34	40	25

2918 POSTER

Tumor responses after steroid switch of prednisolone (P) to dexamethasone (D) in castration-resistant prostate cancer (CRPC) patients (pts) on abiraterone acetate (AA)

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Background: AA is an effective treatment for CRPC. AA has been combined with P 5 mg twice daily to minimize side-effects of secondary mineralocorticoid excess. Long-term use of P could select for androgen receptor (AR) mutations activated by P and we therefore hypothesized that a change in steroid regimen could result in secondary PSA declines in pts progressing on AA and P.
Material and Methods: We prospectively performed a 'steroid switch' from P to D 0.5 mg on 20 pts with a rising PSA (>25% from nadir confirmed after >3 weeks) on AA at the Royal Marsden and University College London Hospitals between January 2011 and February 2013. PSA was measured monthly after switch and restaging scans performed every 3 months or when clinically indicated.
Results: Nine of 20 pts currently continue treatment on AA and D. Eleven pts were discontinued, five (25%) due to PSA progression exclusively and six (30%) due to clinical or radiological progression. Five of 20 patients (25%) had a ⩾50% PSA reduction, confirmed by a second PSA 1 month later in 4 pts and 1 pt had a confirmed ⩾90% decline in PSA (Table 1). The median duration of treatment on AA and D after switch was 2.8 months. Steroid switch was well tolerated with no increase in side-effects from mineralocorticoid excess.
Conclusion: This is the first report of maintained PSA declines after a steroid switch in pts treated with AA and P. Next-generation sequencing of the AR in samples from patients undergoing a switch is currently ongoing. Steroid switch could represent a reasonable and well-tolerated therapeutic intervention in pts progressing on AA and P.
Conflict of interest: *Other substantive relationships: D. Lorente, A. Omlin, C. Pezaro, R. Ferraldeschi, C. Parker, D. Dearnaley, J. De Bono and G. Attard are all employees of the Institute of Cancer Research, which has a commercial interest in abiraterone acetate.*

2919 POSTER

Impact of comorbidity on outcome in men with metastatic castrate-resistant prostate cancer (mCRPC)

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Background: Based on randomized data showing survival improvements, three-weekly docetaxel is the gold standard treatment for patients with mCRPC. Despite this, some patients do not receive treatment, likely due to the assumption of poor tolerability due to comorbid conditions. Here we explore the impact of comorbidity on outcome in men with mCRPC in a population-based observational study.
Material and Methods: Men with mCRPC who were treated with docetaxel at the Institute of Oncology Ljubljana between 2005 and 2012 were eligible. Comorbidity was assessed by using Adult Comorbidity Evaluation (ACE-27) [score 0, 1, 2 or 3] and age-adjusted Charlson Comorbidity Index (aaCCI) [score 0, 1−2, 3−4 or >4]. Accordingly, comorbidity was categorized as none, mild, moderate and severe with higher score indicating a higher level of comorbidity. The association between comorbidity and overall survival (OS) was tested using Cox proportional hazards analysis. Comorbidity was analyzed as both categorical and dichotomous (score 0 vs. ⩾1) variable.
Results: Two hundred and eight men with a median age of 69.9 years were included. At baseline median PSA, Hb and alkaline phosphatase were 217 ng/ml (0->5000 ng/ml), 124 g/l (52–163 g/L) and 2.9U/L (0.57–146 U/L), respectively. Visceral metastases were present in 16% (n = 34) and 44% (n = 91) received opioid analgesia. No, mild, moderate and severe comorbidity was present in 2%, 32%, 53% and 13% using ACE-27 and in 27%, 35%, 29% and 8% when assessed by aaCCI. Ninety six percent (n = 199) of men received three-weekly and 4% (n = 9) received weekly docetaxel. After docetaxel 20% of patients (n = 41) received abiraterone acetate and 8% (n = 17) cabazitaxel. After median follow-up of 14 months, 133 men died. In univariate analysis a higher level of comorbidity was not associated with worse OS (ACE-27: HR 0.96; [95% confidence interval (CI) 0.79–1.17], p = 0.69; aaCCI HR 0.99; [CI 0.87–1.13], p = 0.93). Similarly, when analyzed as dichotomous variable a higher level of comorbidity was not associated with worse OS (ACE-27: HR 0.75 [CI 0.51–1.08], p = 0.12; aaCCI: HR 1.48 [CI 0.37−6.0], p = 0.58). Anemia, a weekly docetaxel schedule, no use of abiraterone and/or cabazitaxel and presence of visceral metastases were significant independent predictors of poor OS in multivariate analysis.
Conclusions: Despite comorbidities, men with mCRPC can have a substantial benefit from docetaxel and other systemic therapies in everyday clinical practice.
No conflict of interest.

2920 POSTER

Docetaxel response after 3 cycles as a predictor of survival in patients with metastatic castration resistant prostate cancer

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Background: The treatment of metastatic castration resistant prostate cancer (mCRPC) has changed in the last few years, with docetaxel still remaining as standard first-line chemotherapy. Nevertheless, we don't have factors able to predict which patients are going to derive the greater benefit from available therapies. Neither we have tools to estimate this benefit when patients have alredy begun therapy. We analyzed PSA response after 3 and 6 cycles of therapy with docetaxel, and tried to find a relationship with survival in these patients.
Material and Methods: We prospectively included consecutive patients with mCRPC that had been treated with at least 3 cycles of docetaxel. Patients with less than 3 cycles were excluded, as well as patients treated with other chemotherapy drugs before docetaxel.

Results: 64 patients were included, with a median age of 72.5 years (range 46−86). 27 patients had a Gleason score >7, 22 patients had a Gleason score ⩽7 and 15 patients had an unknown score. Median PSA at the initiation of docetaxel was 130 ng/ml (range 8.3–3355). 90.6% of patients had bone metastases, 32.8% had nodal metastases, and 4.7% had visceral metastases.
Patients with a reduction of PSA levels higher than 50% of baseline levels had a better progression-free survival (PFS), statistically significant (11 vs 7 months, p = 0.01). Overall survival (OS) results showed also a benefit for this group of patients (24 vs 16 months, p = 0.022).
Conclusions: In our group of patients, reduction of PSA levels above 50% respect to baseline levels could be a surrogate marker for better survival in patients with mCRPC treated with docetaxel. This could help us predict which patients are going to achieve a greater benefit from chemotherapy at an early phase of treatment. Updated data with longer follow-up will be presented at the meeting.
No conflict of interest.

2921 POSTER

A multicenter Phase 1−2 study of enzalutamide in Japanese patients with castration-resistant prostate cancer (CRPC), who had received combined androgen blockade (CAB)

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Background: Enzalutamide (formerly MDV3100) is a novel androgen receptor inhibitor, which has been proven to prolong survival of men with CRPC who have previously received docetaxel (AFFIRM study; Scher et al, NEJM.2012;367:1187−97). While CAB is commonly used in Japan as a primary androgen deprivation therapy, the treatment options after failure of CAB are currently limited to chemotherapy. Therefore, we conducted a dose escalation and expansion Phase 1−2 study to investigate the safety, tolerability, pharmacokinetics (PK), and anti-tumor activity of enzalutamide in Japanese patients with CRPC.
Methods: In the dose-escalation Phase 1, patients with progressive metastatic CRPC were sequentially assigned to receive single, then multiple doses of 80, 160 or 240 mg/day of enzalutamide, with 3 patients at each dose level to assess PK and safety, except for patients at the 240 mg/day who received a single dose of 240 mg then multiple doses of 160 mg/day. We enrolled 38 post-docetaxel CRPC patients with measurable disease as defined by RECIST into the dose-expansion Phase 2 at a dose of 160 mg/day.
Results: 47 patients were investigated in total: 9 in the Phase 1, and 38 in the Phase 2 at a dose of 160 mg/day. Enzalutamide PK parameters were similar to the non-Japanese population. In Phase 2, patients were heavily pre-treated with 84.2% of patients having 2 or more prior hormonal treatments and 78.9% having 2 prior chemotherapy regimens. 42.1% had 10 or more bone metastases and all patients had measurable disease by RECIST. The clinical benefit rate (Complete Response, Partial Response, or Stable Disease) by week 12 was 47.4% (18/38). Maximal PSA declines (>50% from baseline) were observed in 28.9% (11/38) patients. Treatment-emergent adverse events reported in >20% of patients in Phase 2 were decreased weight, decreased appetite, and constipation. No seizures were observed.
Conclusions: This is the first demonstration of the safety, tolerability, and anti-tumor activity of enzalutamide in the Japanese post-docetaxel CRPC patient population, who had received CAB. Enzalutamide at a dose of 160 mg/day was well tolerated, with similar pharmacokinetic, adverse-event, and anti-tumor activity profile to the non-Japanese population.
Conflict of interest: *Ownership: no. Advisory board: H. Akaza: Advisor of Astellas, H. Uemura: Advisor of Astellas, T. Tsukamoto: Advisor of Astellas, S. Ozono: Advisor of Astellas, O. Ogawa: Advisor of Astellas, H. Sakai: Advisor of Astellas, M. Oya: Advisor of Astellas, M. Namiki: Advisor of Astellas, Y. Ohashi: Advisor of Astellas, S. Naito: Advisor of Astellas. Board of directors: no. Corporate-sponsored research: The study was sponsored by Astellas. Other substantive relationships: no.*

2922 POSTER

Docetaxel in combination with Temsirolimus in patients with advanced castration resistant prostate cancer (CRPC): A phase II trial of the Spanish Oncology Genitourinary Group

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Background: Mechanisms of resistance to Docetaxel (D) are not fully understood. Several lines of evidence suggest that mTOR is a potential target in CRPC and preclinical work revealed that combined treatment with Temsirolimus (T) and D had a greater therapeutic effect than monotherapy, both in vitro and in vivo (Fung AS et al. Clin Cancer Res 2009). We previously determined that the combination of these compounds is feasible at reduced doses of both agents and has anticancer activity in patients (pts) with a variety of solid tumors including CRPC. [Duran et al. J Clin Oncol 30, 2012]. The current study aims to evaluate the efficacy of this drug combination in a selected cohort of pts with CRPC after progression to D.
Material and Methods: Pts aged ⩾18, with advanced CRPC progressing after D treatment, ECOG <2, PSA >= 2 ng/ml, testosterone <50 ng/dl, adequate bone marrow, hepatic, pulmonary and renal function were eligible. D was given at 50 mg/m^2 on day 1 together with T 15 mg on days 2 and 16 in a 3 week-cycle. PSA response was evaluated according to PSAWG criteria and toxicity according to NCI-CTCAEv3.0. A two-stage Simon's design was applied.
Results: To date 14 pts have been included in this phase II cohort and full data are available from 11. Median age was 66 (range 55−76), 5 pts had ECOG 0 and all of them had bone metastases. Forty-seven cycles were administered (median: 4; range: 2−10). Mean dose intensity was D 98% and T 90%. The most frequent related adverse events (AEs) of all grades as % of cycles were: anemia (81%), neutropenia (60%) and asthenia (49%). Grade 3−4 AEs as % of cycles were: neutropenia (25%), leucopenia (13%), and febrile neutropenia (6%). Of those pts with sequential PSA data, 44% achieved a PSA response [decline greater than 50%]. Two pts received 8 and 10 cycles of treatment respectively showing sustained clinical benefit. Given these results the study is proceeding to stage II and active recruitment is ongoing.
Conclusions: The addition of Temsirolimus to Docetaxel could revert resistance to the latter in CRPC. This combination seems clinically tolerable with a manageable toxicity profile and promising activity.
Conflict of interest: *Advisory board: Dr. Bellmunt and Dr. Durán have received honoraria for attending Pfizer advisory boards. Other substantive relationships: Dr. Andrea Viqueira is a Pfizer employee*

2923 POSTER

Maximal androgen blockade versus castration alone in patients with metastatic prostate cancer

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Background: Maximum androgen blockade (MAB) consisting of an anti-androgen plus either a luteinizing hormone-releasing hormone agonist (LHRHA) or orchiectomy, is widely used in the treatment of metastatic prostate cancer patients. Although clinical trials failed to prove any significant advantage in favor of MAB over castration alone and MAB has been the subject of considerable controversy.
Material and Methods: This prospective randomized trial was designed to compare MAB using orchiectomy or LHRHA (Goserelin 3.6 mg depot every 28 days) and Bicalutamide 50 mg once daily versus castration alone (orchiectomy or LHRHA) in previously untreated metastatic prostate cancer regarding PSA response, progression free survival (PFS), overall survival (OS) and treatment related toxicity.
This study included 100 eligible patients previously untreated pathologically proven metastatic prostate cancer with ECOG performance status 0−3, adequate hematologic, hepatic and renal function. An informed consent was taken from every patient before study entrance.

Results: This study took place during the period from January 2010 to January 2013, with a median follow up of 18 months (range 6 to 24 months). At three months, there were 35 patients (70%) had PSA normalization (⩽4 mg/dl) in MAB group versus 17 patients (34%) in castration alone group *(P = 0.001)*.
PSA normalization at 6 months, 9 months, 12 months was 90%, 92%, 97.6% respectively in MAB group while it was 82%, 86%, 89.7% respectively in castration only group ($p > 0.005$).
The median progression free survival for MAB was 22.18 months (95% CI, 19.7 to 24.2 months) while the median progression free survival for castration alone was 22 months (95% CI, 18 to 25.9 months) ($p = 0.045$).
The survival rate for MAB group was 82% at 18 month and 70.6% at 24 months while for castration alone group was 80% at 18 month and 70% at 24 months with no statistically significant difference between the two groups. The median overall survival was not reached in either group.
Regarding treatment toxicities. Anemia was seen in 4 patients (8%) in MAB group versus 3 patients (6%) in castration alone group and all were grade 1−2. Hepatic toxicity was recorded in 10 patients (20%) in MAB group where 5 patients were grade 1 and 5 patients were grade 2,while only 9 patients (18%) had hepatic toxicities in castration alone group where 7 patients were grade 1 and two patients were grade 2. Hot flushes was seen in 6 patients (12%) in MAB group versus 3 patients (6%) in castration only group.Impotence was relevant in 11 patients (22%) in MAB versus 5 patients (10%) in castration alone group where all of them were grade 1 (p > 0.005).
Conclusion: MAB as first-line treatment for metastatic prostate cancer, significantly improves the PSA normalization rate at 12 weeks and improves PFS compared to castration alone with no significant difference in overall survival in both treatment groups and with comparable acceptable toxicities. Further studies and longer duration of follow up periods are needed to document such findings.
No conflict of interest.

2924 POSTER

Clinical outcomes (CO) and predictive factors (PRE) evaluation of young (<60 years) castration resistant prostate cancer (CRPC) patients, treated with docetaxel (DOC): Updated results of an Italian multicenter retrospective study (cooperative group for CYCLOP study)

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Background: Prostate cancer is mainly diagnosed in pts over 65 yrs of age, so CRPC is rare in pts ⩽60 yrs. Clinical outcomes of these pts are not clearly defined but there is a common feeling of a worse prognosis for such younger pts. The present study is aimed to assess CO and PRE in this specific population.
Methods: In this multicentric retrospective study, after Ethical Committee approval, we have reviewed the clinical records of all ⩽60 yrs CRPC pts from participating institutions, treated with DOC, both in clinical trials and in clinical practice. We recorded the pre and post-DOC clinical history, the DOC treatment details and outcomes. We have also assessed the ability of a series of selected 18 clinical factors to predict DOC response through a logistic regression analysis. Continuous variables were categorized by quartiles and chosen for the initial model after a univariate chi-square analysis.
Results: To date we have collected a consecutive series of 113 pts from 19 Italian hospitals. The median age was 56.5 yrs (range 41−60). The median baseline PSA was 122 ng/ml (range 2–2721); 93% of the pts had bone metastases while 49%, 10%, and 13% showed nodal, liver and lung metastases, respectively. All but 8 pts received DOC with a 3-week standard schedule: the median number of received DOC courses was 8 (range 1−14). The main grade 3−4 toxicities were anemia (4 pts), neutropenia (15 pts), febrile neutropenia (1 pt), peripheral neuropathy(1 pt). A PSA reduction >50% was observed in 63.2% of the pts while 14% and 7% of the cases showed a partial and complete response, respectively. Having a Gleason score (GS) <8 [(exp(beta) 3.561; p = 0.031], a hemoglobin initial value >12 [(exp(beta) 2.991; p = 0.050], no nodal involvement [(exp(beta) 1.864; p = 0.107], resulted to be independently predictive of a PSA reduction >50%. The median PFS and OS were 8 mos and 19 mos, while the 1-year PFS and OS rates were 18.4% and 70.3%, respectively.
Conclusions: From these preliminary results, we failed to confirm a worse prognosis for younger CRPC since their survival outcomes are similar to those observed in the pivotal trials. Low GS, absence of nodal involvement and good hemoglobin levels are the only predictive factors. Data collection from other Hospitals is ongoing.
No conflict of interest.

2925 POSTER

Survival, efficacy and safety of weekly docetaxel (35 mg/m^2) plus prednisolone chemotherapy for metastatic hormone-refractory prostate adenocarcinoma

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Background: The optimal timing of docetaxel-based chemotherapy for patients with castrate-resistant prostate cancer (CRPC) is of constant debate. Most studies started chemotherapy for rising PSA. The benefits of chemotherapy has to be weighed against its risks. A randomised trial (Tannock et al. 2004) demonstrated improved overall survival (OS) with docetaxel chemotherapy in a 3-week schedule (75 mg/m^2) compared with docetaxel given at the dose 30 mg/m^2 weekly or with with the mitoxantrone-prednisolone combination. However, the 3-week schedule was associated with a significantly higher incidence of grade 3 and 4 neutropenia. Only few studies examined the safety and efficacy of weekly docetaxel regimen. In the current retrospective study our data for weekly docetaxel with 35 mg/m^2 are demonstrated and compared to the results of the TAX 327 study.
Patients and Methods: We reviewed the medical records from 33 patients (median age 71 years; 57−80) with CRPC and a weekly scheduled docetaxel-regimen (35 mg/m^2 day 1 + day 8 + day 15 q3W) + prednisolone 2x5 mg. Chemotherapy was only initiated in cases of symptomatic tumor progression (e.g. pain, hydronephrosis, cachexia etc.). OS, efficacy and safety were assessed.
Results: Median six cycles (1−8 cycles) of docetaxel chemotherapy were delivered. Median PSA at baseline was 163.3 ng/ml (10.1–3190.2) and decreased during therapy in 24 patients (72.7%) for >50% from baseline. Our data show a higher PSA response rate compared to the 45% rate in the 3-weekly arm or 48% in the 1-weekly arm of the TAX327 study. OS from time of CRPC in median was 26 months (6−80 months) and OS from time of initiation of the chemotherapy was 16 months (5−75 months). In one patient the therapy was not tolerated and had to be stopped. In two other cases the dose of docetaxel was reduced for 25% because of neutropenia respectively intolerance. The overall occurence of grade 3 and 4 adverse events was 24.2% (anaemia, neutropenia, diarrhoea, nausea,vomiting) and for neutropenia alone 9.1% (TAX 327 study: 32% for the 3-weekly and 2% for the 1-weekly schedule).
Conclusions: The current 1-weekly docetaxel-chemotherapy schedule with 35 mg/m^2 shows higher PSA response rates compared to both docetaxel regimen of the TAX 327 study. In addiaiton the incidence of grade 3 and 4 neutropenia was much lower than in the 3-weekly arm of TAX 327. However, the OS rate of 16 months in our study was lower than in the 3-weekly arm (18.9 months) and in the 1-weekly arm (17.4 months) of TAX 327, which is likely due that the initiation of chemotherapy was done only in case of symptomatic tumor progress and therefore was started later than in TAX327 study. A prospective randomised study with comparison of the weekly and 3-weekly arm would be useful to answer the question for the optimal chemotherapy regimen.
No conflict of interest.

2926 POSTER

Low-dose metronomic oral cyclophosphamide plus prednisone for metastatic castration resistant prostate cancer (mCRPC) patients

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Background: Although the introduction of new agents in recent years has allowed an improvement in overall survival in mCRPC, the treatment of elderly and poor performance status patients remains a therapeutic challenge. There are few data on the use of cyclophosphamide in this context, so we designed this protocol to evaluate the efficacy and toxicity of the metronomic oral administration of cyclophosphamide and prednisone in patients with mCRPC, not candidates for docetaxel or after progression to it.

Methods: We retrospectively evaluated the medical records of patients with metastatic mCRPC treated with prednisone and cyclophosphamide in our institution. Patients had been previously treated with a docetaxel-containing regimen or were not considered candidates for taxanes, because of important comorbidities or poor Performance Status (PS).
Results: Data from 48 patients treated with cyclophosphamide 50 mg/day vo plus prednisone 5 mg bid from January 2010 to February 2013 have been analyzed. Baseline characteristics of the patients are listed in the Table 1. 46 patients were evaluable for efficacy and toxicity. The PSA response rate (RR) was 26%; clinical benefit (stabilization disease + RR) was obtained in 60% of patients. Median progression-free survival and overall survival was 27 weeks (95% CI 18.9–35.8) and 60 weeks (95% CI 44.7–75.6), respectively. The overall 1-year and 2-year survival rate was 32% and 6%. The treatment was safe and well tolerated, with anemia grade 0−3 in a third of all patients.
The response and survival data were analyzed as a function of previous lines of chemotherapy. The PSA response rate in patients at first-line therapy was 50%; at second or subsequent line was 15%. Progression free survival for first and second line and later was 43 weeks (95% CI 26.9–59.7) and 19 weeks (95% CI 12–26.3) respectively.
Conclusions: In this study with a poor prognosis population, metronomic oral cyclophosphamide plus prednisone have demonstrated efficacy with an excellent tolerance. Oral cyclophosphamide is an interesting alternative to consider in patients non candidates for intravenous chemotherapy.
No conflict of interest.

Table 1. Baseline characteristics of the patients

Characteristic	N
Age, median (range)	77 (56−88)
PS ECOG 1/2/3	30/14/4
Gleason <7/>7/Unknown	27/16/5
Extent of disease	
Ganglionar/Bone/Ganglionar+Bone/Visceral	6/24/11/7
Prior treatment	
Hormonal manipulations 2/3/Unknown	19/28/1
Previous chemotherapy regimes 0/1/⩾2	16/25/7

2927 POSTER

A randomized open-label study comparing the docetaxel plus prednisone regimen versus mitoxantrone plus prednisone regimen for metastatic hormone refractory prostate cancer in Chinese population

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Background: Most patients with metastatic prostate cancer will eventually progress to a hormone refractory state. Docetaxel-based chemotherapy was the standard treatment for symptomatic metastatic hormone refractory prostate cancer (mHRPC). However, the efficacy and safety in Chinese patients are not well established.
Material and Methods: Patients with symptomatic mHRPC, and KPS⩾70 were randomized (1:1) to the regimens of docetaxel (75 mg per square meter od body surface area) every three week plus 5 mg prednisone twice daily (Arm A) or mitoxantrone (12 mg per square meter) every three week plus 5 mg prednisone twice daily (Arm B). Patients were planned to receive 10 cycles of treatment in both groups. The primary endpoint was overall survival. Secondary endpoints were pain-control progression-free survival (PFS), prostate-specific antigen (PSA) response, quality of life and safety.
Results: 228 patients have been randomized, in which 111 patients in Arm A and 109 patients in Arm B were available for analysis. The median cycles of chemotherapy were 8 cycles (range 1−10) in Arm A and 4 cycles (range 1−10) in Arm B. The median overall survival was 21.9 months in Arm A versus 13.7 months in Arm B. The 12-month overall survival rates were 78.6% in Arm A and 51.9% in Arm B. As compared with the patients in Arm B, patients in Arm A had a hazard ratio for death of 0.62 (95% CI, 0.45–0.85; P = 0.003 by the log-rank test) and 38% of reduced risk of death. 61.1% of patients in Arm A had reduction in pain with median pain control time of 3.7 months, compared with 23.1% (p = 0.0011) of reduction of pain with a median pain control time of 2.2 months. The median pain-control PFS was 12.7 months in Arm A versus 5.6 months in Arm B (p = 0.0002). PSA response rates were observed in 35.1% of patients in Arm A versus 19.4% of patients in Arm B (p = 0.02). The grade 3 or 4 adverse events were observed in 74.8% of patients in Arm A versus 67.0% of patients in Arm B. 20% of patients in Arm A and 15.8% of patients in Arm B had improvements in quality of life (p = 0.54).
Conclusions: These data suggests that the 3-week docetaxel plus prednisone regimen was effective in improving overall survival and pain controlling with acceptable toxicities in Chinese patients with mHRPC.
No conflict of interest.

2928 POSTER

HER2 tissue expression in NeuACT, a Phase 2, randomised, open-label trial of DN24-02 in patients (pts) with surgically resected HER2+ urothelial cancer (UC) at high risk for recurrence

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Background: HER2 gene amplification and overexpression (immunohistochemistry [IHC] score 3+) in pts with high-risk UC may be a negative prognostic factor. Publications report a wide variability of HER2 expression in UC, with ⩾2+ HER2 expression by IHC reported in <10% to >50% of cases. DN24-02 is an investigational autologous cellular immunotherapy targeting HER2, based on the same manufacturing platform used for sipuleucel-T. NeuACT (N10−1; NCT01353222) aims to evaluate whether DN24-02 prolongs survival when given as adjuvant therapy following surgical resection in pts with high-risk HER2-expressing UC (Bajorin, et al. ASCO 2012). Here we report an updated analysis of HER2 expression on primary tumour and positive lymph node samples.
Methods: Eligibility criteria include surgical resection of a primary UC, with either ⩾pT2 or pN+ staging, and HER2 expression ⩾1+ by IHC. Surgical specimens are screened for HER2 expression by central pathology laboratory review, and scored with the Dako HercepTest system.
Results: As of March 2013, tumour specimens from 154 pts have been screened. Of these pts, 118 (77%; 95% CI: 69−83%) had a HER2 expression score ⩾1+ in the primary tumour, with 52 (34%) having a ⩾2+ score and 13 (8%) having a 3+ score. Fifty-five pts also had HER2 expression levels evaluated in lymph node samples; 50 of these (91%; 95% CI: 80−97%) had a HER2 expression score ⩾1+ in the lymph nodes, with 30 (55%) having a ⩾2+ score and 10 (18%) having a 3+ score. Gender, primary tumour site, tumour grade and prior neoadjuvant chemotherapy were not significantly correlated with HER2 expression in either the primary tumour or lymph node (p⩾0.10); however, nodal stage was correlated with lymph node HER2 expression (p = 0.014). Preliminary analyses suggest no discernible relationship between the magnitude of immune response and HER2 expression levels.
Conclusions: This interim analysis of NeuACT reports high frequencies (⩾77%) of HER2 expression ⩾1+ in primary tumour and lymph node samples of UC pts. While HER2 expression levels in the lymph nodes correlated with nodal stage, no other baseline variables appear to affect HER2 expression rates; no apparent relationship was observed between immune response and HER2 level. Although interim, these data are consistent with prior studies noting a higher incidence of HER2 expression in UC lymph node tumours compared with primary tumours and suggest that HER2 protein expression is common in high-risk UC.
Conflict of interest: *Ownership: PS − Jounce. TD, MC, ML − Dendreon. Advisory board: DQ − Dendreon, Medivation, Astellas, Pfizer, Bayer, Aveo, Algeta, Novartis, Amgen, Prometheus, Fresenius, Genentech. DB − Dendreon, Pfizer, Eli Lilly, Novartis. Corporate-sponsored research: EP − Dendreon. DQ − Millenium, Sanofi-aventis. DB − Dendreon, Genentech, Pfizer, Novartis, Amgen, Genta. Other substantive relationships: POD, EP − honoraria from Dendreon. PS − consultant for Dendreon, BMS, Jounce, MedImmune, Helsinn Therapeutics. DQ − honoraria from Dendreon, Medivation, Astellas, Pfizer, Bayer, Aveo, Algeta, Novartis, Amgen, Prometheus, Fresenius, Genentech and expert testimony for Medivation, Teva. TD, MC, ML − employee of Dendreon. DB − honoraria from Eli Lilly.*

2929 POSTER

Pre-clinical evidence for cross-resistance between taxanes and abiraterone in castration-resistant prostate cancer (mCRPC)

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Background: A recent study suggested impaired efficacy of docetaxel when given after progression on abiraterone in patients with mCRPC. Our recent pre-clinical data demonstrated that docetaxel, cabazitaxel, and abiraterone all act on AR nuclear transport, which is a crucial step in AR signaling, and provide a mechanistical explanation for potential clinical cross-resistance. In the present study, we aimed to identify cross-resistance between taxanes (docetaxel and cabazitaxel), and abiraterone in an abiraterone-resistant cell line model.
Material and Methods: The abiraterone resistant prostate cancer cell line PC346Abi101 was derived by continuous culturing PC346C cells in the presence of abiraterone (1 μM). We used an MTT-assay to determine the effects of docetaxel, cabazitaxel, mitoxantrone, and abiraterone on cell proliferation. Briefly, cells were seeded in 96-well dishes at a density of 5,000 cells per well in DCC medium. After overnight attachment, PC346Abi101 and PC346C cells were treated for 10 days with docetaxel (0.1–100 nM), cabazitaxel (0.1–100 nM), mitoxantrone (0.1−10 μM), abiraterone (0.1−20 μM), or vehicle control.
Results: We observed that docetaxel and cabazitaxel efficacy was impaired in PC346Abi101 cells, as compared to the parental PC346C cells, suggesting cross-resistance between docetaxel and abiraterone, as well as cabazitaxel and abiraterone. We used mitoxantrone as a control cytotoxic agent and showed that this non-tubulin targeted drug was similarly effective in PC346Abi101 and parental PC346C cells, validating that the observed cross-resistance was specific for the tubulin-targeting agents docetaxel and cabazitaxel. Resistance to abiraterone was confirmed by severely impaired efficacy of abiraterone in PC346Abi101 cells, compared to PC346C cells.
Conclusions: Our *in vitro* data show substantial evidence for cross-resistance between docetaxel and abiraterone, as well as cabazitaxel and abiraterone. This observed cross-resistance with abiraterone seems to be specific for the tubulin-targeting agents docetaxel and cabazitaxel, and is likely to be caused by the effects on AR transport of these compounds. Clinical investigations are warranted to define the most appropriate treatment sequence for these agents in patients with CRPC.
Conflict of interest: *Advisory board: Sanofi, Janssen, Millenium. Corporate-sponsored research: Sanofi*

2930 POSTER

Clinical benefit on abiraterone acetate (AA) in patients (pts) with PTEN loss castration-resistant prostate cancer (CRPC)

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Background: The CYP17A1 inhibitor AA is an effective but costly treatment for CRPC, which is a molecularly heterogeneous disease. It has been postulated that upregulated AKT pathway signalling through PTEN loss results in resistance to AA. We therefore aimed to evaluate the impact of PTEN loss on the anti-tumour activity of AA in CRPC in an attempt to deliver more precise treatment for this disease.
Methods: We first acquired patient-matched hormone sensitive (HS) and castration resistant (CR) tumour samples to determine whether PTEN status changes with castration resistance. Four uM tissue sections were cut and immunostained for PTEN (Cell Signaling Technology), with internal controls for all slides. PTEN was scored on a minimum of 100 cancer cells per slide to calculate an H-score as previously reported (Mod Pathol. (2012)25;902−10). H-score >30 was considered positive. Biochemical response to AA was defined as ⩾50% decline in PSA from baseline, confirmed at least 3 weeks later. Treatment duration and survival were estimated using the Kaplan Meier method.
Results: Patient-matched HS and CR tissue samples were available for 49 pts. Of these, the HS tissue showed staining consistent with PTEN loss in 25/49 pts (51%). In the CR samples PTEN loss was identified in 28/49 (57%). Heterogeneity was evident between HS and CR samples, with changed classification from PTEN normal to PTEN loss in 3 pts (6%) and conversely from PTEN loss to PTEN normal in another 3 pts (6%). We therefore proceeded to classify PTEN status by loss in either HS or CR tissue. AA activity and survival data in 99 pts stratified by PTEN status are presented in the table.

Conclusions: PTEN status does not significantly change with development of castration resistance. AA retains significant activity in patients with PTEN loss, both in chemotherapy naive and docetaxel pre-treated patients in our population. Further biomarker studies, including markers that associate specifically with activation of the Pi3K/AKT pathway are urgently required.

	AA		p
	PTEN normal	PTEN loss	
Pre-docetaxel	**N = 21**	**N = 14**	
PSA decline, N (%)			
⩾50%	16 (76)	9 (64)	
⩾90%	7 (33)	4 (29)	
Time on AA, mo	11.4	12.0	P = 0.56
Median survival, mo	42.7	48.0	P = 0.64
Post-docetaxel	**N = 31**	**N = 27**	
PSA decline, N (%)			
⩾50%	14 (45)	13 (48)	
⩾90%	3 (10)	6 (22)	
Time on AA, mo	5.4	5.0	P = 0.56
Median survival, mo	16.4	13.2	P = 0.53

Conflict of interest: *Other substantive relationships: All authors are employes of the Institute of Cancer Research ICR. The ICR has a commercial interest in abiraterone.*

2931 POSTER

Circulating tumor cells (CTCs) in high-risk localized prostate cancer: Correlation with clinicopathologic characteristics and characterization of relevant surface markers

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Background: The prognostic value of CTC enumeration in metastatic castration-resistant prostate cancer (mCRPC) is well established. However, previous attempts to characterize CTCs in localized prostate cancer have proven challenging (Davis *et al* J Urol 2008). Using the CellSearch system, we employed a modified sample processing method and enriched our cohort for patients with high-risk localized disease to improve CTC yield.
Methods: Patients with high-risk, localized prostate cancer (defined by ⩾1 of the following criteria: ⩾cT3a disease, Gleason score 8−10, or PSA >20 ng/mL) who had chosen prostatectomy for definitive management were prospectively identified. After obtaining consent, 4 sequential 30 mL blood draws were performed. The first 2 blood draws were conducted 2 weeks prior and immediately prior to surgery, while the second 2 blood draws were conducted at 4 weeks and 12 weeks following surgery. The white blood cell (WBC) fraction from each 30 mL blood draw was pooled and Ficoll purified. A total volume of 7.5 mL was transferred to a CellSave tube and CTCs were enumerated using the CellSearch system. Expression of E-cadherin, a marker of epithelial-to-mesenchymal transition (EMT), and CD133, a stem cell marker, were characterized using open channels on the CellSearch platform.
Results: A total of 35 patients were enrolled from Nov 2011 to March 2013. The median age was 65 (range, 48−74), and the following proportions of patients demonstrated the respective high-risk criteria: (1) PSA >20: 29%, (2) Gleason 8−10: 86%, and (3) ⩾cT3a: 91%. Using the modified methodology, CTCs were detectable in 49% of patients prior to surgery, with a mean count of 2.5 cells. Amongst age, high-risk features and other clinicopathologic characteristics, only seminal vesicle involvement was found to be correlated the presence of CTCs prior to surgery. In total, 76% of individually characterized CTCs expressed CD133, and 84% expressed E-cadherin.
Conclusions: Using a simple modification of the standard CellSearch methodology, CTCs are readily detectable in a large proportion of patients with high-risk localized prostate cancer. The presence of CTCs prior to surgery correlates with seminal vesicle involvement. The majority of CTCs detected in this study were CD133 and E-cadherin expressing, suggesting that CTCs have 'stem-like' properties and may carry an intermediate epithelial–mesenchymal phenotype, respectively.
No conflict of interest.

2932 POSTER

Efficacy and safety of abiraterone acetate (AA) in elderly (⩾75 years) chemo-naive patients (pts) with metastatic castration-resistant prostate cancer (mCRPC)

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Background: AA, a specific inhibitor of CYP17, blocks androgen biosynthesis. In pts with mCRPC pre- and post-chemotherapy, AA + prednisone (P) therapy provides significant overall survival (OS) benefit and manageable safety profile. Many pts with mCRPC are diagnosed after the age of 70 y. We present the efficacy and safety results of AA+P vs P only in elderly (⩾75 y) and younger (<75 y) pt subgroups at the prespecified interim analysis (IA3; 55% total OS events) for study COU-AA-302.
Material and Methods: 1088 pts were stratified by Eastern Cooperative Oncology Group performance status (0 vs 1) and randomized 1:1 to AA 1000 mg + P 5 mg po BID vs P only. Co-primary end points were radiographic progression-free survival (rPFS) and OS. Median time to event variables with 95% CI were estimated using the Kaplan–Meier method for elderly (n = 350) and younger (n = 738) pts.
Results: At IA3, median follow-up was 27.1 months. Elderly and younger pts were well balanced in each treatment arm by baseline disease characteristics. Elderly pts treated with AA+P had significant improvements in OS and rPFS vs P only, similar to the younger pts (Table). All secondary end points also favored the AA+P arm for both age subgroups. Overall, elderly pts in both arms (57%) had more grade 3/4 adverse events (AEs) than younger pts (42%). The incidence of AEs of special interest was also more common in the elderly pts, but the safety profile of AA + P was similar among elderly and younger pts (Table).
Conclusions: These subset analyses demonstrate that the efficacy and safety of AA+P are similar for younger and elderly pts. These observations support use of AA + P in elderly men with metastatic CRPC who have not received chemotherapy.

	Elderly (⩾75 y)		Younger (<75 y)	
	AA+P	P	AA+P	P
Efficacy	N = 185	N = 165	N = 361	N = 377
rPFS*, months	14.9	8.3	16.6	8.3
HR (95% CI)	0.63 (0.48–0.83)		0.49 (0.40–0.59)	
p Value	0.0009		<0.0001	
OS*, months	28.6	25.6	35.3	30.9
HR (95% CI)	0.71 (0.53–0.96)		0.81 (0.63–1.03)	
p Value	0.0268		0.0841	
Adverse events (all grades), %	N = 182	N = 164	N = 360	N = 376
Oedema	38	35	25	19
Hypokalaemia	17	10	18	14
Hypertension	22	17	22	12
Hepatotoxicity	21	15	18	10
Cardiac disorders	27	26	18	14

*Median time to event.

Conflict of interest: *Advisory board: Johnson & Johnson. Corporate-sponsored research: Johnson & Johnson. Other substantive relationships: Janssen, Johnson & Johnson*

2933 POSTER

Phosphoproteomic profiling reveals focal adhesion kinase as a mediator of docetaxel resistance in castrate-resistant prostate cancer

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Background: Docetaxel remains the standard-of-care for men diagnosed with metastatic castrate resistant prostate cancer (CRPC), but only ~50% of patients benefit from treatment and all develop Docetaxel-resistant disease. This study aimed to characterize global perturbations in tyrosine kinase signaling associated with Docetaxel-resistance and thereby develop a potential therapeutic strategy to overcome chemoresistance.
Methods: We compared tyrosine phosphorylation events in Docetaxel-sensitive and -resistant DU145 and PC3 prostate cancer cell lines using quantitative mass-spectrometry-based phosphoproteomics. Bioinformatic approaches were used to identify perturbations in protein-protein interaction networks and signaling pathways characteristic of Docetaxel-resistant cells. Effects of the focal adhesion kinase (FAK) inhibitors PF562271 and PF4554878 on Docetaxel sensitivity were characterized, using cell viability, clonogenicity, apoptosis and autophagy as end-points. The role of apoptosis and autophagy in cell death induced by Docetaxel/PF562271 co-treatment was interrogated by pharmacological (Z-VAD-FMK, 3-methyladenine) and genetic (Atg5 knockdown) approaches. The antitumor efficacy of Docetaxel (10 mg/kg) +/− PF4554878 (50 mg/kg) was determined in Balb/c nude mice bearing PC3 xenografts.
Results: Docetaxel-resistant cell lines exhibited perturbations in pathways regulating focal adhesions and the actin cytoskeleton and increased FAK phosphorylation on Y397 and Y576, compared to parental controls. While treatment with Docetaxel or either of the FAK tyrosine kinase inhibitors (TKIs) reduced FAK phosphorylation in the resistant cells, co-treatment with Docetaxel and a FAK TKI was required to reduce FAK phosphorylation to that of drug-sensitive cells. Treatment with a FAK TKI alone did not affect cell viability of the resistant cells, but co-treatment with Docetaxel and a FAK TKI overcame chemoresistance. The enhanced efficacy of co-treatment was not due to increased apoptosis, but rather enhanced autophagic cell death. In tumor-bearing mice, co-administration of Docetaxel and PF4554878 resulted in a greater reduction of tumor growth than either monotherapy, and was also associated with increased autophagy.
Conclusions: Enhanced activation of FAK mediates Docetaxel resistance in CRPC. Our study has identified a clinical niche for FAK TKIs, where co-administration with Docetaxel may be used in CRPC to overcome chemoresistance.
Conflict of interest: *Other substantive relationships: MS is an employee of Pfizer Inc, and has stock ownership in the company. LGH has been the recipient of sponsorship to a Pfizer Research and Development Forum and is a member of the Steering committee for the Pfizer Oncology Forum 2013, Australia.*

2934 POSTER

Cause of death in men with localized prostate cancer: Which clinico-demographic risk factors are important?

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Background: Most men with prostate cancer (PCa) do not die of PCa. We investigated cause of death among men with localized PCa and among PCa-free men, while taking into account clinico-demographic factors.
Material and Methods: PCa data Base Sweden (PCBaSe 2.0) is based on the National PCa Register (NPCR) of Sweden and also contains age- and county matched PCa-free men. We selected all men diagnosed with localized low or intermediate risk PCa between 1997 and 2009 (n = 39,115) and their 78,230 matched PCa-free men. Competing risk regression was used to predict 10-year cause-specific survival. All models were adjusted for age, education level, civil status, and Charlson comorbidity index (CCI), and were performed by PCa risk categories.

Results: Civil status and education level did not have a large effect on PCa-specific death. Table 1 shows 10-year overall mortality by age, CCI, and PCa risk group for married men with an intermediate education level. The risk of dying was smaller for those with low risk PCa than for those without PCa. The proportion of PCa-specific death was smaller for those with CCI=2+ than for those with CCI=0, indicating a self-selection of healthy men to PSA testing and diagnosis of low-risk PCa. As expected, high age and comorbidity were related with increased risk of death. The proportion of PCa-specific death was comparable among age groups (e.g. 32, 35, and 33% of men in respective age groups with intermediate risk disease and CCI=0 die <10 years).

Table 1. Predicted 10-year mortality and proportion of cause-specific death by age, CCI, and PCa risk group for married men with intermediate education level.

	CCI = 0			CCI = 2+		
Age	50	60	70	50	60	70
No PCa						
Overall Risk (%)	3.8	8.9	20.0	8.0	18.8	41.7
PCa	4	5	6	2	2	2
Other cancers	58	40	27	54	38	25
CVD	18	24	28	22	29	33
COPD	4	3	3	5	5	5
Other	17	27	37	16	26	35
Low Risk PCa						
Overall Risk (%)	2.9	7.5	18.2	6.5	16.1	37.7
PCa	14	17	18	5	6	7
Other cancers	58	41	29	66	49	34
CVD	11	17	23	13	21	28
COPD	0	1	2	1	2	3
Other	17	23	28	16	22	27
Intermediate Risk PCa						
Overall Risk (%)	5.0	11.2	24.5	9.0	19.1	40.6
PCa	32	35	33	14	16	16
Other cancers	50	35	23	66	48	32
CVD	8	13	19	10	18	25
COPD	1	1	1	2	3	3
Other	8	15	24	8	16	25

Conclusions: High comorbidity is associated with low PCa-specific death due to competing causes of death and there is a healthy selection phenomenon among men with low risk PCa. Interestingly, the proportion of men with localized low or intermediate risk PCa dying of their disease was very similar, irrespective of age.
No conflict of interest.

2935 POSTER

Metformin to abrogate androgen deprivation therapy-induced insulin resistance and metabolic syndrome

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Background: Androgen-deprivation therapy (ADT) in prostate cancer (PC) decreases insulin sensitivity and increases the risk of the metabolic syndrome (MS). This study assessed the effects of metformin in abrogating ADT-induced insulin resistance.
Methods: In a prospective 12-month study, men beginning ADT and with no history of diabetes mellitus (DM) received metformin for 6 months, followed by no metformin for a further 6 months. Subjects acted as their own controls as all received intervention. The primary outcome measures were the effect of metformin on the Homeostasis Model Assessment of Insulin Resistance ($HOMA_{IR}$) and the Whole Body Insulin Sensitivity Index (WB-ISI), as measure of insulin action in the fasting and stimulated states, respectively. The incidence of MS and related laboratory and anthropometric measures were also assessed.
Results: Twenty-seven patients received ADT and metformin. Median age was 69 years. While all had normal fasting glucose at baseline, 11 (40.7%) had evidence of DM on oral glucose tolerance testing (OGTT). Eleven (40.7%) patients also had MS at baseline. Despite ADT, $HOMA_{IR}$ remained stable during metformin therapy [1.7 (SEM$\pm$0.35) at baseline; 1.9 (SEM$\pm$0.32) at 6 months; P = 0.18]; but increased once metformin was ceased [3.6 (SEM$\pm$2.2) at 12 months; P = 0.07]. There was a significant fall in WB-ISI irrespective of metformin [7.4 (SEM$\pm$1.0) at baseline; 6.0 (SEM$\pm$0.79) at 6 months; 5.2 (SEM$\pm$1.6) at 12 months; P<0.01]. The number of patients with MS remained unchanged during metformin therapy, but 2 further patients developed MS at 12 months. Short-term metformin had no effect on blood pressure or other anthropometric measures, including waist circumference and body mass index, but did improve HDL cholesterol.
Conclusions: Metformin may offset MS in men on ADT. Metformin had a greater impact on fasting metabolic parameters (as measured by $HOMA_{IR}$) compared to its effect after a glucose load (as measured by WB-ISI). Importantly, this study found that a large proportion of PC patients had unsuspected MS and DM, suggesting a role for OGTT in all patients starting ADT.
No conflict of interest.

2936 POSTER

Quality of cancer care in the Netherlands: Variation in treatment of prostate cancer

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Background: Prostate cancer is the most common cancer among males in the Netherlands (>10,000 patients each year). One in every 9 Dutch males will be diagnosed with prostate cancer sometime during life. Due to aging this number will increase to more than 17,000 in 2020. Earlier studies showed that large variation in cancer care exists. Information on quality of prostate cancer care is rare; therefore the Dutch Cancer Society in collaboration with the Netherlands Cancer Registry (NCR), held by the Comprehensive Cancer Centre the Netherlands, has started a study to evaluate four types of cancer including prostate cancer.
Material and Methods: All patients diagnosed with prostate cancer between 2007–2011 were selected from the NCR and included in the study. Patient- and tumour characteristics as well as information on initial treatment were available.
Results: In the period 2007–2011 51,790 patients were diagnosed with prostate cancer and 9986 (%) underwent a radical prostatectomy (RP) as primary treatment. Large variation is observed concerning the number of RPs performed by hospital. The proportion of hospitals in the Netherlands performing 20 or more RPs as initial treatment has increased from 28% in 2005 to slightly over 40% in 2011. This proportion will increase in the near future as the Dutch Association for Urology has indicated in 2012 that each hospital should perform at least 20 RPs each year. The majority of patients with localized prostate cancer is treated with RP or radiotherapy (RT). However, only 6 to 10% of all patients of 70 years or older underwent a RP. Approximately 10% of patients with a pT3 tumour or patients with post-operative positive margins received adjuvant RT as recommended by the Dutch guideline. Stratified analyses showed large differences between the different subgroups; 19% of pT3 tumours with positive margins were treated with RT versus 6% of the pT3 tumours resected radically. Concerning hormonal therapy in combination with RT in high-risk prostate cancer patients large differences were observed by geographic region; overall 64% of these patients received hormonal therapy with a range of 49% to 79%.
Conclusions: The number of performed RPs varied largely over time. This variation will probably decrease in the near future, as a minimum of 20 RPs has been set. Despite the recommendations in the guideline concerning adjuvant RT and combination of RT and hormonal therapy, a large proportion of men does not receive this treatment.
This study was commissioned by the working party 'Quality of cancer care' of the Signalling Committee Cancer of the Dutch Cancer Society.
No conflict of interest.

2937 POSTER

Use of a risk calculator in a prostate unit to reduce overdiagnosis of prostate cancer

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Background: Most prostate cancer (PCa) is detected because of opportunistic screening. It is important to reduce unnecessary biopsies and diagnosing of indolent PCa. PSA as indicator for a biopsy has low specificity, so a web based risk calculator (RC) based on parameters

obtained from a large randomized study of screening for prostate cancer (ERSPC) has been developed. The aim of the current study is to investigate whether use and compliance to RC is safe and effective in reducing the number of unnecessary biopsies.
Materials and Methods: A retrospective descriptive study was performed at the Prostaatcentrum Zuid-West Nederland (PCZ). Men referred for potential PCa screening were analyzed. Excluded were men with a previous diagnosis of PCa, or without PSA measurement and physical examination. For all men risk calculation was performed based on PSA, prostate volume, rectal examination and previous biopsy result. When the chance calculated with RC on a positive biopsy was >20%, or when >12.5% combined with a relevant chance of finding significant prostate cancer (Gleason $\geqslant$7 and clinical stage >T2b), a positive biopsy advice was given. Effects were compared to a historical PSA biopsy cutoff value of 4 ng/ml.
Results: 408 men over a 26 months period were included. A positive RC advice (n = 274) led to 220 biopsies and diagnosis of 143 (detection rate = 65%) cancers. 96 of 143 cancers (67%) were significant. Despite a negative biopsy RC advice (n = 134), 33 biopsies were performed, finding 4 (detection rate = 12%) cancers, 1 was significant, while 29 patients had a benign outcome. When also taking indolent PCa into account, the number of potentially unnecessary biopsies increased up to 32 (97%). This compared to 77 negative biopsies (35%) when having a positive RC advice. Follow-up of patients having an initial negative RC advice (n = 48), showed detection of 4 cancers (12%), one significant tumor (2.1%), while in men who had a positive RC advice and a negative biopsy at first (n = 37), 3 significant PCa (8.1%) were detected.
Due to RC, 11 men were biopsied with a PSA<4, while 138 men were NOT biopsied though having a PSA of >4.
Conclusion: Overall compliance to RC advise was 78.8%. A reduction of biopsies of 33% was obtained compared to traditional PSA cut-off, while missing only 2 relevant cancers.
No conflict of interest.

2938 POSTER

Prevalence of non-metastatic castration-resistant prostate cancer (CRPC) at high risk of bone metastases in 19 countries in 2013

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Background: CRPC is a growing public health concern that has not been adequately quantified. In the absence of metastases (M0), CRPC represents a transitional disease state defined by increases in serum prostate-specific antigen (PSA) despite androgen-deprivation therapy (ADT). PSA kinetics can identify men who are likely to progress to develop metastases, and who may benefit most from interventions to halt or delay disease progression. We developed a patient-flow model to estimate prevalence of M0 CRPC at high risk of developing bone metastases in selected populations with high incidence rates of PC.
Methods: The model estimates 5-year limited-duration prevalence of PC and M0 PC using incidence and survival data from cancer registries from 19 countries (EU5 [France, Germany, Italy, Spain, UK], Europe [11], Australia, Canada, and US). Research conducted with urologists and oncologists in these countries provide details of M0 PC treated with ADT. The model assumes that M0 PC patients must receive continuous ADT ($\geqslant$6 months GnRH therapy or bilateral orchiectomy) as a prerequisite for CRPC development. PSA relapse rates from literature sources were used to quantify M0 CRPC. Electronic medical record studies in the US, Denmark, and Sweden provide estimates of patients who have PSA doubling time (DT) $\leqslant$6 months, a definition commonly used to define high risk disease.

Table: Five-year prevalence in 2013.

	PC	M0-PC, % of PC	M0 CRPC	High risk CRPC, % of PC
Australia	81583	85	3249	2
Austria, Switzerland	55387	86	2617	3
Belgium, Netherlands	79749	85	4581	3
Canada	116842	92	5284	2
Czech, Hungary, Poland	90758	80	9198	5
Denmark, Finland, Norway, Sweden	93296	79	7010	4
EU5	992453	85	65120	4
US	979102	92	43341	2

Results: Under the base case scenario, holding incidence and survival relatively constant, prevalence of PC is driven by size and aging in the populations, and most cases represent M0 disease (Table). In 2013, we estimate that a total of 43341 men in the US, 65120 in EU5, 23406 across Europe-11, and 8533 in Canada and Australia are estimated to have M0 CRPC. Approximately 50−60% of M0 CRPC cases will have PSA DT $\leqslant$6 months, which suggests that 2−5% of all PC may be considered high risk M0 CRPC.
Conclusion: A dynamic patient-flow model was developed using latest cancer registry data, as well as physician research in 19 countries, to consider how patients progress through courses of treatment and disease states after diagnosis of PC to estimate the prevalence of M0 CRPC and high risk M0 CRPC. We estimate that high risk M0 CRPC constitutes a relatively small proportion of all patients living with PC.
Conflict of interest: *Ownership: AL, JA and GH − Own Amgen stock. Corporate-sponsored research: BB, SW − Amgen. Other substantive relationships: AL, JA and GH employed by Amgen*

2939 POSTER

Prognostic value of initial PSA, PSA Nadir and time to Nadir PSA for biochemical failure in patients with intermediate-risk prostate cancer treated with radiation therapy without androgen deprivation

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Background: To assess the relationship between pre-treatment PSA (iPSA), PSA Nadir value (nPSA) and time to PSA Nadir (TnPSA) to biochemical failure (BF) in intermediate-risk prostate cancer patients treated with radical radiotherapy (EBRT).
Methods and Materials: Patients with intermediate-risk prostate cancer who did not receive androgen deprivation therapy were eligible for analysis. Patients were treated with four different EBRT regimes; 50 Gy in 20 fractions EBRT and a 10 Gy single-fraction high-dose rate brachytherapy boost, 66 Gy in 22 fractions EBRT, 72 Gy in 36 fractions EBRT or 76 Gy in 38 fractions EBRT. All patients had a minimum of 2-year follow-up. BF was defined as PSA nadir+2ng/ml.
Results: A total of 267 patients treated between May 2001 and November 2010 were included in this study. With a median follow-up time of 65 months, the median time to nadir was 41 months with a median nadir value of 0.27ng/ml. A total of 34 patients had developed biochemical failure (13%) at a median time to failure of 29 months. On univariate and multivariate analyses, the iPSA, nPSA and TnPSA were all found to be associated with BF ($p < 0.001$). A cut-off value for the iPSA was found to be 11.6ng/ml. A nPSA value of >0.3ng/ml and TnPSA of $\leqslant$24 months were found to be associated with worse biochemical failure free survival (bNED) rates. When all three poor prognostic indicators were pooled together a significant association was found. Patients who had an iPSA $\geqslant$11.6 ng/ml, nPSA >0.3ng/ml and TnPSA $\leqslant$24 months had a bNED rate at 5-years of 0% ($p < 0.001$).
Conclusions: nPSA, TnPSA and lower iPSA are all independently associated with better bNED rates. When pooled together, a significant relationship with BF was found whereby all patients with an iPSA $\geqslant$11.6ng/ml, TnPSA $\leqslant$24 months and nPSA >0.3ng/ml developed BF. This association has not been reported previously and warrants further investigation.
No conflict of interest.

2940 POSTER

Characterization of pathway to non-metastatic (M0) castration-resistant prostate cancer (CRPC) and high risk of bone metastases according to treating physicians in 19 countries

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Background: Androgen-deprivation therapy (ADT) represents standard of care for prostate cancer (PC) patients (pts) with signs of recurrence after primary therapy (tx). Nearly all ADT-treated M0 pts relapse to develop CRPC, with a median time to relapse of 18−24 months (mos) (Felici 2012). This study surveyed physicians who treat M0 PC pts in 19 countries to estimate ADT use and CRPC, and explore definitions of high risk of developing bone metastases (BM).
Methods: A 45-minute online survey was completed by urology and oncology practitioners from 19 countries with high or increasing prevalence of M0 PC. Eligibility ensured respondents were responsible for tx decisions in the care of M0 PC, and had $\geqslant$10 pts on ADT. Sampling of oncology (vs. urology) specialists reflected M0 PC tx pattern in the country. Sampling ensured regional distribution and practice type. Country-level weights were applied during analysis to account for differences in prevalence of M0 PC.
Results: In total, 441 physicians completed the survey representing 98689 PC pts under their care, of which 76386 (77%) had M0 PC.

Table (abstract 2940): ADT use, CRPC, and high risk according to treating physicians

	Physicians surveyed	Any ADT, % of M0 PC	ADT ⩾6 mo, % of M0 PC	CRPC by 2 yrs, %	High risk, % of CRPC	Expect to develop BM, % of CRPC
Location						
USA	65	34	22	69	45	49
EU5: France, Germany, Italy, Spain, UK	171	43	35	76	60	70
Austria, Switzerland	19	32	25	95	58	50
Belgium, Netherlands	38	36	32	89	57	45
Denmark, Finland, Norway, Sweden	43	46	35	72	82	81
Czech, Hungary, Poland	45	68	55	77	54	56
Australia	30	25	21	73	73	79
Canada	30	29	22	78	77	78
Total	441	38	29	75	57	63
Specialty						
Urologists	387	38	28	75	57	63
Oncologists	54	62	47	81	57	56

Respondents were primarily urologists (88%) (Table). Of M0 PC, 38% received ADT: 37% (28104) gonadotropin-releasing hormone (GnRH) tx and <2% (1251) bilateral orchiectomy. ADT use was highest in Eastern Europe. Across regions, 74% (20729) of GnRH pts received ⩾6 mos, 48% (13594) continuously; of these, 75% have or will develop CRPC. Among CRPC pts, 57% were currently considered high risk, and 63% expected to develop BM in the future. Gleason score (>8), prostate-specific antigen (PSA) level (⩾20 ng/mL) and PSA doubling time (⩽6 mos) were most commonly used to determine high risk of BM.

Conclusion: This study characterised clinical states and pathway to M0 CRPC and high risk of BM as described by treating physicians. The results confirm that most pts who are treated continuously with ADT develop CRPC within 2 years, and approximately 50−60% will be considered at high risk for BM.

Conflict of interest: *Ownership: JA, AL − own Amgen stock. Corporate-sponsored research: KH, AG − Amgen. Other substantive relationships: JA, AL − employed by Amgen, VS − consultant for Amgen*

2941 POSTER

In-vivo isolation of circulating tumor cells in prostate cancer patients by a medical device

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Background: CTCs are discussed as a prognostic and stratification biomarker, and may help to assess the treatment efficacy. The aim was to demonstrate proof of concept of in vivo CTC isolation in Prostate cancer patients (PCa).

Material and Methods: A medical device (CellCollector) was inserted in a cubital vein for 30 minutes. The interaction of target CTCs with the CellCollector was mediated by antibodies to the epithelial cell adhesion molecule (EpCAM). To confirm binding of CTCs to the wire, immunohistochemical staining against Cytokeratin and CD45 was performed. There were 226 applications of the device in 16 metastasized PCa (PCa-m) with up to 8 wire applications per patient, 24 localasized PCa (PCa-l) with up to 3 wire applications per patient as well as 19 men with benign prostate hypertrophy (BPH) and 21 women as control group with only one wire application.

CTC counts from 22 PCa patients with 58 applications were directly compared to the CellSearch technology.

Results: We obtained *in vivo* isolation of CTCs in 73 of 98 applications to PCa patients (74.5%). The sensitivity for metastasized PCa was (86.2%) and for local PCa (57.5%), respectively. Follow up data of one patient with PCa-m: 2009 diagnosed PCa with multiple metastases. 2 years later PSA of 11.2ng/ml and 25 CTCs. After transurethral resection and removal of a brain metastasis, CTCs decreased to 20 cells with no effect on PSA levels. 4 months later we observed 187 CTCs and a PSA level of 76ng/ml, which was correlated with the patient condition.

Median CTC counts in PCa-l (n = 18) were18.2 before radical prostatectomy and decrease to 2.8 and 1.4during 6 and 12 months follow up. A direct comparison of the CellCollector and CellSearch® resulted in detection rates of 65% (13/20) and 20% (4/20), respectively.

Conclusion: We demonstrate the use of CTCs besides PSA during therapy adjustment in PCa patients In summary the CTC detection rate of the CellCollector in PCa-m and PCa-l in comparison to the CellSearch® method increased by 26% and 45%.

No conflict of interest.

2942 POSTER

Baseline bone mineral density in men with prostate cancer commencing with androgen deprivation therapy (ADT): Characteristics of quantitative ultrasound (QUS) of the heel as triage test compared to dual energy x-ray absorptiometry (DXA)

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Background: Androgen deprivation therapy (ADT), part of treatment for prostate cancer, puts patients at an increased risk for developing osteoporosis. Assessment of bone mineral density (BMD) is considered standard of care in patients commencing ADT, most commonly by dual energy x-ray absorptiometry (DXA). Alternative ways of estimating BMD like quantitative ultrasound (QUS) measurement of the heel are explored as DXA is expensive, non-portable and uses ionising radiation. This study explored the value of QUS as compared to DXA in patients commencing ADT.

Methods: In a consecutive retrospective cohort study of 60 patients with prostate cancer initiating ADT, BMD was measured with DXA and QUS.

Results: No significant correlations were found between the separate DXA T-scores and worst DXA T-score, and the QUS T-scores. Mean difference between the worst DXA T-score and QUS T-score was −0.7 (SD 1.49).

If QUS would have been used as screening tool, with a threshold of T ⩽ −0.5 to perform a DXA, then relevant osteopenia/osteoporosis (worst DXA T-score ⩽−2.0) would have been missed in 1/18 (5.6%, 95% CI: 0.1%-27.3%) patients. The negative predictive value (NPV) is 0.95 (95% CI: 75.1%-99.9%). At a threshold of QUS of T < = 0.7 the NPV would be 0.89 (95% CI: 70.8%-97.7%). Using QUS as screening test prior to DXA and a QUS threshold T-score ⩽−0.5 would avoid 21 (35%, 95% CI: 43%-48%) DXA-scans at the cost of missing 1 (5.6%) case.

Conclusion: QUS testing cannot replace DXA scans fully since correlations between QUS and DXA T-scores in prostate cancer patients starting with ADT are absent. However, QUS can be incorporated in the diagnostic strategy as triage test prior to DXA to reduce the need for DXA scans.

No conflict of interest.

2943 POSTER

Dose intensity of abiraterone acetate and administration of post-abiraterone chemotherapy for metastatic castration-resistant prostate cancer (mCRPC) − a real world analysis

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Background: New treatment options for metastatic CRPC have emerged over the last 3 years for post-docetaxel (D) therapy including cabazitaxel (C), abiraterone acetate (AA) and enzalutamide. AA is also approved for use in chemo naive patients. Oral therapy poses challenges such as adherence. Our study aimed to study dose intensity and persistence with AA in pre-D as well as post-D men using real world data and to evaluate the frequency of administration of chemotherapy post-AA.

Methods: mCRPC patients were identified from 1Jan2010 through 30June2012 using a large US national claims based database. The number of days of drug supply was calculated from quantity and dosage information associated with each prescription record. All patients initiated AA in 2011 and those with a gap of 2 months or more after last AA dose were considered discontinued. Study subjects were censored at the time of loss to follow-up or treatment discontinuation, whichever occurred first. MPR (Medication possession ratio) was defined as total AA days divided by days from initiation of AA to censoring. Persistence was defined as average length of continuous therapy duration for AA initiators. The cumulative persistence rate was estimated using Kaplan Meier analysis. Results were stratified by pre and post D group. Post AA regimen usage was determined in patients who discontinued AA by Dec 2011.
Results: Median age was 72 years. Median number of monthly AA refills was 4. MPR was similar in post-D (0.69) and pre-D (0.67) group. In pre-D setting, 421 patients initiated AA of which 137 (32.5%) discontinued AA within 3 months and 244 (58%) discontinued within 6 months. In post-D setting, 313 patients initiated AA of which 94 (30%) discontinued within 3 months and 118 (60.1%) discontinued within 6 months. In the evaluable pre-D group (N = 74), use of D and/or C post-AA occurred in 31.1% of patients. In the evaluable post-D group (N = 34), 44% of patients received D and/or C post-AA.
Conclusion: The observed persistence and dose intensity of AA for mCRPC patients in a real world setting suggest that better patient selection is warranted to address disease and patient heterogeneity and examination of factors responsible for suboptimal adherence may be important. The rate of post-AA chemotherapy with D and/or C appears low. Given the limitations of observational study design, further prospective research into patient profiles who discontinue AA, optimal sequencing of agents and the discovery of predictive biomarkers is required.
Conflict of interest: *Corporate-sponsored research: The funding for this research provided by Sanofi*

Proffered Papers Session (Tue, 1 Oct)
Gynaecological Cancer

3000 ORAL

Clinical study of autologous dendritic cell therapy targeting mucin 1 for treatment of ovarian cancer patients in first remission

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Background: Cvac is an autologous cellular therapy targeted to elicit a T cell response to tumors that over-express mucin 1 such as epithelial ovarian cancer (EOC). CAN-003 is a phase 2b study evaluating the effect of Cvac on progression free and overall survival, as well as safety and immune responses, in patients in remission from EOC.
Design: Patients were eligible if they had stage III or IV EOC and obtained a complete response to standard first or second line platinum/ taxane based chemotherapy. The first 7 patients received Cvac to allow evaluation of manufacturing in the US and for safety evaluation. Patients were then randomized either to Cvac therapy or standard of care (SOC). Patients in the active group were treated with up to 10 doses of Cvac, 4 weekly for 7 doses, and 8 weekly for three additional doses. The trial is closed to enrolment and will be completed in 2013.
Results: 63 patients were enrolled into the trial; 36 Cvac and 27 SOC of which 42 were in first remission and 21 were in second remission. Patients were mostly Caucasian; 1 was African American and 2 were Asian.
10 SAEs were reported in total. 7 SAEs in Cvac patients and 3 SAEs were reported in SOC; none were unexpected and only one (abdominal pain) was classified as possibly-related to Cvac.
Interim analysis has shown positive trends in PFS; as of 17 August 2012, the median PFS for days on study as 365 days for Cvac, 421 day for non-randomized Cvac, and 321 days for OSC. Updated PFS data will be presented at the meeting. As expected, assessment of anti-mucin-1 responses have indicated no humoral response, however, interim immune results show a T cell response that was mucin 1-specific after 3 Cvac doses. T-cell responses throughout the course of Cvac treatment will be presented at the meeting.
Conclusion: Study data show that immunotherapy with Cvac is well tolerated. Immunological outcomes are consistent with the mechanism of action and the interim trends are encouraging for PFS.
No conflict of interest.

3001 ORAL

Vintafolide therapy shows greater efficacy in patients with folate receptor positive tumors selected by 99mTc-etarfolatide

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Background: Folate drug conjugates can target tumor cells overexpressing membrane bound folate receptor (FR) present on most ovarian cancers (OC) but not other tissues. ^{99m}Tc-etarfolatide (ETAR) allows for real-time tumor imaging of FR expression. This companion agent was investigated in the randomized phase 2 PRECEDENT trial* which demonstrated that the desacetylvinblastine folate conjugate vintafolide (VINTA) combined with pegylated liposomal doxorubicin (PLD) improved PFS over standard therapy in platinum-resistant OC (PROC) patients (pts) (NCT00722592). We now analyse the efficacy of VINTA+PLD in pt subgroups from this trial.
Methods: Women with PROC, ECOG PS of 0−2, and $\leqslant$2 prior systemic cytotoxic regimens were randomized 2:1 to VINTA+PLD or PLD alone. Before randomization, pts were scanned with ETAR to determine FR status. The primary endpoint was progression free survival (PFS) in the ITT population of pts with measureable disease (mITT). The internal consistency of the VINTA+PLD benefit over PLD was evaluated in subgroups defined by baseline pt and disease characteristics (ie, CA-125 levels, PS, etc).
Results: Demographic characteristics at screening were generally balanced between arms. Over 80% of pts scanned with ETAR were FR positive (FR+). Outcomes favored VINTA+PLD over PLD for all subgroups defined by typical baseline factors; hazard ratios for those subpopulation groups were generally close to that of the mITT population (HR = 0.626, 0.409–0.959 95% CI, $P = 0.031$), ranging from 0.524 to 0.794. The most notable benefit was seen in the subgroup of pts identified as FR(100%) (all identified lesions FR+) by ETAR scan. These pts had greater benefit from VINTA+PLD (HR = 0.381, 0.172–0.845 95% CI, $P = 0.013$) vs pts with $\geqslant$1 or 0 FR+ lesions (HR = 0.547, 0.304–0.983 95% CI, $P = 0.041$ and 1.806, 0.369–8.833 95% CI, $P = 0.468$, respectively). Of note, FR+ tumors not treated with VINTA progressed more rapidly than FR negative tumors (~1.7 months vs 5.4 months), supporting FR expression as an adverse prognostic factor. All AEs were grade 4 or lower and most were grade 1−2. Fatigue, anemia, stomatitis, nausea were commonly reported. AEs were generally similar between groups.
Conclusions: VINTA+PLD is the first combination to show improved PFS over standard therapy in PROC. The subgroup analysis indicates selection for pts likely to benefit from therapy with VINTA can be achieved using a companion diagnostic agent such as ETAR. A randomized phase 3 trial is ongoing.
*Supported by Endocyte, Inc.
Conflict of interest: *Advisory board: Endocyte, Inc. Merck. Corporate-sponsored research: Endocyte, Inc.*

3002 ORAL

Olaparib plus chemotherapy, followed by maintenance monotherapy, in women with platinum-sensitive recurrent serous ovarian cancer (PSR SOC): BRCA1/2 mutation (BRCAm) and interim overall survival analyses

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Background: We have shown that addition of the oral PARP inhibitor olaparib (200 mg BID capsules on days 1−10 per 21-day treatment cycle)

to carboplatin AUC4 plus paclitaxel, followed by olaparib 400 mg BID as maintenance monotherapy (OC4P), led to a statistically significant improvement in progression-free survival (PFS) vs carboplatin AUC6 plus paclitaxel alone, followed by no maintenance therapy (C6P), in patients (pts) with PSR SOC (Oza *et al* ASCO 2012). Here, we report results of an interim overall survival (OS) analysis and a prespecified exploratory analysis of efficacy by BRCAm status from this open-label, randomized Phase II trial (NCT01081951; sponsor, AstraZeneca).

Materials and Methods: Germline BRCAm status was known for 35/162 pts at study entry. Tumour BRCAm status was determined for 91 pts by retrospective testing of archival samples. Efficacy outcomes for BRCAm analyses: PFS by central review (RECIST 1.1); PFS2 (time to start of second subsequent therapy after first progression, or death). OS was a secondary endpoint.

Results: Of 162 pts randomized (81 per arm), 156 were treated (OC4P, n = 81; C6P, n = 75) and 121 began the maintenance/no further therapy phase (OC4P, n = 66; C6P, n = 55). BRCAm status was known for 107/162 pts, of whom 41 (38%) had a BRCAm; 7 more had BRCAm of unknown significance. A greater PFS benefit with OC4P vs C6P was seen in pts with BRCAm (HR = 0.21; 95% CI 0.08–0.55; $P = 0.0015$) vs pts with no BRCAm/BRCAm of unknown significance (HR = 0.77; 95% CI 0.41–1.44). In the overall population, there was no statistically significant difference between arms in interim OS (38% maturity: HR = 1.37; 95% CI 0.82–2.27; $P = 0.2238$; medians not reached); this analysis was potentially affected by an imbalance in early censoring (OC4P, n = 2; C6P, n = 15) after 16 pts withdrew consent (1 pt lost to follow up). In pts with BRCAm, but not the overall population, a retrospective assessment of PFS2 showed an improvement with OC4P vs C6P (HR = 0.35; 95% CI 0.13–0.88; $P = 0.0258$). OS analyses have yet to be performed by BRCAm status (insufficient events in pts with a BRCAm).

Conclusions: Olaparib plus carboplatin AUC4 and paclitaxel, followed by maintenance monotherapy, led to the greatest clinical benefit in pts with BRCAm. An interim OS analysis in all pts showed no benefit in the OC4P arm, but the PFS2 improvement in pts with BRCAm suggests the benefit is maintained beyond first progression in this subgroup. Olaparib maintenance therapy will be evaluated in two Phase III trials in ovarian cancer pts with BRCAm.

Conflict of interest: *Ownership: E. Lowe & J. Read are employees of AstraZeneca and own AstraZeneca stock. Advisory board: C. Poole has been a remunerated consultant and advisory board member for AstraZeneca. Other substantive relationships: C. Poole has been CI and PI of other AstraZeneca-sponsored clinical trials*

3003 ORAL

Quality of life in patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (AEOC) receiving either pazopanib monotherapy or placebo after first-line chemotherapy: AGO-OVAR16 results

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Background: Results of the double-blind, randomized, placebo-controlled phase 3 trial AGO-OVAR16 (VEG110655) indicate that pazopanib monotherapy prolongs progression-free survival (PFS) in women without disease progression after first-line chemotherapy for AEOC (HR = 0.766, P=.0021; median PFS 17.9 months [M] vs placebo 12.3 M). The impact of treatment and correlation of disease progression on health-related quality of life (HRQL) was also assessed.

Materials and Methods: HRQL was measured with EQ-5D, EORTC QLQ-C30 (QLQ30), and the ovarian cancer module (OV28) at baseline (BL) and day 1 of week (W) 13 and M 7, 10, 13, 16, 25, and 31. For patients who discontinued treatment early, regardless of reason, HRQL was also measured at end-of-treatment and first post-treatment visits. For patients on treatment, mean changes from BL were compared between treatment groups via mixed-model repeated measures analysis of covariance. After disease progression (RECIST), data of the first available assessment were pooled and described by summary statistics.

Results: 894 patients had BL HRQL scores. Patient compliance with HRQL assessment was high, ranging from 97% at BL to 76% at M25 for all scales except OV28 'sexual functionality' and 'other chemotherapy side effects' that were excluded from the analysis. The QLQ30 Global Health Status (GHS) remained constant on placebo up to M25 but declined on pazopanib. Between-arm differences on the GHS were statistically significant but were less than or at the low end of the range of published minimally important difference (MID 5−10 points, Table). Treatment differences favoring placebo on the EQ-5D were statistically significant and below the MID (0.08 points). Similar results were obtained for the OV-28 scales, except for abdominal/GI symptoms, which substantially favored placebo.

Table: Treatment difference (pazopanib minus placebo scores) in GHS change from BL

Time point	W13	M7	M10	M13	M16	M25
Δ score	−4.4	−5.6	−6.3	−2.4	−0.4	−5.5
P	<0.001	<0.001	<0.001	0.185	0.847	0.024

After disease progression, GHS and EQ-5D changes from BL were worse than scores observed for patients with no disease progression, as were 12 of 14 QLQ30 subscales and all functional scales of the OV28.

Conclusions: Pazopanib monotherapy maintenance treatment in AEOC is associated with a small, statistically significant decline in HRQL during treatment. However, the treatment, which delays progression by 5.6 M, may also delay the further declines in HRQL that are associated with disease progression.

Conflict of interest: *Corporate-sponsored research: (AD)GSK AD was PI of the phase I/II trial preceeding this phase III trial. Other substantive relationships: (AD) Glaxo SmithKline (2 times reasonable honoraria for lecture prior to trial acrual) (SK) Employee of GSK*

3004 ORAL

Adjuvant radio(chemo)therapy in lymph-node positive vulvar cancer − The AGO CaRE-1 study

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Background: While the majority of patients with vulvar cancer can be cured by surgery alone, women with lymph-node metastases often show unfavorable outcome. It is not clear whether postoperative (chemo)radiotherapy improves outcome in all patients with lymph-node positive vulvar carcinoma compared to surgery alone.

Material and Methods: Patients with primary squamous-cell vulvar cancer treated at 29 gynecologic cancer centers in Germany 1998–2008 were included in a centralized database and analyzed retrospectively to examine clinical outcome and relapse patterns.

Results: A total of 1,618 patients were documented with a median follow-up of 38.8 months. UICC-stage distribution was 580 (35.9%) T1b, 818 (50.6%) T2, 160 (9.9%) T3 and 31 (1.9%) T4; in 29 (1.8%) cases the tumor stage was unknown. 495 patients (30.6%) had lymph-node metastases (N+). Median progression-free survival (PFS) of these patients was 15.9 months and overall survival (OS) 46.9 months, compared to 99.1 and 208.8 months for node-negative patients. 172 (34.8%) patients had 1, 102 (20.6%) patients 2, 62 (12.5%) patients 3 and 87 (17.6%) patients >3 positive lymph-nodes (for 72 (14.6%) patients the number was unknown). 254 (51.3%) N+ patients underwent adjuvant radio/chemotherapy (212 [83.5%] received radiotherapy alone, 36 [14.2%] radiochemotherapy and 6 [2.4%] chemotherapy only). Median PFS and OS in these patients were significantly longer compared to N+ patients without adjuvant treatment [PFS: 18.5 vs. 12.0 months, p = 0.0003, HR 0.63 (95% CI: 0.50–0.81); OS: 111.6 vs. 37.1 months, p = 0.029, HR 0.71 (95% CI: 0.52–0.97)]. This effect could be observed in all node-positive subgroups and remained consistent in multivariate analysis of all N+ patients adjusted for age, ECOG, UICC-stage, grade, invasion depth and number of positive nodes (PFS: HR 0.57, 95% CI: 0.43–0.74; OS: HR = 0.61, 95% CI: 0.43–0.86).

Conclusions: This large multicenter study in vulvar cancer shows that prognosis of node-positive patients was improved with adjuvant radiotherapy but still remains poor compared to the outcome of node-negative

patients. In other squamous cell carcinomas, adjuvant chemoradiation is superior to radiotherapy alone; this approach might therefore be the best to further improve outcome in vulvar cancer. In addition, definitions of standardized radiation treatment protocols according to field arrangements need to be determined.
No conflict of interest.

3005 ORAL

Vaginal brachytherapy versus external beam pelvic radiotherapy for high-intermediate risk endometrial cancer: Long term results of the randomized PORTEC-2 trial

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Background: For endometrial cancer (EC) patients with features of high-intermediate risk (HIR), the vagina is the most frequent site of recurrence after surgery alone. Pelvic external beam radiotherapy (EBRT) reduces the risk of vaginal and pelvic recurrence, but without survival benefit. PORTEC-2 was the first randomized trial comparing the efficacy of vaginal brachytherapy (VBT) and EBRT. At a median follow-up of 45 months the results indicated that VBT is highly effective in ensuring vaginal control with fewer side effects and better health-related quality of life than EBRT. The current analysis was done to evaluate long-term results.
Methods: The PORTEC-2 trial was a multicenter randomised trial. After surgery, patients were allocated (1:1) to pelvic EBRT or VBT. Eligible patients had a HIR EC: age >60 and (FIGO 1988) stage 1C grade 1−2 or stage 1B grade 3; any age and stage 2A. Primary endpoint was vaginal recurrence (VR), which was expected to be 2% at 3 yrs in the EBRT group. The trial was powered (85%) to detect a clinical relevant absolute difference of 6% in VR (2% vs. 8% at 3 years). Analysis was done by intention-to-treat, using the competing risk method for VR, pelvic (PR) and locoregional recurrence (LRR, defined as vaginal and/or pelvic recurrence) and distant metastasis (DM), and Kaplan Meier for overall (OS) and disease free survival (DFS).
Results: 427 patients were randomized between 2002–2006 (214 to EBRT and 213 to VBT). At a median follow-up of 85 months, 5-year total actuarial rates of VR were 2.4% in the VBT arm versus 1.4% after EBRT ($p = 0.52$); PR 5.2% vs 0.9% ($p = 0.007$); LRR 6.6% vs 2.4% ($p = 0.025$) and DM 9.3% vs 6.6% ($p = 0.37$). Five-year rates of vaginal and pelvic recurrence as first failure were 1.4% and 1.9% in the VBT group, and 0.9% and 0.5% in the EBRT group ($p = 0.41$ and $p = 0.24$). There were no significant differences in 5-year OS (83.9% vs. 83.8% $p = 0.79$) and DFS (81.1% vs. 81.9% $p = 0.57$).
Conclusions: Long-term analysis of the PORTEC-2 trial confirms that VBT is effective in preventing vaginal recurrence. Despite the significantly increased total pelvic recurrence rate in the VBT arm, most were combined with DM and rates of pelvic recurrence as first failure, distant metastases, OS and DFS were similar. As patient reported quality of life after VBT was shown to be better than after EBRT, VBT remains the treatment of choice for patients with high-intermediate risk endometrial carcinoma.
No conflict of interest.

Poster Session (Sun, 29 Sep)
Gynaecological Cancer

3006 POSTER

Age-related heterogeneity of ovarian epithelial carcinomas in a nationwide population (USA)

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Background: Ovarian epithelial carcinomas (OEC) pose significant health care problems in elderly women. While efforts have been increasing to detect genetic biomarkers and OEC therapeutic targets, potentially relevant correlations of chronological 'age-at-diagnosis' (AAD) with descriptive characteristics and clinical behaviors of these usually lethal cancers have not been fully explored in the general population.
Methods: Records accrued in the National Cancer Institute's Surveillance Epidemiology and End Results Database (SEER 18 registries, time period 2000 through 2009), yielded 51,253 cases of primary invasive OEC (~28% of the USA total). This number enabled robust linkage of three AAD subsets (<45, 45−64, >64 years) to classical descriptors: (i) stage (I−IV) standardized by the International Federation for Gynecologic Oncology (FIGO), and (ii) morphology (serous and others) and grades (1−4) recommended by the International Classification of Disease for Oncology (ICD-O-3). Age-specific IR (ASIR) estimated from AAD curves for each descriptor, and fitted for period and birth-cohort effects, tested the reported distinctions for P >.001. Stages or grades of AAD subsets then were compared using age-adjusted incidence rates (IR) and IR ratios (IRR) at P <.001. Comparisons of actuarial or Kaplan–Meier vital statistics were ovarian cancer specific.
Results: The median age of microscopically confirmed OEC (96% of total cases) was 62 years (IR=14.5): 10% of cases appeared before 45 (IR =3.0), 45% from 45−64 (IR=22), and 45% after 64 (IR= 41). FIGO stages and ICD-O-3 morphologies were documented together in 83% of confirmed cases. Grades were enumerated in 62%. Extra-pelvic OEC in FIGO stage III accounted for 42% of staged cases, but IRR of FIGO stages III−IV/I−II (extra-pelvic/intrapelvic), increased exponentially in the ascending order of AAD: 0.92, 1.8, 3.7. The IRR of high/low grades (3−4/1−2) also ascended in AAD order: 0.86, 2.0, 2.9. Serous morphology was always predominant in the high grade extra-pelvic OEC: 47%, 61%, 61%. Parsing of ovarian-specific deaths, registered within 24 months after initial OEC diagnosis, disclosed exponential AAD-dependent increases in the death IR (=0.3,= 3.7, =13), as well as in the originally ascribed IRR (III−IV/I−II): 6.9, 8.3, 11. Median months of survival per AAD subset respectively diminished: 38, 30, 14.
Conclusions: Known genetic heterogeneities in OEC have engendered the prevalent models of OEC bimodal oncogenesis and morphologic diversity. Present findings align age-at-diagnosis to stage of presentation, morphologic expression and survival duration. These signs of age-effect modifications on OEC natural history imply a chronologically determined interplay of epigenetic or host factors. AAD thus warrants integration as a critical variable in translational investigations of OEC molecular genetics or therapeutic trials.
No conflict of interest.

3007 POSTER

The roles of chitinase 3 like 1 in cervical cancer in vitro

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Background: Chitinase 3 like 1 (CHI3L1) is a 40 kDa mammalian glycoprotein which is related in amino acid sequence to the chitinase protein family but has no enzymatic property. Several studies have reported that CHI3L1 could be used as a serum marker in patients with several solid tumours including cervical cancer (CxCa) in which high serum CHI3L1 is associated with poor prognosis and short survival time. Although functions of CHI3L1 in mediating cell proliferation, anti-apoptosis, migration, and angiogenesis have been reported in several human cancers, not all functions activated by CHI3L1 are covered in one cancer but the action is rather dependent on the cancer type. The previous study on microarray showed an increasing level of CHI3L1 in precancerous and CxCa compared with normal suggesting its role in tumour progression. Thus, this study aimed to find the virtual function of CHI3L1 which contributes to the progression of CxCa in terms of cell proliferation, migration, anti-apoptosis, and angiogenesis.
Methods: The recombinant CHI3L1 protein was produced and used for HeLa and CaSki cell treatment. The treated and untreated cells were examined for cell proliferation by MTS assay, cell survival by Live-Dead cell assay, cell migration by wound healing and transwell chemotaxis assays, and angiogenesis by Matrigel tube formation assay.
Results: The results showed that CHI3L1 could activate angiogenesis by promoting endothelial cell migration and tubular formation. Likewise, CHI3L1 could induce both of CaSki and HeLa to form vascular-like structures. In contrast, CHI3L1 could not protect apoptosis of both CxCa cell lines from gamma irradiation while cell proliferation and migration directed by CHI3L1 were dependent on type of cell line.

Conclusions: CHI3L1 protein is a potent factor in which it can induce angiogenesis through its regulation of endothelial cells. The predominant function of CHI3L1 as an angiogenic factor is worth to further investigate for its receptor which may benefit the CxCa patients in term of targeted therapy leading to the improved quality of life and longer overall disease-free survival.
No conflict of interest.

3008 POSTER

Qualitative and quantitative mtDNA alterations in HPV16-positive cervical neoplasia

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Background: Human papillomaviruses (HPV) are known to be the etiological agents of cervical cancer which represents the second most common malignancy in women worldwide. Recently, mitochondrial DNA (mtDNA) mutations have been found in many types of cancer. Here we analysed mutations in the D-loop region of mtDNA and the relationship between mtDNA copy number, HPV16 viral load and MnSOD (manganese superoxide dismutase) mRNA expression level in HPV16-positive samples.
Material and Methods: DNAs were isolated from cervical specimens (using High Pure PCR Template, Roche Diagnostics) from 60 women with different cytology. RNAs were isolated (Trizol reagent, Invitrogen) in order to determine MnSOD mRNA expression levels. DNA PCR amplification and sequencing were used for mtDNA mutations. Real-time PCR (Applied Biosystems) was used to determine mtDNA copy number and HPV16 DNA viral load using in house designed primers.
Results: In patients with normal cytology and ASCUS (Atypical Squamous Cells of Undetermined Significance), HPV16 was absent. 72.2% (13/18) LGSIL (Low-Grade Intraepithelial Lesion) and 93.3% (14/15) HGSIL (High-Grade Intraepithelial Lesion) patients presented infection with HPV16 in single or co-infection (with HPV18, 31 and 33). We detected a significantly greater incidence of mtDNA mutations in D-loop region in LGSIL and HGSIL patients ($P<0.05$). HPV16-positive individuals were more likely to carry mtDNA mutations than HPV-negative controls ($P<0.003$). Furthermore, mtDNA copy number increased during lesion development when compared to control samples. We also observed MnSOD mRNA upregulation during cervical lesion development, from normal epithelium to HGSIL. Moreover, HPV16 viral load was significantly higher in HGSIL patients than in ASCUS/LGSIL and was strongly associated with the increased MnSOD mRNA level ($p < 0.005$).
Conclusions: These findings suggest that mtDNA alterations might be cofactors involved in HPV-induced cervical dysplasia. MtDNA mutations and copy number increase could play a role in cervical precursor lesions and cancer but their role in the mechanism of carcinogenesis remains to be solved.
No conflict of interest.

3009 POSTER

Ubiquitin-proteasome system is activated by oxidative stress and contributes to docosahexaenoic acid-induced degradation of oncogenic HPV E6/E7 viral proteins

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Background and Aims: Oncogenic human papillomavirus (HPV) E6/E7 proteins are essential for the onset and maintenance of HPV-associated malignancies. The aim of the present study was to investigate whether and how the omega-3 fatty acid, docosahexaenoic acid (DHA) influences E6/E7 viral proteins and the fate of oncogenic HPV-infected cells.
Material and Methods: Oncogenic HPV-infected cell lines and the cell lines transiently or stably expressing different ubiquitin-proteasome system (UPS) reporters that reflect UPS activity were exposed to DHA, and the relationship between E6/E7 oncoproteins, mitochondrial reactive oxygen species (ROS) and cell death were monitored using various in vitro approaches.
Results: DHA diminished E6/E7 protein levels in a time-dependent manner and led to functional restoration of known E6/E7 binding targets, p53 and retinoblastoma tumour suppressors, and apoptosis in oncogenic HPV-infected cancer cells. Additionally, DHA exposure increased the ubiquitination and proteasomal degradation of E6/E7 oncoproteins as well as three different UPS reporter substrates, and UPS inhibition abrogated these effects of DHA, suggesting that E6/E7 viral proteins undergo cellular UPS-mediated degradation in response to DHA via augmented global UPS activity. Further study showed that DHA-induced mitochondrial ROS overproduction was responsible for the increases in UPS activity and degradation of E6/E7 oncoproteins. Meanwhile, exogenous oxidative stress and pharmacological induction of mitochondrial ROS had similar effects as DHA, and inhibition of ROS abolished the increased intracellular UPS activity, destabilization of E6/E7 viral proteins, and apoptosis.
Conclusions: We propose that by promoting mitochondrial ROS production, DHA enhances the global UPS activity and simultaneously accelerates UPS-dependent destruction of oncogenic HPV E6/E7 viral proteins, thereby inducing apoptosis in HPV-infected cancer cells. These findings unravel a novel function of DHA in UPS regulation, and provide evidence for use DHA as a mechanistically unique anticancer agent to treat HPV-associated tumours.
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No conflict of interest.

3010 POSTER

Interleukin-17 produced by tumour microenvironment promotes self-renewal of CD133+ cancer stem-like cells in ovarian cancer

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Background: Inflammatory cytokines have been proposed to be the components of niche for cancer stem cells (CSCs), and could affect the characteristics of CSCs, such as self-renewal and metastasis. IL-17 mainly produced by Th17 and macrophages is a new pro-inflammatory cytokine, and has been proved one of markers for the poor prognosis in ovarian cancer. However, the effects of IL-17 on the characteristics of CSCs remain to be explored. Our present study is aimed to explore the effects and the mechanisms of IL-17 on self-renewal of CSCs in ovarian cancer.
Material and Methods: Ovarian CSCs (OCSCs) were obtained from A2780 cell line by serum-free culture selection and from primary tumour tissues of ovarian cancer by CD133-labeled magnetic activated cell sorting (MACS). IL17 receptor (IL-17R) expression on OCSCs was verified by real-time PCR, flow cytometric and immunofluorescence analysis in A2780-derived OCSCs and primary OCSCs respectively. The sources and location of IL-17-positive cells were defined by immunohistochemistry and immunofluorescence. Sphere formation assay was used to determine the ability of self-renewal of CSCs before and after treatment of recombinant IL-17. Western blot and immunofluorescence were used to determine the activity of NF-κB and P38 MAPK signalling mediated by IL-17. Downstream genes of NF-κB and P38 MAPK signalling were analysed by gene expression profiling and verified by real-time PCR.
Results: IL-17-positive cells (CD4-positive cells or CD68-positive macrophages) located in the niche of OCSCs in ovarian cancer. Also, Real-time PCR, flow cytometric and immunofluorescence analysis showed IL-17R expression on OCSCs both from A2780 cell line and primary ovarian cancer tissues. More importantly, the growth and sphere formation capacities of OCSCs were significantly enhanced by recombinant IL-17 in a dose-dependent manner, or when OCSCs were transfected with IL-17. Subcutaneous transplantations of IL-17-OCSCs into nude mice showed greater tumorogenic capacity than vector-OCSCs. To elucidate the underlying mechanisms of IL-17 on self-renewal of OCSCs, we explored NF-κB and P38 MAPK activation in OCSCs by IL-17 treatment and found IL-17 really did activate NF-κB and P38 MAPK, which also proved by the inhibition of IL-17 role on self-renewal of OCSCs by specific inhibitor to NF-κB and P38 MAPK. To gain further insights into which target genes involved in IL-17-induced OCSCs self-renewal, we did gene profiling in OCSCs changed by IL-17 and found that 14 downstream genes (GATA6, ZIC3, IRX4, STAT3, HOXD9, FOXO3, PAX6, TP53, ETV5, SP1, NFATC1, BCL2 SOX2, TCL1A) might mediate IL-17-enhanced self-renewal of OCSCs.
Conclusions: Our present results indicate that IL-17 signalling contributes to ovarian cancer malignancy through the promotion of OCSCs self-renewal, and that targeting IL-17 may offer benefit for the patients with ovarian cancer.
No conflict of interest.

3011 POSTER

Effect of hypoxia, glucose deprivation and glycogen phosphorylase inhibition on ovarian clear cell cancer cell line proliferation

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Background: The hypothesis that ovarian clear cell cancer (OCCC) cell lines are resistant to hypoxia and glucose deprivation, possibly because of their high glycogen content was tested.

Methods: 10 ovarian cancer cell lines (PEO1m, ES-2, OV2008, SKOV3, TR175, TOV21G, JHOC-5, JHOC-7, JHOC-9 and OVISE) were cultured under 4 conditions: normal (21% Oxygen, standard DMEM media), hypoxia (1% Oxygen), glucose deprivation (glucose-free DMEM) and combined hypoxia and glucose deprivation and proliferation was assessed using the Sulphorhodamine B (SRB) assay after 7 days in culture. Glycogen content was assayed in 6 cell lines (PEO1m, TOV21G, SKOV3, JHOC-5, JHOC-9 and OVISE) and the effect of siRNA knock-down of glycogen phosphorylase (PYGL) on proliferation was measured with SRB assays.
Results: Glucose deprivation decreased proliferation by 43% in the 5 validated OCCC cell lines (TOV21G, JHOC-5, JHOC-7, JHOC-9 and OVISE) and by 57% in the 5 non-OCCC cell lines ($p = 0.42$). Hypoxia decreased proliferation by 32% in the OCCC compared with 28% in the non-OCCC cell lines ($p = 0.79$). Combined hypoxia and glucose deprivation decreased proliferation by 64% in the OCCC and by 82% in the non-OCCC cell lines ($p = 0.34$). The non-significant differences in response to glucose deprivation, with or without hypoxia, were driven entirely by JHOC-7 which did not show any decrease in proliferation under those conditions. Similarly, there was no difference in proliferation when the comparison was between the 5 OCCC cell lines and the 2 high-grade serous cell lines (PEO1m and TR175). Glycogen content was 5−6-fold higher in SKOV3, JHOC-5 and OVISE ('glycogen-rich') compared with PEO1m, TOV21G and JHOC-9 ('glycogen poor'). Proliferation was reduced to a similar extent under the 4 culture conditions in the glycogen-rich and glycogen-poor cell lines ($p = 0.72–0.79$). When cultured under normal conditions, siRNA PYGL knockdown reduced proliferation by 78% in PEO1m, 65% in TOV21G, 44% in SKOV3, 34% in JHOC-9 and 42% in OVISE cells ($p = 0.0001–0.006$).
Conclusions: Contrary to prior reports, OCCC cell lines are not more resistant to hypoxia or glucose deprivation than other ovarian cancer cell lines. High glycogen content does not predict resistance to glucose deprivation. Access to glycogen stores is important for proliferation in these cell lines even when there is plentiful glucose in the media. Targeting glycogen could be a novel therapeutic strategy in OCCC.
No conflict of interest.

3012 POSTER

Development of a prognostically relevant "angiogenic signature" in ascites from patients with advanced ovarian cancer

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Background: The main purpose of the proposed project is to use the expression of angiogenic factors in of ascites from patients with ovarian cancer, in order to establish an 'angiogenic profile' which can be used to predict response to chemotherapy as well as anti-angiogenic therapy.
Materials and Methods: Twenty samples of supernatant from ascites (10 from platinum sensitive and 10 from platinum resistant patients) were analyzed using a Protein Arrays method. Proteome Profiler Array Kit® has been used to detect 55 angiogenic factors in every sample. The results were analysed using a densitometry program, and the factors exhibiting statistically significant difference were detected. ELISA was used to confirm the results.
Results: Protein Arrays highlighted 16 factors with statistically significant difference between patients resistant to platinum chemotherapy compared to the chemosensitive ones. Nine factors with statistically significant difference relevant to Chemoresistant patients (Angiogenin, Amphiregulin, Endothelin-1, HB-EGF, IGFBP − 1, IGFBP −3, Platelet Factor 4 (PF4), TIMP- 4 and VEGF), and 7 factors with statistically significant difference relevant to Chemosensitive patients (Angiopoietin-1, FGF basic, GM-CSF, IL-1β, MIP- 1α, PDGF-AB/PDGF-BB, and Thrombospondin-2). Nine factors were examined using ELISA in the same samples (Angiogenin, Angiopoietin-1, TIMP- 4, IL-1β, Endothelin-1, IGFBP −3, MIP- 1α, Angiopoietin-2 and VEGF). Seven factors out of nine were in agreement with the Arrays results (Angiopoietin-1, TIMP- 4, IL-1β, Endothelin-1, MIP- 1α, Angiopoietin-2 and VEGF). Finally, using suitable bioinformatics software 8 additional random samples were characterized as sensitive/resistant with over 75% success and 98% accuracy, in predicting resistance/sensitivity.
Conclusion: There is a strong indication that our Arrays method is able to demonstrate an 'angiogenic signature' for predicting response to chemotherapy.
No conflict of interest.

3013 POSTER

Ovarian cancer stem cells (OCSCs): Therapy for advanced chemo-resistant ovarian cancer

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Background: Invasive and mesenchymal property of Ovarian Cancer Stem Cells (OCSCs) with CD44+/CD133+ has made them promising target for targeted treatment. Chemotherapy treatment uses medicine to weaken and destroy cancer cells in body, including cells at original cancer site and any cancer cells that may have spread to another part of body. Chemotherapeutic drugs for advanced chemo-resistant ovarian cancer are yet to be well defined. Combination of drugs is also not fully known. Our objective is to define chemotherapeutic drugs and its action in OCSC which is the major reason for chemo-resistance in case of advanced chemo-resistant ovarian cancer patients.
Methods: A total of forty biopsy proven advanced chemo-resistant ovarian cancer patients in the age group of 22−36 years were selected randomly and tested for CD44/CD133 via flowcytometry. Isolated OCSCs were cultured for ex vivo drug sensitivity towards Platinum, Anthracyclin, Docetaxel, Rapamycin, Sunitinib, Sorafenib and Gefitinib. Correlation was drawn between cell differentiations, % of stem cells and drug response. Accordingly chemotherapy was designed for a particular patient.
Results: We detected OCSCs in 90% of cases. Among positive samples ex vivo drug sensitivity was seen in 8(20%) to Rapamycin, 2(5%) to Sunitinib, 2(5%) to Sorafenib, 2(5%) to Gefitinib, 6(15%) to Platinum, 2(5%) to Anthracyclin, 2(5%) to Docetaxel and rest showed no sensitivity to any drug.
Conclusions: Thus primary aim to target OCSCs at onset of tumors in ovarian cancer patients to control metastasis and relapse of disease was somewhat obtained. Most interestingly, we found that the chemotherapeutic drugs which were less prescribed for ovarian cancer showed greater sensitivity in comparison to the widely used ones. We like to do Animal model study followed by Phase I, II and III Human Clinical Trial to establish our hypothesis for better management of chemo-resistant ovarian cancer.
No conflict of interest.

3014 POSTER

MicroRNA-145, a p70 S6 kinase-activated microRNA, regulates N-cadherin expression and epithelial–mesenchymal transition

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Background: Ovarian cancer is highly metastatic with a poor prognosis (5-year survival <25%), and understanding the underlying mechanisms is of obvious importance. Epithelial–mesenchymal transition (EMT) has been identified as of potential importance in ovarian cancer metastasis. N-cadherin is critically involved in the EMT. Yet, very little is known about the factors regulating N-cadherin expression. Recently, we demonstrated that p70 S6 kinase ($p70^{S6K}$), a downstream effector of phosphatidylinositol 3-kinase/Akt, which is frequently activated in ovarian carcinoma, plays a key role as intracellular signaling mediator for the effects of multiple growth factors in the tumor microenvironment. However, the molecular details of how $p70^{S6K}$controls the malignant properties are still poor understood.
Material and Methods: Expression of Twist, SOX9, and N-cadherin expression was measured by reverse transcription-PCR. The functional effects of $p70^{S6K}$ were examined further using overexpression and knockdown approaches. The putative microRNA (miRNA) was investigated by in silico prediction. A luciferase reporter assay was conducted to confirm miRNA-target interaction.
Results: Here we show that $p70^{S6K}$is a pivotal regulator of N-cadherin, which was mediated through activation of the transcription factors Twist and Sox9. Interestingly, we found that upregulation of Twist and Sox9 was due to increased mRNA stabilities. Using multiple in silico algorithms, we showed that miR-145 may play a critical role in regulating Twist and Sox9. We demonstrated direct targeting of miR-145 to the 3'-untranslated regions of Twist and Sox9. Notably, overexpression of miR-145 significantly suppressed, whereas inhibition of miR-145 enhanced N-cadherin expression and EMT, suggesting that inappropriate expression of miR-145 contributes to the metastatic phenotype. On exploring how $p70^{S6K}$ might regulate miR-145, we found that $p70^{S6K}$ could regulate miRNA biogenesis.

Conclusions: These results illustrate a novel regulatory role of p70^{S6K}-dependent miR-145-Twist/Sox9 signaling axis in the regulation of N-cadherin and EMT properties in ovarian cancer and could have important clinical implications.
No conflict of interest.

3015 POSTER

p70 S6 kinase promotes a critical step in ovarian cancer metastasis by modulating tumor-mesothelial cell adhesion through a P-cadherin-beta1-integrin crosstalk

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Background: Ovarian cancer is the leading cause of death of all gynecologic tumors. These deaths are largely due to the fact that most patients are diagnosed at an advanced stage. Unlike most solid tumors, ovarian cancer rarely disseminates through the vasculature but metastasizes by the implantation of tumor spheroids onto the peritoneum, and successful adhesion is the first rate-limiting step in the metastasis formation of ovarian cancer cells. This unique metastatic mechanism poses distinct therapeutic challenges, in which current treatments are not effective. Unraveling the molecular mechanisms underlying this process may lead to new therapeutic targets.
Material and Methods: We employed overexpression and knockdown approaches to investigate the molecular mechanisms of ovarian cancer spheroids which most closely mimic the *in vivo* ovarian carcinoma adhesion to human primary mesothelial cells *in vitro* and different extracellular matrix components, and utilized an intraperitoneal ovarian cancer model to test metastasis *in vivo*.
Results: Here we report a novel function of p70^{S6K} in the peritoneal adhesion of ovarian cancer cells, which is the first rate-limiting step in ovarian cancer metastasis. Ectopic expression of active p70^{S6K} significantly enhanced, whereas depletion of p70^{S6K} expression or inhibition of its activity resulted in diminished ovarian cancer spheroid adhesion to the mesothelium and specific extracellular matrix proteins. These effects were accompanied by an increase in the expression of P-cadherin and beta1 integrin. Furthermore, we provided evidence for the existence of a crosstalk between P-cadherin and beta1 integrin. In particular, we demonstrated that an upregulation of beta1 integrin occurred as a consequence of P-cadherin expression. In an attempt to establish the regulatory mechanism whereby P-cadherin exerted its transacting functions, we found that the upregulation of beta1 integrin mainly due to posttranslational events. Using an experimental metastatic mouse model, we showed that loss of p70^{S6K} significantly attenuated the metastatic spread of ovarian cancer cells to the peritoneum. Targeting the P-cadherin/beta1-integrin interplay also abolished the metastatic dissemination of ovarian cancer cells in mice.
Conclusions: These data strongly support a new function of p70^{S6K} in ovarian cancer metastasis, and provide evidence that a novel interplay between P-cadherin and beta1-integrin is essential for this process.
No conflict of interest.

3016 POSTER

Mechanism of action of the acyclic nucleotide phosphonate, cidofovir, in treatment of human papillomavirus associated neoplasia

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Background: The acyclic nucleotide phosphonate (ANP) Cidofovir is approved for treatment of cytomegalovirus (CMV) associated retinitis. Cidofovir is also used off label for treatment of human papillomavirus (HPV) associated neoplastic lesions, especially vulval intraepithelial neoplasia (VIN). With CMV, cidofovir targets the viral polymerase, but HPV uses host cell DNA polymerase to replicate, hence in this setting the mechanism of action of the compound is unclear. This study examines the mechanism of action of cidofovir in a HPV transformed cell model designed to represent VIN.
Methods: A HPV naturally transformed short term cell line derived from a VIN biopsy and HPV negative primary human epidermal keratinocytes (HEKs) were dosed with their predetermined IC50 concentrations of cidofovir. At 12 and 36 hours post treatment cells were lysed, RNA was extracted and used to examine gene expression in apoptotic pathways by qPCR array analysis. At 12, 36 and 72 hours post treatment protein was extracted to examine cleaved caspase 3 activity via an in cell fluorescence assay. Finally, 96 hours post treatment cells were fixed, stained with Propidium Iodide (PI) and examined for cell cycle status via FACS analysis.
Results: The apoptosis qPCR array showed specific responses in the HPV positive cell line, with BCL2A1 gene upregulation and genes such as BCL2L10, BIRC3, HRK and P53 down regulated at both time points. The cleaved caspase 3 activity kit showed no significant evidence of apoptosis in the HPV transformed cell line. However, flow cytometry showed a G2-M block in the cell cycle and increases in cell size in HPV transformed cells treated with Cidofovir.
Conclusions: These data give insight in to the mechanism of action of Cidofovir in HPV associated lesions. At a transcriptional level several apoptotic genes were flagged as differentially expressed in comparison to the untreated control and HPV negative cells. At the protein level, however, cleaved caspase 3 activity did not appear to be altered, indicating the absence of apoptosis. This, combined with the FACS analysis suggests that Cidofovir produces an anti-proliferative effect in HPV positive cells by causing cell cycle arrest. Further work is needed to examine how this effect is occurring and its relevance in the clinical setting.
No conflict of interest.

3017 POSTER

Loss of HOXD10 expression induced by upregulation of miR-10b accelerates migration and invasion activities of ovarian cancer cells

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Background: Small and large noncoding RNAs (ncRNA) contribute to the acquisition of aggressive tumor behaviors in diverse human malignancies. Two types of ncRNAs, microRNA-10b (miR-10b) and homeobox (HOX) transcript antisense RNA (HOTAIR), can suppress translation of the HOXD10 gene, an mRNA encoding a transcriptional repressor that inhibits the expression of cell migration/invasion-associated genes in human malignancies. We investigated the relationship of the miR-10b/HOTAIR/HOXD10 axis to migration/invasion activity in epithelial ovarian cancers.
Materials and Methods: We used 8 ovarian cancer cell lines and 68 primary ovarian cancers. Expression of miR-10b and HOTAIR was evaluated by real-time PCR, and HOXD10, matrix metallopeptidase 14 (MMP14) and ras homolog family member C (RHOC) proteins were investigated using Western blotting and/or immunohistochemistry. Cell migration and invasion activities of ovarian cancer cell lines were investigated using transwell migration and Matrigel invasion assays after treatment for knockdown and/or overexpression of miR-10b and HOTAIR.
Results: Overexpression of miR-10b induced a decrease of HOXD10 protein, and upregulated the migration/invasion activity of ovarian cancer cell lines ($P<0.05$). In these cells, a significant increase of MMP14 and RHOC was observed. No significant upregulation of HOXD10 was observed in cells treated with HOTAIR-siRNA. Positive signals for HOXD10 and MMP14 were observed in 47 (69%) and 25 (37%) of 68 patients with ovarian cancer. An inverse correlation between HOXD10 and MMP14 immunoreactivities was observed ($P<0.05$), and miR-10b expression was also inversely correlated with HOXD10 expression ($P<0.05$).
Conclusions: The present results suggest that downregulation of HOXD10 expression by miR-10b overexpression in epithelial ovarian cancer cells might induce an increase of pro-metastatic gene products, such as MMP14 and RHOC, thus contributing to acquisition of metastatic phenotypes.
No conflict of interest.

3018 POSTER

Pelvic lymphatic drainage pathways in relation to the autonomic nerves: implications for radical hysterectomy

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Background: Radical hysterectomy with pelvic lymphadenectomy (RHL) is the treatment of choice for early-stage cervical cancer. Nowadays, emphasis lies on radical removal of the tumor and surrounding parametrium as well as preservation of the autonomic nerves. The Wertheim-Okabayashi (WO) and the Swift are regularly performed procedures. The WO is characterized by the excision of the deep layers of the vesico-uterine ligaments (VLs), whereas the Swift operation is more radical in removing the sacro-uterine ligaments (SLs). Cervical cancer mainly spreads via local growth and lymphatics. While the autonomic network has been studied extensively, the pelvic lymphatic system is remarkably far less understood. The aim of this study is to reveal the lymphatic pathways of the cervix, related to those of the bladder, rectum and autonomic nerves. We determined whether the possible surgical extensions in parametrectomy during RHL are oncologically and functionally necessary.

Material and Methods: A series of 9 female fetal pelves with an embryonic stage 8, 10, 12, 14, 15, 16, 17, 19 and 20 weeks were studied. Paraffin embedded blocks were sliced in transverse sections of 8 or 10 μm. Analysis was performed by conventional histological staining and immunohistochemical staining with S100, a pan-neuron marker and LYVE-1, a lymphatic endothelial marker. A 3D reconstruction was developed to show the relation between the lymphatics and nerves.
Results: The fetal lymphatic drainage pathways from the pelvic viscera are separated. There are no ventro-dorsal connections between the cervix, bladder and/ or rectum. Three major pathways can be detected: the supra-ureteral and infra-ureteral pathways, running in the cardinal ligaments (CLs) respectively superior and inferior to the ureter, and the dorsal pathways running in the SLs towards the rectal pillars. The VLs contain nerve fibers towards the bladder and external genitalia and lymph vessels draining the bladder. The lymphatics from the bladder and cervix are separated by a continuous thin fascia sheath.
Conclusion: During RHL wide excision of the CLs and radical resection of the SLs is necessary to warrant accurate removal of the cervix-draining lymph vessels. Nerve fibers in the VLs innervating the bladder might be preserved in early-stage cervical cancer. However, this is based on the analysis of fetal specimens and has to be investigated in the adult by microscopic analysis.
No conflict of interest.

3019 POSTER

Thrombocytosis as a poor prognostic factor in ovarian cancer

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Background: Thrombocytosis (TC) is often observed in epithelial ovarian cancer (EOC). A recent study suggested increased production of cytokines in tumour and host tissue which could lead to paraneoplastic TC and hypothesizes that targeting these cytokines might have therapeutic potential. We describe characteristics of EOC patients with and without TC and analyse the significance of thrombocytosis on survival.

Table 1.

	No thrombocytosis (n = 414)	Thrombocytosis (n = 289)	P*
Platelets, median (IQR**)	325 (271–376)	591 (498–702)	0.000
Age, median (IQR)	64 (57–72)	63 (56–71)	0.596
Histology, n (%)			0.004
Serous	263 (63)	215 (74)	
Endometroid	57 (14)	20 (7)	
Other	94 (23)	54 (19)	
Stage, n (%)			0.000
1	95 (23)	23 (8)	
2	50 (12)	17 (6)	
3	207 (50)	188 (65)	
4	54 (13)	58 (20)	
Unknown	8 (2)	3 (1)	
Residual tumour, n (%)			0.000
No	239 (58)	83 (29)	
Yes	152 (36)	181 (62)	
Unknown	23 (6)	25 (9)	
Performance status, n (%)			0.000
0–1	368 (89)	208 (72)	
⩾2	36 (9)	72 (25)	
Unknown	10 (2)	9 (3)	
Chemotherapy, n (%)			0.905
Carboplatin & paclitaxel/docetaxel	350 (84)	249 (86)	
Carboplatin single agent	46 (11)	27 (9)	
Other	11 (3)	8 (3)	
No chemotherapy	7 (2)	5 (2)	
Surgery, n (%)			0.385
Primary	376 (91)	253 (87)	
After neoadj. CT	25 (6)	23 (8)	
No surgery	13 (3)	13 (5)	
CA-125			
median (IQR)	99 (29–356)	367 (133–1300)	0.003
Unknown	25 (6)	22 (8)	0.301

*t-test for continuous variables, Fisher's exact test for categorical variables; **IQR = interquartile range.

Materials and Methods: Women registered in the Danish Gynecologic Cancer Database in 2005–2006 with EOC FIGO stage IC-IV were included. Missing data were collected by review of medical records. Patients were followed until death or January 1, 2012. TC was defined as platelet count $>450\times10^9$/l and was registered prior to 1st course of 1st line chemotherapy (CT). The association of TC with progression-free (PFS) and overall (OS) survival was investigated by multivariate analysis adjusted for histology, stage, residual tumour, performance status, primary vs. secondary surgery, CT regimen, and CA-125.
Results: Overall, 703 patients were included of whom 289 (41%) had TC. Characteristics of patients are shown in Table 1. Median OS was 2.3 years (IQR 1.1–5.1) in TC patients vs. 4.3 years (IQR 1.8–5.8) in patients without TC (log rank: $p < 0.0001$). For PFS, corresponding numbers were 1.0 years (IQR 0.6–2.0) vs. 1.6 years (IQR 0.9–4.5) ($p < 0.0001$). TC was independently associated with shorter OS, HR 1.32 (95% CI 1.05–1.66), but not with PFS, HR 1.14 (0.94–1.38).
Conclusion: TC is associated with reduced OS. The effect of targeted therapy aimed at reducing TC in EOC patients should be studied in a prospective setting.
No conflict of interest.

3020 POSTER

Pharmacokinetics of concomitant cisplatin and paclitaxel administration by hyperthermic intraperitoneal chemotherapy (HIPEC) to patients with peritoneal carcinomatosis

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Background: Intraperitoneal chemotherapy has been advised as a treatment option for epithelial ovarian cancer (EOC) with peritoneal carcinomatosis. Although its treatment length is considerably shorter, intraoperative hyperthermic intraperitoneal perfusion chemotherapy (HIPEC) has a number of benefits over simple intraperitoneal chemotherapy administration. While the pharmacokinetics of cisplatin (CDDP) and paclitaxel (PTX) administered separately during HIPEC have already been studied before, their concentrations in concomitant administration during HIPEC has not previously been measured. The primary aim was to examine the pharmacokinetics of both drugs during HIPEC in patients affected by peritoneal carcinomatosis from advanced epithelial ovarian cancer.
Materials and Methods: Ten women, nine with advanced EOC, underwent cytoreductive surgery (CRS) and HIPEC with CDDP 100 mg/m^2 and PTX 175 mg/m^2) for 90 minutes. Blood, perfusate and tissue samples were harvested during HIPEC for pharmacokinetic study in ten patients. Intra and postoperative morbidity was noted.
Results: No death was noted perioperatively and during the first 30 postoperative days. Severe surgery-related complications (i.e. grade 3–4 CTCAE) were seen in three patients: one patient had intestinal perforation (grade 4) that required reoperation, one had colo-vaginal fistula (grade 3) that required surgical intervention and one had neurogenic urinary bladder obstruction that involved increased levels of plasmatic creatinine (grade 3). Severe chemotherapy related toxicity (i.e. grade 3–4 CTCAE) was observed in seven patients: two with grade 4 and five with grade 3. Renal toxicity was observed in one patient, grade 3. Haematological toxicity was observed in five patients: anaemia (except the first two postoperative days) grade 3 (three patients), thrombocytopenia (one patient grade 3, one grade 4) and leukopenia (two patients grade 3, one grade 4 all treated with administration of G-CSF). The mean maximum concentration of perfusate CDDP and PTX were 26.09 $\pm$8.5 μg/ml and 73.1$\pm$13.5 μg/ml respectively. The mean maximum concentration of plasma CDDP and PTX were 1.92 $\pm$0.4 μg/ml and 0.062$\pm$0.006 μg/ml respectively. Finally, the mean concentration of CDDP and PTX in peritoneal tissue after 90 minutes of HIPEC were 28.70 $\pm$10.8 μg/g and 34.43 $\pm$16.16 μg/g respectively.
Conclusions: HIPEC with concomitant CDDP and PTX delivery following CRS is feasible, fairly safe, and associated with a highly favourable pharmacokinetic profile, despite its short treatment duration. Larger studies with a more homogenous patient cohort and adequate follow-up should be performed to demonstrate its efficacy.
No conflict of interest.

3021 POSTER

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with cisplatin and paclitaxel in advanced ovarian cancer with peritoneal carcinomatosis: Results of a multicenter prospective observational study

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Background: Cytoreductive surgery (CRS) associated to hyperthermic intraperitoneal chemotherapy (HIPEC) have been recently reported with favourable oncological outcomes as treatment of advanced epithelial ovarian cancer (EOC) with peritoneal carcinomatosis (PC). The aim of this study was to demonstrate the feasibility of CRS and HIPEC with cisplatin (CDDP) and paclitaxel (PTX) for the treatment of advanced EOC.
Materials and Methods: This is a multicentre prospective observational study including patients affected by primary or recurrent EOC with PC treated with CRS and HIPEC with CDDP (100 mg/m^2) and PTX (175 mg/m^2). Patients were included between April 2007 and December 2012 at St. Orsola-Malpighi Hospital (Bologna, Italy) and Papa Giovanni XXIII Hospital, (Bergamo, Italy). Peritoneal cancer Index (PCI), Completeness of Cytoreduction (CC) score and perioperative morbidity were noted. The survival results during follow-up were recorded.
Results: 48 patients were included. The mean age was 54.6 years (s.d. ±9.6 range 33−72). 27 patients (56%) had primary EOC and 21 (44%) had recurrent disease. Mean PCI was 10.5 (s.d. ±6.6; range, 0−28). According to the intraoperative tumour extent, the tumour volume was classified as low (PCI <15) or high (PCI ⩾15) in 33 (69%) and 15 (31%) patients respectively. CC0 was achieved in 39 (81.3%) and CC1 in 9 (18.8%) patients. The mean ICU stay was 5.7 days (s.d. ±6.07 range 1−34) and the mean hospital stay was 24.3 days (s.d. ±10.10 range 1−77). No intraoperative death was observed. Reoperation was required in 6 patients (12.5%). Three patients (6.2%) died within 30 days from the procedure. Severe complications (grade 3−4 CTCAE 3.0) were seen in 17 patients (35.4%). During the follow-up period recurrence occurred in 29 patients (60.4%) with a mean recurrence time of 8.9 months (s.d. ±6.3; range 2.2−25.5). The median disease-free survival was 6.3 months and the median overall survival was 11.3 months.
Conclusions: CRS and HIPEC with CDDP and PTX for advanced EOC with PC is feasible with acceptable morbidity and mortality. Additional follow-up and further studies are needed to determine the effects of HIPEC on long term survival.
No conflict of interest.

3022 POSTER

Individualized prediction of overall survival following postoperative radiotherapy in patients with early-stage cervical cancer: A Korean Radiation Oncology Group study (KROG 13−03)

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Background: A nomogram is a predictive statistical model that generates the continuous probability of a clinical event such as death or recurrence. The aim of the study was to construct a nomogram to predict 5-year overall survival following postoperative radiotherapy for stage IB−IIA cervical cancer.
Material and Methods: The clinical data from 1,702 patients with early-stage cervical cancer, treated at ten participating hospitals from 1990 to 2011,were reviewed to develop a prediction nomogram based on the Cox proportional hazards model. Demographic, clinical and pathologic variables were included and analyzed to formulate the nomogram. The discrimination and calibration power of the model was measured using a concordance index (c-index) and calibration curve.
Results: The median follow-up period for surviving patients was 75.6 months and the 5-year overall survival probability was 87.1%. The final model was constructed using the following variables: age, number of positive pelvic lymph nodes, parametrial invasion, and lymphovascular invasion. The nomogram predicted the 5-year overall survival with a c-index of 0.69, which was superior to the predictive power of the International Federation of Gynecology and Obstetrics (FIGO) staging system (c-index of 0.54).
Conclusions: A survival-predicting nomogram that offers an accurate level of prediction and discrimination was developed based on a large multi-center study. The model may be more useful than the FIGO staging system for counseling individual patients regarding prognosis.
No conflict of interest.

Table 1. Multivariate Cox proportional hazards model for overall survival

Variable	Hazard ratio	95% CI	*P*
Age	1.01	1.00–1.03	.048
Number of pelvic lymph nodes	1.22	1.13–1.33	<0.001
Lymphovascular invasion			
No	1.00		
Yes	1.34	0.96–1.86	0.083
Parametrial invasion			
No	1.00		
Yes	1.99	1.45–2.73	<0.001

3023 POSTER

Neo-adjuvant low dose fractionated radiotherapy and chemotherapy in locally advanced carcinoma cervix: Phase II clinical study

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Background: Carcinoma of the uterine cervix is a major public health problem in developing countries in south-east Asia. Majority of the cases are locally advanced (>FIGO stage IIB) with bulky tumors and response to standard chemoradiation is suboptimal due to tumor size and hypoxia. Radiobiologically, chemo-potentiating effect of low dose radiation therapy (LDRT) in the range of 40–100 cGy enhances cell killing by cellular arrest in G2 phase (induced radio-resistance) thus augmenting the effect of cell cycle specific chemotherapy. The aim of this phase II study was to evaluate the safety and efficacy of a neoadjuvant regimen combining two cycles of paclitaxel and carboplatin with LDRT prior to definitive chemoradiation in advanced cervical cancer.
Material and Methods: Patients with squamous cell carcinoma cervix (FIGO stage IIB–IIIB) were included in the study. Patients received two cycles of paclitaxel (175 mg/m^2), carboplatin, (area under the curve of 5), and four 80-cGy fractions of radiotherapy (two each on Days 1 and 2). This sequence was repeated on Days 22 and 23. Clinical and radiological response (MRI) to the neoadjuvant treatment was determined after 3 weeks. All patients underwent subsequent concurrent chemoradiation (50 Gy of external beam radiotherapy with concurrent Cisplatin followed by brachytherapy). The sample size was determined by Simon's two stage design for phase II studies (α= 0.05, power = 0.8) with H_0 ("bad" response probability, 50% according to literature) and H_1 ("good" response probability, 80%).
Results: Total 24 patients (80% IIIB and 20% IIB) were recruited in the study. Mean gross tumor volume (GTV), based on T2 high resolution MRI, before and after neoadjuvant treatment were 92.05 cc and 24.8 cc respectively ($p < 0.0001$, paired t test). Neoadjuvant treatment resulted in significant reduction (>50%) in GTV volume in 75% cases. Clinical complete response was found in 90% patients at 6 weeks. The incidence of grade 3 and 4 neutropenia was 33% and 8% respectively during the entire period of treatment. There was no other grade 3 or 4 acute non-hematological toxicity.
Conclusions: Neo-adjuvant LDRT and chemotherapy prior to definitive chemoradiation is a novel and feasible approach in cervical cancer with a favorable toxicity profile. This treatment paradigm resulted in significant reduction in the GTV, superior response rate and therefore is a good alternative option for bulky, hypoxic cervical tumors.
No conflict of interest.

3024 POSTER

Assessing the quality of life in patients with endometrial cancer treated with adjuvant radiotherapy

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Purpose: The current study evaluates long-term quality of life and sexual function of patients with endometrial cancer who received adjuvant radiotherapy (RT).
Materials and Methods: Hundred and forty-four patients with the diagnosis of endometrial carcinoma, who received adjuvant radiotherapy in our

department between 2000 and 2009, were included in this study. The median age of the patients was 64 years (range, 48−88 years). Quality of life was evaluated by using EORTC QLQ-C30 questionnaire and the CX-24 module. Surgery was total abdominal hysterectomy and bilateral salphingo-oophorectomy (TAH + BSO) in 136 (94%) cases, an additional pelvic + paraaortic lymph node dissection was performed in 120 (83.3%) patients and only pelvic lymph node dissection in 17 (12%) patients. Adjuvant radiotherapy was vaginal brachytherapy (BRT) in 76 (53%) patients, external beam radiation therapy (EBRT) in 52 (36%) patients, and EBRT + vaginal BRT in 16 (11%) patients.
Results: Compared to patients who received vaginal BRT alone, symptom score ($p = 0.01$), lymphedema ($p = 0.03$), pain ($p = 0.02$), and diarrhea ($p = 0.009$) scores were higher and physical functioning ($p = 0.01$), role functioning ($p = 0.03$) and sexual enjoyment ($p = 0.01$) were significantly lower in patients undergoing EBRT. Vaginal BRT when added to EBRT did not worsen the symptom scales and sexual functions. Physical functioning was worse in patients who received systemic chemotherapy ($p = 0.01$). In patients younger than 65 years, body image ($p = 0.02$), sexual activity ($p < 0.001$) and sexual concern ($p < 0.001$) were significantly higher, while fatigue ($p = 0.005$) was significantly higher in patients older than 65 years. Obese patients experienced higher rates of lymphedema ($p = 0.02$), cognitive functioning ($p = 0.03$) and role functioning ($p = 0.02$) scores were significantly higher in patients with normal body weight. With increasing stage of the disease, lymphedema ($p = 0.008$), peripheral neuropathy ($p = 0.02$), fatigue ($p = 0.02$), pain ($p = 0.04$), and diarrhea ($p = 0.009$) were increased. Deterioration in body image ($p = 0.02$), and emotional functioning ($p = 0.004$) were observed when follow-up interval became longer.
Conclusion: EBRT negatively affects quality of life and sexual functions in endometrial cancer patients. Vaginal BRT provides higher quality of life. Body mass index when in normal limits improve the quality of life.
No conflict of interest.

3025 POSTER

The impact of an automatically generated survivorship care plan on patient reported outcomes (ROGY care): Results of a pragmatic cluster randomized controlled trial among endometrial cancer patients

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Background: More patient tailored information for cancer survivors is needed. Evidence on effects of implementing Survivorship Care Plans (SCPs), recommended by the IOM, is limited. Aim of this pragmatic cluster randomized trial is to assess the impact of SCPs in routine clinical practice. Primary endpoint is patient satisfaction with information. Secondary endpoints are QoL and health care use.
Material and Methods: We built an SCP-application in the web-based Registrationsystem Oncological GYnecology (ROGY), used in our area since 2006. By clicking the SCP-icon in ROGY, a personalized SCP is automatically generated. Twelve hospitals were randomized to usual care or SCP care. In usual care, gynecologists did not have access to the SCP-icon. In SCP care, SCPs are personally discussed and handed to patients. All newly diagnosed endometrial cancer patients (age $\geqslant$18) were asked to complete a questionnaire after surgery, 6, 12 and 24 months after diagnosis. The questionnaire included the EORTC INFO25 and asked whether patients actually received an SCP. We expected 150 endometrial cancer patients: 75 per arm. We hypothesized that patients receiving SCP care are more satisfied with the information.
Results: 201 patients (74%) returned a questionnaire after surgery: 109 SCP arm, 92 usual care arm. Of the patients in the SCP arm, 69% reported receiving an SCP. Analyses according to randomization arm showed that patients in both arms reported similar scores on all scales of the INFO25, including satisfaction with care (87% vs. 82%, SCP vs usual care, $p = 0.20$). Analyses according to actual care received showed that patients who received SCP care reported significantly higher scores (4−18 points) on all scales of the INFO25, including satisfaction with care (91% vs. 78%, SCP vs usual care, $p = 0.046$) compared to those who did not receive SCP care.
Conclusions: Even in a situation where SCPs are automatically generated, still one third does not receive an SCP. But, those who receive SCP care report better information provision and satisfaction. Follow-up measures will show whether this ultimately results in better QoL and decreased health care use.
No conflict of interest.

3026 POSTER

Compliance to multimodality cancer therapy in gynaecologic malignancies

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Background: To evaluate treatment compliance and referral delays to multimodality cancer directed therapy in Gynaecologic malignancies at a tertiary care centre in a developing nation.
Material and Methods: A total of 124 patients of gynaecologic cancer were evaluated in our study. All patients were initially seen in multi-disciplinary clinic at our institute. The patients were assessed as per age, site, stage of disease, intent & modality of treatment. Compliance was studied with regard to patients that were able or unable to complete the stipulated cancer directed therapy. Referral delay from surgery to radiotherapy, delay in treatment from surgery to starting of radiotherapy and radiation waiting period were calculated for all patients. Overall treatment time was calculated for all compliant patients.
Results: Median age for presentation was 54 (35−81) years. The most common site was carcinoma cervix (73%), majority (61%) of the patients presented in stage III disease. Eighty eight per cent of the patients were treated with radical intent. Majority (84%) of the patients were subjected to multimodality cancer directed therapy. Median delay in radiotherapy referral after surgery was 35 (−20 to56) days, median radiation waiting period was 43 (9–132) days, median delay from surgery to start of radiation therapy was 74 (62–134) days. Seventy one per cent of the patients were compliant to therapy, for compliant patients median overall treatment time was 128 (21–224) days.
Conclusions: More than two third of the patients were patients compliant to multimodality cancer directed therapy. For compliant patients substantial delays were noted from the start to completion of cancer therapy. All these referral time gaps add to the increased overall treatment time, i.e. 18.2 weeks (128 days) in this study. It has been proven that overall treatment time influence the local control as well as survival. Even after careful evaluation of patients, more than one fourth of the patients could not comply to the stipulated treatment plan. Our study will help for preparing the benchmark for cancer practice in developing nations for gynaecologic malignancies.
No conflict of interest.

3027 POSTER

Use of immunotherapy in complex treatment of patients with dysplasia and preinvasive carcinoma of the cervix

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Background: Standard treatment for dysplasia and preinvasive cervical carcinoma does not always lead to the elimination of the virus, and therefore desire to develop a comprehensive treatment that combines systemic and local effects is justified. The purpose of the study was to evaluate effectiveness of immunomodulatory antiviral drug Oxodihydroacridinilacetat sodium in complex treatment of dysplasia and preinvasive carcinoma of the cervix.
Material and Methods: Study included 20 patients with cervical preinvasive carcinoma and carcinoma in situ underwent cone biopsy in 2012 divided into two groups. First group included 10 patients underwent cone biopsy with application of immunomodulatory antiviral drug Oxodihydroacridinilacetat sodium, second group was control and included 10 patients underwent cone biopsy alone. All patients were performed HPV test before and after treatment. Patients treated with antiviral drug were performed examination of immune status before and after treatment. Patients' monitoring was done with the use of cytology and HPV test.
Results: Mean age in both groups was similar (37.1 vs. 35.2 years). HPV test showed that the predominant one was 16 genotype of HPV, which was found in 7 of 10 patients in group 1, and in 8 of 10 patients in group 2. In three patients it was combined with 18 genotype and in in one case it was combined with 58 genotype. Persistence of HPV-infection after treatment during first two month of monitoring was found in 1 of 10 patients in group 1 and in 3 of 10 patients in group 2. A second course of antiviral drug in patient with persistent HPV in group 1 led to the elimination of the virus. In group 2, in two of three patients with persistent HPV disease there was found a relapse within a few months after treatment. Examination of immune status before and after application of antiviral drug found that the drug has a strong immunomodulatory effects resulting in an increase in the absolute content of CD3+CD19− T-cells by increasing the absolute number of cytotoxic CD3 + CD8 + T-lymphocytes. At that there was marked an expressed local reaction in the remote cone in the form of clusters of lymphocytes. Observed effect of the drug is associated with significant immunostimulatory effect, concluded in strenghtening of effector function of

T-cell immune response. This in turn contributes to the migration of immune cells to the site of inflammation caused by infection and strengthening the capacity of cytotoxic cells to recognize and lyse the abnormal cells.
Conclusions: Monitoring of patients with cervical preinvasive carcinoma and carcinoma in situ after treatment should include HPV test. The observed effect of the drug Oxodihydroacridinilacetat sodium on the immune status and morphology of neoplasms suggests a opportunity to stabilizate neoplastic transformation that takes place under the influence of persistent HPV infection with the immunotherapy.
No conflict of interest.

3028 POSTER

Long-term survival analysis of cervical cancer patients treated with chemoradiation in an outpatient setting

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Background: Chemoradiation (CHRT) with Cisplatin is the standard treatment of locally advanced cervical cancer (LACC) since 1999. In November 2000, the Multidisciplinary Gynecological Oncology Group of our Centre implemented this treatment modality in an outpatient setting. The first 200 consecutive patients (pts) treated in our Institute were then followed prospectively. The main purpose was to analyse the overall survival (OS) and disease free survival (DFS) of our pts and to check if our findings are comparable with clinical trial data. Patterns of treatment failure were also analysed.
Material and Methods: Clinical files were reviewed for staging, toxicities until discharge from our centre and DFS. For OS, if vital status not on clinical records, we either contacted by phone the pts or a first degree relative or checked pts vital status through a National Patient Registry (NPR). Treatment (outpatient setting): cisplatin 40 mg/m^2 (6 weekly cycles), external beam radiation (ERT) 40−50 Gy (in 4−5 weeks) and brachytherapy (BRT) 20−25 Gy (point A, 2 fractions), during 8 weeks (medium). From the initial cohort, 2 patients were excluded, one due to histopathologic diagnosis of small cell carcinoma and the other due to previous hysterectomy. Survival analysis concerns the efficacy reviewed until March/2013.
Results: 198 patients: median age of 50 years (26−79), histopathologic distribution: 178 (89%) squamous cell carcinomas; 12 (6%) adeno-squamous carcinomas; 8 (5%) adenocarcinomas. More than 50% of our patients were staged ⩾ IIB. In march/2013: median follow-up time (intention to treat) of 76.9 months (1.4–145.5), with an overall survival of 67% at 8 years (global mortality rate of 29.8%). Forty nine (49) (24.7%) patients were lost to regular follow-up, but definitive survival data was obtained for 173 pts (26 pts lost to follow up had their vital status included in NPR). Causes of death: from the 149 patients reviewed, 25 had deaths related to cervical cancer, 4 due to causes not related to the disease and 29 died by unknown causes. Treatment failure was observed in 59 (29.8%) patients: 7 by disease progression during CHRT (2 regional only; 3 regional and distant; 2 distant only), 18 by persistence of the disease after CHRT, and 34 by relapse (16 distant and 18 regional). Two (2) pts had distant late relapses with pathology confirmation.
Conclusions: The OS of our cohort is comparable with published clinical trial data. This finding, observed outside of a clinical trial, in an outpatient setting of consecutive pts is remarkable since staging in our cohort had higher proportions of pts IIB and higher. This observation reflects the activity of CHRT in LACC. Risk for treatment failure was greater in the first 36 months, but unexpected late relapses (over 60 months) were observed.
No conflict of interest.

3029 POSTER

Results of a phase I dose escalation trial of hyperthermic intraperitoneal cisplatin after neoadjuvant chemotherapy and complete cytoreductive surgery and followed by maintenance bevacizumab in initially unresectable ovarian cancer

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Background: Hyperthermic intraperitoneal chemotherapy (HIPEC) may improve the outcome for patients (pts) with initially inoperable ovarian cancer who are offered complete cytoreductive surgery (CCRS) after a response to neoadjuvant chemotherapy. The aim of this study was to identify the recommended dose of cisplatin for HIPEC at CCRS after neoadjuvant carboplatin and paclitaxel (CP).
Methods: Pts were treated with 6 cycles of CP followed by CCRS and HIPEC using cisplatin heated for one hour at 42ºC+/−1ºC. Four dose levels of cisplatin were tested: 50, 60, 70 and 80 mg/m^2. Dose limiting toxicities (DLTs) were defined as a grade ⩾ IIIb surgical adverse event according to the Dindo classification, during the 1st post-operative month. Dose escalation used a Continual Reassessment Method using a one-parameter logistic model in a Bayesian framework, with a target percentage of DLT set at 20%. After surgery, maintenance bevacizumab (15 mg/kg) was offered for 22 cycles, every 3 weeks.
Results: From 08/11 to 10/12, 30 patients were recruited in 7 comprehensive cancer centers. Median age was 58 (range 22−66). Median Peritoneal Cancer Index (PCI) at CCRS was 11 (range 1−35). Median hospital stay was 18.5 days (range 10−69 days). No DLT occurred at the first 3 dose levels (N = 4, 4 and 5 pts respectively). At dose level 4 (80 mg/m^2, N = 17), four DLTs occurred: 2 renal failures, 1 peritonitis and 1 hemorrhage. The estimated DLT probability at dose 80 mg/m^2 was 17%, 95% confidence interval, 6−35%. Eight weeks after surgery, creatinine clearance was reduced to <30 ml/min in 3 (10%) pts, and between 30 and 60 ml/min in 6 (20%) pts (table below). Twenty pts received at least 1 course of maintenance bevacizumab and 10 did not (4 due to previous DLT, 2 due to progression and 4 for miscellaneous reasons). Only one pt stopped maintenance therapy due to adverse events (lymphocyst).

Level	Nb pts	Creatinine clearance 8 weeks after the surgery Cockroft formula, ml/min			DLT
		<30	30−59	⩾60	
1: 50 mg/m^2	4	0	2	2	0
2: 60 mg/m^2	4	0	1	3	0
3: 70 mg/m^2	5	0	1	4	0
4: 80 mg/m^2	17	3	2	12	4
Total	30	3	6	21	4

Conclusions: Based on DLT observations, cisplatin 80 mg/m^2 could be recommended by the model. However we recommend a dose of 70 mg/m^2 considering prolonged impairment of the renal function observed at the level 4. Renal toxicity appears as the limiting morbidity of cisplatin-based HIPEC. Longitudinal analysis of creatinine level is on-going. Careful initial selection of patients is required to avoid long-term renal morbidity.
Conflict of interest: *Other substantive relationships: This trial has been supported by Roche but the company had no involvement in the design or interpretation of the trial.*

3030 POSTER

Adjuvant chemotherapy in the management of cervical cancers − a prospective randomized study

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Background: Concurrent Chemoradiation (CTRT) is the standard of care for locally advanced cervical cancers in India. Translation of the benefits

of this strategy in our patient population is sub-optimal, as compared to that of the west. Evidence of the success of chemotherapy in recurrent setting and its theoretical possibilities to tackle micro metastases, made us envisage this study to look at the role of Adjuvant chemotherapy (Adjuvant CT) in addition to Chemoradiation.
Materials and Methods: Between June 2008 and July 2009, 80 patients with squamous cell CA of Cervix, stage IB to IIIB, age <60 years, ECOG 1&2, Hb >10 gm%, normal renal and liver functions, were treated with the standard CTRT (pelvic EBRT 50 Gy/25 fractions & concurrent Cisplatin 40 mg/m^2 weekly) followed by Brachytherapy. They were then randomized to either receive no further treatment or Adjuvant CT with Cisplatin 50 mg/m^2 i.v day 1 & 5FU 600 mg/m^2 i.v day 1, given every 4 weekly for 2 cycles. These patients were then followed up & analyzed to compare the local & distant failures, toxicity profiles, DFS & OS.
Results: Out of 40 patients in each arm, 36 patients of the CTRT arm & 37 of Adjuvant CT arm were analyzable. The median periods of follow up were 34.4 Months and 35.8 months respectively. CR was seen in 69.44% with CTRT versus 72.97% with Adjuvant CT [P = 0.8149]. Number of patients having failures at the end of follow up were 13 (36.11%) in CTRT arm [6 with local failure comprising residual (3) and recurrence (3), 4 with distant failures, and 3 having both] as compared to 10 patients (27.02%) in Adjuvant CT arm [8 local failures, comprising residual (3) and recurrence (5), 2 with distant failures, and 2 having both] [P = 0.4567]. DFS & OS were 63.88% vs.67.56% [P = 0.8079], and 80.55% vs. 83.78% [P = 0.7676] in the CTRT arm & Adjuvant CT arm respectively (none significant). Toxicity profiles had no significant difference in both arms except, Adjuvant CT arm had higher acute grade I [P = 0.3975] & II anemia [P = 0.6741] & higher grade II leucopenia [P = 0.7997]. Higher number of patients (25 vs. 20) [P = 0.3410] with late toxicities (equivalent grades) were seen in the Adjuvant CT arm, which also had an earlier time of onset (5.83 vs.6.53 months).
Conclusions: In a select group of patients with good performance status, normal hemoglobin levels, and renal & liver functions Adjuvant CT following standard CTRT was well tolerated, and shows a trend towards a better disease free and overall survival.
No conflict of interest.

3031 POSTER

Prior chemotherapy improves the immune response to a synthetic long peptide cancer vaccine against HPV16: A phase I toxicity-immunogenicity study in cervical cancer patients

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Background: Therapeutic vaccination of persistent human papilloma virus (HPV) infections and associated diseases including (pre-)cancer requires the induction of robust and consistent T cell responses. This can be obtained by vaccination with a vaccine consisting of 13 synthetic (28−35 amino acid) long peptides (ISA 101®) of the E6 and E7 oncoproteins of HPV16. Such immunogens are more efficiently processed and presented than intact proteins by professional antigen presenting Dendritic Cells (DC). In a preclinical mouse model we have shown marked synergism in eradication of established HPV16 E6/E7+ tumors between platinum-based chemotherapy and HPV16 SLP vaccination.
Material and Methods: In a phase 1 toxicity/immunogenicity clinical study, end stage cervical cancer patients (n==18) were treated with carboplatin and paclitaxel (carbotaxol), after which 12 patients received a single dose of the therapeutic HPV vaccine (300 μg/peptide) in Montanide ISA-51 adjuvant. Six patients served as non-vaccinated controls. Immunophenotyping by 11 parametric flow cytometry was performed on PBMC samples collected prior to, during and after chemotherapy. HPV16-specific and common microbial antigen-specific immune responses were measured in PBMC samples of patients by lymphocyte stimulation test and by cytokine production in the supernatant of these lymphocyte cultures.
Results: Following carbotaxol chemotherapy, the PBMC samples of these patients showed shifts in leukocyte composition associated with improved memory T cell immune responses and increased dendritic cell function. Patients treated with chemotherapy and HPV vaccine (ISA101®), but not non-vaccinated control patients, exhibited robust and sustained HPV16-specific proliferative T responses to a single dose of the vaccine. The observed synergy is in line with data from the preclinical mouse model.
Conclusions: In patients with end-stage HPV16+ cervical cancer, standard chemotherapy with carbotaxol followed by a single dose of HPV-SLP vaccine permits the induction of a robust HPV16-specific T cell response. These findings set the stage for a randomized phase II study of chemo-immunotherapy to compare chemotherapy alone with chemo-immunotherapy in patients with cervical cancer.
Conflict of interest: *Ownership: Cornelis Melief has Stock appreciation rights in ISA pharmaceuticals BV. Corporate-sponsored research: ISA Pharmaceuticals BV has provided the vaccine for this study.*

3032 POSTER

Definitive chemoradiotherapy (CRT) for advanced cervical cancer (CC): Should it be different in elderly?

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Background: CC is third women's malignancy in the world and the second in Brazil. Elderly represents around 10% of these patients (pts), however, Brazilian screening CC program is done up to 65 y.o. In this group, disease is usually diagnosed in advanced stages and most of them receive no treatment or less intensive oncological therapies, due to comorbidities and impaired performance status.
Methods: Retrospective analysis of pts ⩾65 y.o. with CC consecutively admitted at a Brazilian university cancer center from Aug/2008 to Feb/2012. We performed a descriptive analysis of baseline performance status (PS), stage disease (FIGO), histology, body mass index (BMI), treatment received, and overall survival, by Kaplan–Meier method.
Results: 900 medical records were analyzed, 75 pts (8%) fulfilled the inclusion criteria. Median age was 73.4 y.o. (± 5.5 y). Squamous cell carcinoma (SCC) was the most common histology (71 pts, 94.7%). 67 (89.3%) had PS 0 or 1 and 52 pts (69.3%) were eutrophic (BMI 18.5−25 kg/m^2). Regarding of staging, 18 pts (24%) were stage I, 35 pts (46.7%) II, 8 pts (10.7%) III, 12 pts (16%) IVa and 2 pts (2.7%) IVb at initial presentation. 24 pts (32%) underwent surgery (hysterectomy, adnexectomy, pelvic and paraaortic lymphadenectomy). Adjuvant treatment with radiotherapy (RT) was done in 13 patients (total dose of external RT in pelvis ranged from 39.6 to 45 Gy, parametrial boost ranged from 14 to 20 Gy and 4 inserts from 7 to 7.5 Gy of brachytherapy); 8 of them did concomitant platinum-based chemotherapy (CT). 30 pts underwent definitive CRT, 17 pts definitive RT, 1 palliative CT and 3 exclusive best supportive care. In CRT group, 18 pts received cisplatin (CDDP 40 mg/m^2/w/6w) and 12 carboplatin (AUC 2/w/6w). During definitive CRT, treatment was discontinuated in 39% of pts who received CDDP and 25% of pts in carboplatin group due to toxicity. CDDP group presented more nefrotoxicity: 5 pts (28%) had renal failure during treatment, with median decrease of 23% in creatinine clearance, versus 1 pt (8.3%) in carboplatin treatment. Besides, CDDP group presented more radiodermatitis and stroke. Myelosuppression and diarrhea were similar in both groups. In median follow up of 26.1 m, mOS was not reached.
Conclusions: Despite elderly, more than 60% of pts underwent full CRT and age should not be the only factor to guide therapeutic decisions in CC. Carboplatin was better tolerated than CDDP in CRT group, but prospective trials are necessary to evaluate the best option in this population.
No conflict of interest.

3033 POSTER

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for the treatment of advanced epithelial ovarian carcinoma: Upfront therapy, first recurrence or later?

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The strategy of cytoreduction and hyperthermic intraoperative intraperitoneal chemotherapy (CRS + HIPEC) has been proposed as a treatment for advanced epithelial ovarian carcinoma (CEO), although there is currently no data to support what is the best time in the natural history of disease to carry out.
Methods: We analyzed a consecutive series of patients with advanced CEO, collected prospectively in a center with a peritoneal malignant disease treatment program. Patients were treated with CRS + HIPEC in different developmental stages of the disease: the onset, in first or second recurrence or more.
Results: Were included in this study 42 patients with advanced CEO treated with CRS + HIPEC: 15 patients at the onset of the disease, 19 patients in first recurrence and 8 patients in second recurrence or more. The degree of cytoreduction achieved was complete (CC0) in 75% of cases and residual <2.5 mm. (CC1) in 25%. Severe morbidity was 26.2% with a hospital mortality of 3 patients (7%). After a median follow up of 24 months,

the median survival of patients treated at the onset of the disease was 77.8 months, the first recurrence group was 62.8 months and the second recurrence or more group was 35.7 months, the disease free survival was 21.1 months, 18 months and 5.7 months respectively. The overall survival curves in the onset of the disease and first recurrence group did not differ significantly, but instead both groups showed statistical significance compared to the second recurrence or more group ($p < 0.03$).
Conclusion: The strategy of CRS + HIPEC in the treatment of advanced CEO achieves promising results in terms of survival and disease free survival. The optimal timing of implementation of this strategy appears to be at the onset of the disease or in the first recurrence. These results warrant further evaluation in a randomized trial.
No conflict of interest.

3034 POSTER

A nomogram predicting the risks of distant metastasis following postoperative radiotherapy for uterine cervical carcinoma: A Korean radiation oncology group study (KROG 12−08)

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Background: To develop a nomogram predicting the risks of distant metastasis following postoperative adjuvant radiation therapy for early stage cervical cancer.
Material and Methods: We retrospectively reviewed the medical records of 1,069 patients from ten participating institutions. These patients were divided into two cohorts: a training set (n = 748) for construction of the prediction model, and a validation set (n = 321) for external validation. The demographic, clinical, and pathological variables were included in the univariate Cox proportional hazards analysis. Clinically established and statistically significant prognostic variables were utilized to develop a nomogram. A concordance index and Hosmer-Lemeshow test were performed to validate its discrimination and calibration ability.
Results: The model was constructed using four variables: histologic type, pelvic lymph node involvement, depth of stromal invasion, and parametrial invasion. This model demonstrated good calibration and discrimination, with an internally validated concordance index of 0.71 (Hosmer-Lemeshow test, P >0.99) and an externally validated c-index of 0.65 (Hosmer-Lemeshow test, $P = 0.56$). Compared to FIGO staging, which showed a broad range in terms of distant metastasis, the developed nomogram can accurately predict individualized risks based on individual risk factors.
Conclusion: The devised model offers a significantly accurate level of prediction and discrimination. In clinical practice, it could be useful for counselling patients and selecting the patient group who could benefit from more intensive/further chemotherapy.
No conflict of interest.

3035 POSTER

Community based practices for endometrial cancer referred for adjuvant treatment to a tertiary care hospital in northern India − 10 years audit

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Purpose and Objectives: An increasing trend in incidence rates of endometrial cancer (EC) has been reported by cancer registries in India because of changes in lifestyle. The present retrospective study was done to assess the demography and management practices within the community doctors referred for adjuvant treatment to a tertiary care hospital in a northern part of India.
Material and Methods: Between Jan 2000- Dec 2011, 2314 gynaecological cancer patients were registered in the Department of Radiotherapy. Medical records were retrieved for referral patterns, demography, staging work up and surgical practices within the community; adjuvant treatment received and follow-up policies. Disease free survival (DFS) and overall survival (OS) was calculated from time of registration and computed by Kaplan–Meier method. Death due to any cause or loss to follow-up was considered as an event for survival analysis i.e. assuming the worst case scenario.
Results: Seventy one patients had been referred following surgery for an EC. The mean age (range) at presentation was 55.2 (38−80 years). Postmenopausal vaginal bleeding was the most common presenting symptom with mean (range) duration of 12.9 (1−48 months). About half (45%) were referred from community based gynaecologists, a third from other medical centres in the state and 6% by surgical oncologists. Ultrasonography 32(45%) was the preferred prestaging imaging modality with a rising trend for pre-operative MRI (20%) in later years. FIGO stage I−IV was 42%, 16%, 20% and 2% respectively. However 20% of patients could not be staged because of inadequate documentation. Type 1 endometroid carcinoma was (70%) and total abdominal hysterectomy with bilateral salpingo-oophrectomy (90%) was the commonest surgery. Pelvic lymph-node dissection (PLND) was done in one fourth of patients and only 6% had extended lymph-node dissection. The average number of bilateral PLND done was 10%; however only 3% harbored positive nodes.
The EC risk category was 9 (13%)-low risk, 17 (24%)-intermediate risk, 19 (27%)-high risk group and 26 (36%) could not be assigned due to insufficient surgico-pathological details. Adjuvant radiotherapy (in 90%) with or without vaginal brachytherapy was administered while 5 (7%) with stage III and IV also received adjuvant taxane based chemotherapy. Patients were kept on clinical follow up and imaging was done as and when required. Recurrences were documented in 10 patients (all in high risk group) and presented at multiple sites. The median DFS and OS was 14.3 and 17.5 months respectively with 30% alive and disease free and nearly half of the patients were lost to follow-up without disease at time of analysis, all being regarded as 'events'.
Conclusions: In a resource constrained setting, assuring uniformity of treatment and determining patterns of failure in an infrequent disease such as EC is a challenging task given various avenues of service providers and poor compliance to follow-up.
No conflict of interest.

3036 POSTER

The role of adjuvant therapy in uterine sarcomas after definitive surgery

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Purpose: To analyze prognostic factors for survivals and evaluate the impact of postoperative radiotherapy (PORT) on pelvic failure in uterine sarcoma treated with radical surgery.
Patients and Methods: Between 1990 and 2010, 75 patients received radical surgery with (n = 24) or without (n = 54) radiotherapy. Carcinosarcoma (CS) and non-carcinosarcoma (non-CS) patients were 24 and 54, respectively. Prognostic factors such as age, histologic type, stage, menopause, initial hemoglobin, mitotic count, size were defined as prognostic factors for survival. The median follow-up period was 84 months (range, 15–236 months).
Results: 5-year overall (OS) and pelvic failure-free survival (PFFS) of total patients were 71% and 83%, respectively. Loco-regional failure was 25%(n = 6) and distant failure was 17% (n = 4) in carcinosarcoma, whereas loco-regional failure was 6%(n = 3) and distant failure was 24%(n = 13) in non-carcinosarcoma. Histologic type ($p = 0.047$) and stage ($p = 0.006$) were significant predictors of OS in multivariate analysis. However none of the factors analysed were significant predictors of PFFS. PORT significantly reduced pelvic failure in carcinosarcoma (90.9% vs. 46.3%, $p = 0.032$), but not in non-carcinosacorma (88.9% vs. 90.2%, $p = 0.935$).
Conclusion: This study suggests that PORT reduced pelvic failure in carcinosarcoma patients, but not in non-carcinosarcoma uterine sarcoma patients. As failure patterns were mostly distant metastases in non-carcinosarcoma, further attempt with more effective systemic therapy is considered.
No conflict of interest.

3037 POSTER

Impact of "ketofol" sedation on dosimetric parameters in patients undergoing high-dose rate intracavitary radiotherapy

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Background: To relief pain and distress of women undergoing high-dose rate intracavitary radiotherapy (HDR-ICRT), a new intravenous anaesthetic protocol combined propofol and ketamine was developed in collaboration with anaesthesiologist. This new sedation protocol was proved to be safe and provide satisfactory sedation level during HDR-ICRT in our previous study. There is an impression that the application and packing are easy

to carry out. The primary aim is to investigate retrospectively an impact of this sedation on dosimetric parameters in patients with cervical cancers undergoing HDR-ICRT.
Material and Methods: All patients with cervical cancer consecutively treated with 3-channel brachytherapy between December 2008 and May 2012, who received following sedation protocol were evaluated. We administered propofol by using an patient-controlled analgesia (PCA) pump as an initial loading of 10 mg, followed by a maintenance infusion at 2 mg/kg/min, a demand bolus of 20 mg with a limit of four times per an hour, and lockout of 5 min and ketamine in the dose of 1 mg/kg diluted in normal saline 100 ml. As a control, 33 patients, 92 procedures, who received ICRT-HDR before introduction of this protocol were evaluated. We compared the ICRU rectal dose, ICRU bladder dose and the laterality of point A dose between before and after the introduction of this intravenous anaesthesia.
Results: ICRU rectal dose were 80.7±24.4% vs. 66.8±25.4% ($p < 0.00001$) for control vs. sedation group, respectively. There was no significant difference in ICRT bladder dose and the laterality of point A dose 77.4±30.2% vs. 72.6±25.4% and 1.01±0.03 vs. 1.00±0.06 for control vs. sedation group, respectively.
Conclusions: This new sedation protocol reduced ICRU rectal dose during HDR-ICRT.
No conflict of interest.

3038 POSTER

Treatment results of image-guided high-dose-rate interstitial brachytherapy for recurrent uterine cancer

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Background: In order to evaluate the effectiveness of image-guided high-dose-rate interstitial brachytherapy (HDR-ISBT) for recurrent uterine cancer, we analyzed our clinical experience.
Methods and Materials: Between May 2003 and October 2010, 43 patients were treated by HDR-ISBT with or without external beam radiotherapy. The minimum follow-up time for survivor was 24 months (median follow-up: 41 months, range: 24–109 months). Previous treatment before ISBT was radical hysterectomy (Group A) for 27 patients, radical hysterectomy with postoperative radiotherapy (Group B) for 7 patients and radical radiotherapy (Group C) for 9 patients. We implanted the treatment applicator by transrectal ultrasonography. We used template guidance and no-ambulatory implant technique for first 5 patients and free-hand and ambulatory implant technique for latest 38 patients. We also started MRI-assisted CT-based planning for latest 38 patients. Fourteen patients were treated with a combination of HDR-ISBT (median 30 Gy/ 5 fractions; range: 27−36 Gy) and external beam radiotherapy, and the other 29 with HDR-ISBT alone (median 54 Gy/ 9 fractions; range: 42−54 Gy).
Results: The two-year local control and overall survival rates were 81% and 79%, respectively. The 2-year local control rate was 89%, 86% and 56% for Group A, Group B and Group C. Grade 3−4 late complication occurred in 9 patients (21%) with 11 events (3 genitourinary, 7 gastrointestinal and 1 vaginal complications).
Conclusions: Our image-guided HDR-ISBT for recurrent uterine cancer showed promising preliminary results. However, worse local control rate was observed for the tumor recurred after radical radiotherapy.
No conflict of interest.

3039 POSTER

Primary vaginal cancer − the Edinburgh Cancer Centre experience

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Background: Primary vaginal cancer is a rare cancer. The European age standardized incidence rate is 0.6 per 100,000 female populations. We report on patients treated at single institution from January 2000 to Dec 2011 with radical radiotherapy. Our primary objective is to evaluate clinical outcome measured as relapse free survival (RFS) and overall survival (OS) at 2 years. Secondary objective is to assess radiotherapy related chronic morbidity.
Materials and Methods: From January 2000 to December 2011, 34 patients were treated for primary vaginal cancer. Case notes of 33 patients were reviewed retrospectively [1 note untraceable]. 11 patients were excluded [vaginal melanoma − 2, vaginal cancer palliative treatment − 3, VAIN 3−3, upfront chemotherapy − 1, surgical resection only − 1]. The remaining 23 patients were included in the final analysis.
Results: Median follow-up was 34 months [range 4–129 months]. Median age at diagnosis was 65 years [range 43−86].

FIGO Stage	Number of Patients
I	9 (39.1%)
II	4 (17.4%)
III	7 (30.4%)
IV	3 (13.1%)

87% received external beam radiotherapy [EBRT] either alone or in combination with chemotherapy and/or brachytherapy [BT] (n = 20). EBRT dose to pelvis was 45 Gy or 50 Gy (Mean EBRT dose 46.2 Gy). 13% received BT alone following local resection (n = 3). RFS at 2 years was 69.9% and 2 year OS was 74%. Cancer specific 2 year OS was 82.6%. There were 10 cases of relapse. Local relapse was the most common cause of treatment failure (n = 7/10). Of the 7 local relapse, 1 patient relapsed at 18 months which was treated with local excision and she is alive at 129 months. 33.3% of patients with Stage I disease relapsed (n = 3/9) and 50% of patients with > Stage I relapsed (n = 7/14). The estimated relative risk of relapse in > Stage I was 1.501 [95% CI 0.52–4.34]. 60.9% were non-smokers (n = 14), 30.4% were smokers (n = 7), and 8.7% smoking status unknown (n = 2). The estimated relative risk of relapse in smokers was 1.298 [95% CI 0.496–3.052]. Vaginal stenosis was the most common toxicity (n = 10) followed by radiation proctitis (n = 5). Toxicities were predominantly grade 1−2. There was 1 case of grade 4 recto-vaginal fistula.
Conclusion: Local relapse was the commonest cause of treatment failure. Relapse was common in patients with > Stage I disease. Smokers appeared to have a higher risk of relapse. The toxicities were generally low and well tolerated apart from one instance of grade 4 recto-vaginal fistula. Our 2 year RFS and OS was similar to that quoted in literature.
No conflict of interest.

3040 POSTER

Clinical efficiency of brachytherapy with different dose rate for carcinoma of the uterine cervix

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Purpose: Brachytherapy is an integral component of the definitive treatment carcinoma of the uterine cervix. In our Institute we are developing a guideline for clinical practice of low-dose-rate (LDR), middle-dose-rate (MDR) and high-dose rate (HDR) brachytherapy for locally advanced cervical cancer.
Material and Methods: In the present investigation were studied the data about 645 patients with carcinoma of the uterine cervix, who obtained the radiotherapy in Petrov Research Institute of Oncology Ministry of Health, Saint Petersburg. For treating all patient was used the combine (EBRT + Brachytherapy) radiotherapy. Brachytherapy with LDR (0.5 Gy/h) was underwent 221 patients. Adapted three modes for fractionating the summary target dose (STD): the first mode − 20 Gy, once a week, STD=80 Gy (BEDe=86, BEDl=148); the second mode − 20 Gy, once a week, STD=100 Gy (BEDe=107, BEDl=186); the third mode − 20 Gy, once a week, STD=120 Gy (BEDe=129, BEDl=223). Also three modes for fractionating STD were studied with MDR brachytherapy (227 patients) and HDR brachytherapy (197 women): the first mode − 7 Gy, once a week, STD=28 Gy (BEDe=48, BEDl=106); the second mode − 7 Gy, once a week, STD=35 Gy (BEDe=60, BEDl=133); the third mode − 7 Gy, once a week, STD=42 Gy (BEDe=71, BEDl=160).
Results: In all stages five-year overall and local control survival composed 55±2%, ten-year − 46±3%. The overall five-year survival of patients with stage I b − 80±4%, II b − 63±3%, III b − 35±3%, local control survival in the cases stage I b − 80±6%, II b − 64±5%, III b − 35±4%, the differences between the stages are statistically reliable ($p < 0.05$). The total number of acute toxicity among patients treated with MDR brachytherapy substantially ($p < 0.05$) was 10% less in comparison with LDR and HDR, due to the reliable ($p < 0.05$) decrease of a quantity early urinary bladder toxicity (to 6% in comparison with HDR), and rectum toxicity (to 8% − with LDR). The total number of late toxicity among patients treated with HDR brachytherapy substantially ($p < 0.05$) was 5% more in comparison with MDR and 8% more in comparison with LDR, due to a reliable ($p < 0.05$) increase in the quantity of early urinary bladder toxicity (to 5% in comparison with LDR).
Conclusion: Substantial changes in the length of life of patients depending on the brachytherapy with different dose rate we did not found. Quantity early and late toxicity depend from different dose rate brachytherapy for combine radiotherapy carcinoma of the uterine cervix.
No conflict of interest.

3041 POSTER

Outcome of the cervix uteri cancer patients treated with or without concurrent chemotherapy and radiotherapy incorporating high dose rate brachytherapy: An experience from Saudi Arabia

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Background: Concurrent Chemo-Radiotherapy (CRT) plus Brachytherapy (BT) have become the standard treatment modalities for cervix uteri cancer stage IB2-IVA.
Aim of the study: This is a retrospective study evaluating the demographic data, survival outcome, pattern of failure and prognostic factors of cervix uteri cancer patient treated with concurrent chemo-radiotherapy incorporating high dose rate brachytherapy at single instituation in Saudi Arabia.
Materials and Methods: A review of 60 cervix uteri cancer patients with stages IB- IVA; treated with radiotherapy with and without concurrent cisplatin plus high dose rate (HDR) brachytherapy; between January 2004 and December 2010. The overall survival (OS) and disease free survival (DFS) were analyzed using Kaplan–Meier methods. Univariate and multivariate analysis were used to detect the significant prognostic factors.
Results: Most of patients (50 patients; 83 %) had Squamous cell carcinoma. Stage IIB was the most common presentation (41 patients; 68 %). All patients completed the planned external beam radiotherapy (EBRT) and the brachytherapy (BT) treatment course. Forty Seven patients (78%) received Cisplatin concurrent with EBRT. The median follow up period was 24 Months (range, 6 −77 Months). The 2 and 4 years overall survival was 82%, and 79 % respectively, prolongation of the overall treatment time more than 56 days and the pretreatment hemoglobin (Hb) level ($\leqslant$10 g/dL) negatively predict the overall survival in the univariate and multivariate analysis ($p = 0.039$ and $p = 0.008$ respectively). The 2 and 4 years DFS were 80% and 69% respectively, with vaginal extension was the only significant factor determining the relapse ($p = 0.048$). The 2 and 4 years loco-regional and distant metastasis free survival were 78 % & 70 % and 82% &79 % respectively. Vaginal extension was the only negative predictor factor for the loco regional control ($p = 0.045$), while the grade was the only factor for the distant metastases free survival ($p = 0.037$). Grade 3 or 4 late rectal reaction was reported in 2 patients (3 %), severe vaginal adhesion in one patient (1.5%), while no patients developed grade 3 or 4 urinary reaction.
Conclusion: Concurrent chemo-radiotherapy is an effective treatment modality for cervix uteri cancer patients. The overall treatment time and pretreatment Hb level were the most important predictor factors for survival, while vaginal extension and grade of the tumor were negative predictor factors for loco-regional and distant metastases free survival respectively.
No conflict of interest.

3042 POSTER

Dosimetry study on use of image guidance for radical vaginal vault brachytherapy

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Background: The aim of this study is to model the doses to the organs at risk (OARs) using CT planning for radical treatment using vaginal vault brachtherapy (VBT).
Material and Methods: Patients had a planning CT scan with the vaginal cylinder in situ. The cylinder diameter was based on clinical examination of the patient using commercially available solid cylinders. The OARs were outlined. The total EQD2 doses to the OARs were modeled using an α/β ratio = 3 Gy, an EBRT component of 45 Gy in 25 fractions and 21 Gy in3 fractions of HDR VBT using a line source and prescribed at 0.5 cm depth from cylinder surface to the cranial 4 cm of the vagina. The 0.1cc, 1cc and 2cc doses for the bladder, rectum, sigmoid and small bowel were calculated and correlations with cylinder diameter, vaginal length and the angle of cylinder relative to the couch top were assessed using the Pearson's correlation coefficient with 2-tailed significance testing.
Results: 95 consecutive patients were scanned, median vaginal length = 11 cm (7−16 cm); median angle of cylinder relative to couch top was −2.9º (4.8º − −20.8º). The cylinder diameter only showed a correlation with d0.1cc bladder ($r = -0.205$; $p = 0.046$). The sigmoid d0.1cc, d1.0cc and d2.0cc correlated with vaginal length $r = 0.251$ ($p = 0.015$), 0.28 ($p = 0.006$) and −0.349 ($p = 0.001$) respectively. The small bowel d0.1cc, d1.0cc and d2.0cc correlated with vaginal length $r = -0.263$ ($p = 0.01$), −0.264 ($p = 0.01$) and −0.252 ($p = 0.01$) and with angle relative to couch top $r = 0.202$ ($p = 0.01$), 0.219 ($p = 0.035$) and 0.222 (0.032).

	Bladder	Rectum	Sigmoid	Small bowel
D 0.1cc (Gy), Median (range)	7.4 (5.2−11.2)	7.6 (4.5−9.9)	5.7 (1.5−9.2)	5.1 (0.3−9.6)
D 1.0cc (Gy), Median (range)	6.6 (4.6−9.1)	6.5 (4.0−8.3)	4.7 (1.3−7.1)	4.1 (0.3−7.9)
D 2.0cc (Gy), Median (range)	6.2 (4.3−8.7)	5.9 (3.6−9.0)	4.1 (1.2−6.6)	3.7 (0.3−7.4)
EQD2 D 2.0cc (Gy) (EBRT + VBT), Median (range)	77.9 (43.3−103.8)	74.4 (57.3−108.6)	60.1 (43.3−81.5)	56.4 (43.3−89.3)
No. exceeding target tolerance dose	(target $\leqslant$90 Gy) 4 (4.2%)	(target $\leqslant$70 Gy) 67 (70.5%)	(target $\leqslant$70 Gy) 16 (16.8%)	(target $\leqslant$70 Gy) 22 (23.3%)

Conclusion: When combining radical EBRT and VBT ($\geqslant$21 Gy in 3 fractions) image guidance can reduce the significant risk of exceeding the OAR's target tolerance doses. These cases cannot be predicted based on cylinder diameter. Potentially high doses can be delivered to the OARs especially the rectum which could result in significant late toxicity.
No conflict of interest.

3043 POSTER

Quantification of air gaps using CT in vaginal vault brachytherapy

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Background: Vaginal vault brachytherapy is an effective adjuvant treatment but the presence of air gaps could impact efficacy especially due to the steep dose fall off.
Material and Methods: Patients receiving adjuvant vaginal vault brachytherapy get a planning CT scan with vaginal cylinder in situ prior to the first brachytherapy fraction. The vaginal cylinder diameter is chosen based on the clinical examination and confirmed using a perspex dummy vaginal cylinder developed in our institution which also accurately measures vaginal length. Patients are treated using solid vaginal vault cylinders with a fixed range of diameters (2.0, 2.6, 3.0 and 3.5 cm) available commercially. The CT scans were analysed using Brachyvision® to identify the presence of air gaps and measure the volume, position relative to the vaginal vault and the angle of cylinder relative to the couch top. Correlations were assessed using the Pearson correlation coefficient with 2-tailed significance testing.
Results: 101 consecutive patients were scanned, 66 patients had an air gap identified along the length of the vaginal cylinder but only in 30 cases (29.7%) were these within the cranial 4 cm constituting the treatment volume. The median volume of the gaps within the treatment length was 0.315 cm^3 (0.01–4.84 cm^3) and made up a median of 1.27% of the treatment volume (0.03–20.64%). No correlation was identified between the air gap volume and the vaginal length or the angle of cylinder relative to the couch top. There was a negative correlation between the air gap volume and the cylinder diameter (Pearson coefficient = −0.426; $p = 0.019$).
Conclusion: The practice to choose the vaginal cylinder diameter based on the clinical assessment and inserting the largest diameter cylinder that can be accommodated in the vagina helps to keep air gaps within the treatment volume to a minimum and the dosimetric impact is deemed to be not significant.
No conflict of interest.

3044 POSTER

Uncertainties of organs at risk delineation in MRI guided adaptive cervix cancer brachytherapy: A multi-institutional study

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Background: Contouring uncertainties can undermine the overall gain of high-precision radiotherapy techniques. We aimed to quantify uncertainties of organs at risk contouring in cervix cancer MR image-guided adaptive brachytherapy (IGABT).
Materials and Methods: 10 radiation oncologists from 10 centres participating in EMBRACE study (intErnational study on MRI-guided BRachytherapy in locally advanced CErvical cancer; www.embracestudy.dk) contoured bladder (B), rectum (R) and sigmoid colon (S) in 6 patients treated with IGABT. Contours were compared with expert consensus (EC) delineations qualitatively and by calculating conformity index (CI), absolute inter-delineation distances (IDD), and deviations of B top, urethro-vesical junction and RS junction position.
Results: Uncertainties were most prominent at transition of S to posterior pelvic location and RS junction. In 2 (3.3%) B and 2 (3.3%) R contours, bowel and muscles were included, respectively. For S, inclusion of Douglas pouch, bowel, parametria and HR CTV was found in 1 (2%), 3 (5%), 6 (10%) and 1 (2%) delineation. CI for B, R and S was 0.80 (SD 0.07), 0.70 (SD 0.10) and 0.49 (SD 0.16). B top, urethro-vesical junction and RS junction were at 1 (SD 4), 2 (SD 5) and 9 (SD 14) mm from the EC delineation. Higher absolute IDDs were obtained for S (13±4 mm) when compared to B (3±0.5 mm) and R (3±0.5 mm) ($p < 0.001$). Dosimetric consequences of these uncertainties were reported recently [Hellebust, Radiother Oncol 2013].
Conclusions: Variation was more prominent for sigmoid colon when compared to bladder and rectum. Respecting delineation guidelines is needed to minimize uncertainties and their dosimetric impact.
No conflict of interest.

3045 POSTER

A study to evaluate the association between dose volume parameters and vaginal toxicity in patients of cervical cancer undergoing image based brachytherapy in a protocol setting

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Background: Although dose volume parameters have been recommended for the bladder, rectum and sigmoid, the parameters for vagina have not been recommended primarily because of high uncertainties that exist in dose reporting. Data from a single institution have reported no correlation with the vaginal side effects. The aim of the study was evaluate the association between the dose volume parameters and vaginal toxicity in patients with cervical cancer treated with image guided brachytherapy at our institute.
Material and Methods: Thirty-five patients treated with image guided brachytherapy for cervical cancer were included in the study. All patients received external pelvic radiotherapy and dose of 46 Gy over four and a half weeks was delivered along with concurrent weekly cisplatin followed by high dose rate brachytherapy 7 Gy in four fractions. The contouring was done on MRI and DVH parameters were reported in accordance with the GEC-ESTRO guidelines. The vaginal wall was contoured on MRI as well as the CT done in subsequent brachytherapy fractions. The D1cc, D2cc, D5cc and D 10cc were calculated. This was correlated to the vaginal toxicity (assessed by CTCAE version 3) at one year of completion of treatment.
Results: The mean vaginal volume was 27.9±5.9cc.The mean 1cc, 2cc,5cc and 10cc physical doses to the vagina for each brachytherapy fraction were 14.16± 1.2 Gy, 10.84±1.67 Gy, 6.71± 0.98 Gy and 4.21±0.64 Gy respectively. The mean 1cc,2cc, 5cc and 10cc iso-effective doses for vagina were 164.15±24.46 Gy, 123.89±11.05 Gy, 83.65±4.21 Gy and 65.26±2.23 Gy respectively. Vaginal shortness was observed in 22/35 patients (62.8%); Grade −1 in 12/35 patients (34.2%), grade-2 in 9/35 (25.7%) and grade- 3 in only one patient (2.8%). Grade-1 vaginal dryness was observed in 9/35 patients (25.7%), none of the patients had grade2−3 vaginal dryness. Ten patients (28.5%) had contact bleeding. No association could be demonstrated between the dose volume parameters and vaginal toxicity in the present study.
Conclusions: The lack of association between dose volume parameters of vagina with vaginal morbidity may be due to uncertainties involved in the delineation of vaginal wall and dosimetry. A longer follow up could result in more patients with vaginal morbidity. Future research in a larger patient cohort is required to study the clinical effect of dosimetric parameters on the vaginal morbidity.
No conflict of interest.

3046 POSTER

Adjuvant treatment of vulvar cancer with IMRT

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Background: There are very few studies regarding IMRT (Intensity Modulated Radiation Therapy) and the treatment of vulvar cancer. Therefore, we will present our experience on IMRT treatment in adjuvant vulvar cancers, at our Department.
Material and Methods: Retrospective analysis of vulvar cancer treated with surgery and adjuvant IMRT between January 2009 and February 2012. All pacients were treated with IMRT (sliding window), in a Clinac 2100CD (linear accelarator), with photon energy 6MV. For dosimetry, the inversed planning system was used. It was evaluated the PTV (Planning Target Volume) coverage, the dose's homogeneity distribution and the dose tolerance of the organs at risk (rectum (D40), bladder (D40), bowel (D35) and bone marrow (V20)).
The acute toxicity (gastrointestinal, genitourinary, hematologic and skin) was evaluated according to the RTOG (Radiation Therapy Organization Group) criteria.
Results: Thirty women, with a median of age of 75 years old, were treated with adjuvant IMRT. All patients completed treatment in its entirety. The mean dose delivered was 62.32 Gy (50−66 Gy). The mean volume that received less than 95% of the dose on the PTV was 2.12% and only one patient received more than 107% on PTV prescribed dose. The average dose received by the organs at risk were: bladder (31.51 Gy), rectum (33.04 Gy), bowel (23.85 Gy) and bone marrow (22.27 Gy).
The average D40 in rectum was 28.4 Gy, D40 in bladder was 26.09 Gy, D35 in bowel was 26.4 Gy and bone marrow V20 was 48.59 Gy. Nine patients developed grade 3 skin toxicity but this did not lead to treatment interruption. No patients had grade 3 gastrointestinal, genitourinary and hematologic toxicity. Out of the thirty patients, 14 (50%) died, and 14 (50%) were alive at the time of the present analysis. Nine (30%) had loco-regional relapse, and 1 (3.3%) had distant metastasis.
Conclusion: IMRT seems to be a promising treatment in vulvar cancer. IMRT planning has a proper PTV coverage with considerable sparing of organs at risk and is well tolerated by patients. We also achieve with IMRT a low loco-regional relapse, as mentioned in the literature.
No conflict of interest.

3047 POSTER

Nomogram for prediction of outcome for patients with endometrium cancer: a pooled analysis of PORTEC-1 and PORTEC-2 trials

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Background: Postoperative radiotherapy for endometrial cancer improves locoregional control without a survival benefit. To allow treatment decision support for individual patients and generation of new evidences and hypotheses, accurate statistical models to predict locoregional relapse (LR), distant relapse (DR), overall survival (OS) and disease-free survival (DFS) are required.
Methods: Clinical trial data from the PORTEC-1 (N = 714) and PORTEC-2 (N = 427) trials and of the registration group with grade 3 and deep invasion (N = 99) were pooled for this analysis (total N = 1240). Data from pathology review were used if available; otherwise original pathology was used. The common clinical trial variables which were clinically relevant and eligible according to data constraints were: age, stage at randomization, given treatment (external beam radiotherapy (EBRT), vaginal brachytherapy (VBT) or no adjuvant treatment), FIGO histological grade, depth of invasion, width of the uninvolved myometrium, minimal distance of tumor to serosal surface, involvement in cornuae and vascular invasion. The multivariate analyses were based on the cox proportional hazards regression model.

Variables were ranked according to their predictive power by using a bootstrap scheme (N = 1000). Performance of the models was expressed by the c-index, which has similar properties as the area under the ROC curve (0.5, random prediction and 1, perfect prediction). Validation performance was tested with a 10-fold cross-validation scheme to avoid overfitting.
Results: The accuracy of the developed models was good with training accuracies between 0.68 and 0.79. The validation performances were consistent for all outcomes, between 0.67 and 0.76. Ranking of the variables to their predictive power showed that age, tumor grade and vascular invasion were highly predictive for all outcomes, and given treatment for locoregional relapse. Nomograms were developed for locoregional relapse, distant relapse, disease-free and overall survival and will be presented.
Conclusion: The provided models are internally validated and are able to accurately predict long-term outcome for endometrium cancer patients after surgery and optionally no extra treatment, EBRT or VBT. These models should allow decision support in daily clinical practice, i.e. patient counseling and shared decision making, selection of patients who may benefit most from adjuvant treatments, and generation of new hypotheses.
No conflict of interest.

3048 POSTER

CyberKnife® fractionated stereotactic radiotherapy for loco-regionally recurrent uterine cervical carcinoma

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Background: Currently there is no standard treatment option for recurrent uterine cervical carcinoma. Surgery, in high selected cases, and of radiation and chemotherapy, or the combination of different modalities can be chosen according to the patient specific characteristics. There is not high-level evidence for the usage of Stereotactic Fractionated Radiotherapy (FSRT). We aim to challenge the role of CyberKnife® FSRT for loco-regionally recurrent uterine cervical carcinoma, especially for those who are not convenient for intra-cavitary brachytherapy because of the localisation of the tumour.
Material and Methods: We retrospectively evaluate the cases that underwent CyberKnife® FSRT for loco-regionally recurrent uterine cervical carcinoma.
Results: Six patients with a median age of 54 (range, 48−67) underwent CyberKnife® FSRT between July 2010 and July 2012. Primary tumour FIGO stage was I−II in all cases. Median time for the recurrence after primary treatment was 30 months (range,16–282). Primary therapy at the time of initial diagnosis was surgery (n = 3) and chemo-radiotherapy (n = 3). Histology of tumours was adenocarcinoma (n = 3), squamous-cell carcinoma (n = 2) and clear cell carcinoma (n = 1). Pelvic radiotherapy (RT) (45 Gy) was applied for the patients who had not receive RT as primary treatment at the time of initial diagnosis (n = 3). All patients underwent CyberKnife® FSRT with fiducial tracking. No complication was observed after fiducial placement. CyberKnife® treatments had given with a median number of 75 nodes (range, 59−86) and 236 beams (range, 115–365). Prescription dose and PTV characteristics of each patient are summarised in Table 1. Median value for the PTV dose maximum and minimum was 112% and 94% of the prescribed dose, respectively. Bladder and rectum maximum doses were kept below 38 Gy in all cases with a median value of 26.7 Gy (8.3–33.2) and 25.7 Gy (21.3–33.8) respectively. No acute toxicity was observed in any of the patients but one who had severe sub-ileus after treatment and died in 3 months. One patient died 1 month after treatment because of comorbidities. Partial tumour regression (n = 2) and progression (n = 2) was detected at 5 month follow-up. One patient with partial tumour regression died at 9th month because of distant disease progression. Two patients with local tumour progression died at 5th and 11th months. Median survival of the patients was 6 months (range, 1−11).

Table 1. Prescription dose and PTV characteristics.

Patient ID	D*pres*. (Gy)	Pres. Isodose (%)	n*F*	PTV *V (cc)*	PTV CI	PTV nCI	PTV HI	PTV coverage(%)
1	25	93	5	89.8	1.1	1.2	1.0	95
2	30	85	6	110.7	1.4	1.4	1.1	99
3	25	92	5	37.9	1.6	1.7	1.0	99
4	25	84	5	126.4	2.0	2.0	1.1	99
5	20	86	5	20.0	1.8	1.8	1.1	99
6	20	85	5	89.8	1.5	1.5	1.1	100

D*pres*, prescription dose; n*F*, number of fractions; V, volume; CI, conformity index; nCI, new conformity index; HI, homogeneity index.

Conclusions: Our series with a limited number of the cases does not show an effective tumour control or survival improvement with FSRT for loco-regionally recurrent uterine cervical carcinoma.
No conflict of interest.

3049 POSTER

Effect of varying bladder volumes with and without a bladder catheter on dosimetry in high dose rate vaginal vault brachytherapy for endometrial cancer

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Background: Vaginal vault brachytherapy (VBT) is used in the adjuvant treatment of endometrial cancer. It is used alone or after external beam radiotherapy (EBRT). Severe late bowel and bladder toxicity have been reported in 5% of patients, particularly when VBT is added to EBRT. Bladder volumes may affect the dose to organs at risk (OAR). This study looks at the impact of bladder fullness on OAR dosimetry in the presence or absence of a bladder catheter.
Material and Methods: 3D CT plans were reviewed for 28 patients randomly selected from a group of 115 patients treated with high dose rate VBT at our centre. All patients were treated with a single source vaginal cylinder applicator. 5 patients had empty bladders following catheter insertion and received VBT alone. The remaining 23 patients were not catheterised, but were asked to empty their bladder before applicator insertion. 11 patients received VBT alone (22 Gy/4f) and 12 in combination with EBRT (8 Gy/2f). Dose was prescribed to 5 mm from the applicator surface. The rectum, bladder, sigmoid and small bowel were contoured by a radiation oncologist and checked by an expert radiologist. D2cc per gray was measured for each OAR taking into account the different fraction size. Independent samples t tests and Pearson correlation were analysed.
Results: The median bladder volume was 57 cm^3 (44−67) and 67 cm^3 (38–308) with and without a catheter respectively. The bladder volume was significantly smaller when a catheter was used (p = 0.01), although 40% of patients without a catheter had a small bladder (<57 cm^3). Table 1 summarises Pearson correlation between bladder volumes and D2cc per gray for each OAR. There was a significant negative correlation between bladder volume and dose to small bowel (r= −0.45, p = 0.02).

	Bladder	Rectum	Sigmoid	Small bowel
Pearson correlation, r	0.31 p = 0.11	0.22 p = 0.25	−0.27 p = 0.16	−0.45 p = 0.02

Total EQD2 doses were calculated for the 12 patients who received combination EBRT and VBT. Rectum, sigmoid and small bowel received an additional median EQD2 dose of 7.3 Gy (5.3−9.9), 2.4 Gy (1.1−5.2) and 4.7 Gy (0−8.2) respectively.
Conclusions: Routine practice in many centres is to minimise bladder volumes, by using a catheter or emptying bladder before treatment. Our data shows no advantage in having a smaller bladder with respect to dosimetry to bladder, rectum and sigmoid. We confirm previous findings that some bladder filling reduces small bowel dose. This is particularly important in those patients also having EBRT. Further work is being done using a fluid intake protocol in order to achieve bladder filling without the complications of a catheter.
No conflict of interest.

3050 POSTER

Dose escalation with intensity modulated radiotherapy in the treatment of locally advanced cervical cancer

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Background: The standard treatment of locally advanced cervical cancer is concurrent chemoradiation. Radiotherapy with newer treatment technologies such as intensity modulated radiotherapy (IMRT) seems to be effective with minimized toxicity.
Material and Methods: Patients who were diagnosed with locally advanced cervical cancer between 7/2009−8/2012 and treated with IMRT

+ concurrent weekly cisplatin with a minimum follow up of 6 months were included in this retrospective analysis. All patients had a CT based treatment planning with proper immobilization prior to treatment. PET-CT and MRI fusion was performed with the planning CT images. The GTV is defined as all known gross disease determined from radiographic studies, clinical information, physical examination and biopsy results and GTVln was determined to be metastatic lymph nodes seen in the PET-CT. CTV1 consisted GTV + cervix and uterus, CTV 2 consisted of parametria and superior third of the vagina, CTV3 included the common, external and internal iliac and presacral lymph nodes. Around CTV1, a 15 mm; around CTV2 a 10 mm; around and CTV3 a 7 mm uniform expansion was used for PTV1, PTV2 and PTV3. For PTVln 7 mm uniform expansion was used around GTVln. A total of 45 Gy in 25 fractions was given to PTV1+PTV2+PTV3 and 62.5 Gy to PTVln using simultaneous integrated boost (SIB) technique. Image guidance was performed daily with electronic portal kV and weekly with cone beam CT. All patients were evaluated for 3D conformal inracavitary brachytherapy. Treatment response was evaluated with physical examination and PET-CT 3 months after the conclusion of the treament.
Results: A total of 49 patients were included. Median age was 55 and 80% were stage IIB. Forty seven percent of the patients had pelvic and 10% had paraaortic metastases according to the PET-CT. All of the patients who had lymph node metastases received escalated dose with SIB except 3 patients who had dissection. The majority of the patients concluded planned chemotherapy and intracavitary brachytherapy. Forty seven patients had a PET-CT for response evaluation and there were 76% complete and 11% partial metabolic response. Progressive disease was seen in 6 patients (13%) and only 1 of them was within the irradiated area. With a median follow up of 19 months (6−41 months) estimated 2 year local, regional and distant control rates were 93%, 80% and 78%. Among the 22 patients who were treated with SIB, 2 of them received in field recurrence. Two year overall survival rate was 89%. None of the patients experienced $\geqslant$ grade 3 toxicity.
Conclusion: Concurrent chemoradiation with IMRT and dose escalation can be performed efficaciously in locally advanced cervical cancer.
No conflict of interest.

3051 POSTER

Rectum and bladder dose calculation from external beam radiotherapy (EBRT) and high dose rate brachytherapy (HDR-BT) in cervix uteri cancer patients: From 2D dose calculations to 3D dose optimization to clinical results − A single institution experience

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Background: Estimation of the rectum and bladder dose in cervix uteri cancer patients treated with radiotherapy including (HDR-BT) is a crucial step in the treatment planning evaluation and its sequences results.
Material and Methods: Include 2 series: (1) Ten applications of HDR-BT, in which comparison between orthogonal and computed tomography (CT) based planning was done. In orthogonal planning: Dose to point A, rectum and bladder were defined according to ICRU 38 recommendations, while in CT-based planning: DVH was done for rectum and bladder. (2) Include 60 patients with stage II−IVA treated with chemo-radiotherapy (45 Gy/25F of EBRT, weekly Cisplatin) plus HDR-BT (6−7 Gy X3−4 Fractions). Point A, rectal and bladder point dose were determined according to ICRU 38 and used initially for orthogonal film calculation. GEC-ESTRO recommendations were used later for CT planning and 3D optimization. Mean (M), maximum (Max) dose and dose volume histogram (DVH) were generated form the EBRT and BT and correlated with the reported toxicities.
Results: (1) The M dose at ICRU rectum point is 3.4 Gy$\pm$1.2 and 21% of the rectum volume from CT was encompassed by 3.4 Gy isodose line,. while M dose to the ICRU bladder point is 2.9 Gy $\pm$1.2 and 17% of the bladder volume derived from CT was encompassed by 2.9 Gy isodose line. The Max dose to rectum and bladder derived from the CT was 1.7 and 2.8 times higher than the dose to ICRU reference points ($p = 0.053$ and $p = 0.005$).
(2) The Max dose reported to the rectum from EBRT and BT was ranged between 49.1–65.2 Gy, with M value of 56.2 Gy$\pm$4. The average of the maximal dose to the rectum from EBRT was 45.8 Gy$\pm$ 1.8 (41.2–51.6 Gy) and from BT was 10.4 Gy $\pm$3.9 (2.5–20.7 Gy). The Max dose to the bladder from EBRT and BT was ranged between 45.4–68.1 Gy with M value of 57.7 Gy $\pm$4. The average of the Max bladder dose from EBRT was 45.2 Gy $\pm$2.2 (40−51 Gy) and BT 12 Gy$\pm$3.7 (5.8–20.9 Gy). Converting these physical dose to biologically effective dose using linear quadratic model, the iso effective total dose (EBRT+BT) EQD2; was 67.4 Gy as a Max dose to the rectum and 73.1 Gy as a Max dose to the bladder. The majority of patients (80−85%) reported grade 1 or 2 acute reactions of the rectum or bladder, however all patients completed their planned course of treatment. Grade 1&2 late rectal and bladder reactions were reported in 4 patients (7%) and 3 patients (5%) respectively.Grade3&4 late rectal reactions were occurred in 2 patients, one patient developed grade 3 proctitis, and the other one developed recto-vaginal fistula (grade 4). None of the patients developed grade 3or4 bladder reactions.
Conclusion: Using our dose and regimen of EBRT and BT with current treatment planning protocol, yield acceptable reported toxicity for the rectum and bladder.3D planning optimization is an emerging methods and should be applied for EBRT and BT whenever possible.
No conflict of interest.

3052 POSTER

Interfraction dose variance in relationship to vaginal cylinder insertion geometry and organ at risk filling for HDR brachytherapy

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Background: In HDR vaginal cylinder brachytherapy, an individualized treatment plan is generated on an initial planning CT and then used for subsequent fractions regardless of changes in interfraction anatomy and cylinder insertion angle. In this study, we analyzed the variance in bladder and rectal doses by comparing the planned dose (PD) to the delivered dose (DD) per fraction in relationship to the cylinder insertion angle, bladder and rectal volume, and cylinder treatment length.
Materials and Methods: We analyzed vaginal cylinder applications from 27 consecutive patients treated postoperatively with external pelvic irradiation and vaginal brachytherapy (VBT) in 2012. VBT consisted of three treatments of 5 Gy prescribed to a 5 mm depth. For each patient, a planning CT simulation scan was performed with a cylinder in place and was used in the generation of a treatment plan. A repeat scan was performed prior to each of the three treatments. The bladder and rectum were outlined on all CT-image sets and reviewed by two physicians. The initial plan parameters were applied to the treatment scans and DVHs were generated for the bladder and rectum. From these DVHs, the dose to 2cc of the bladder and rectum were recorded. From each treatment scan, the x angle (in relationship to the midplane) and y angle (in relationship to the table) of cylinder insertion were determined and recorded. Bladder and rectal volumes were also recorded.
Results: The mean doses and cylinder insertion angles are shown. The DD to the bladder was greater than the PD ($p = 0.01$ by paired t-test), whereas the DD to the rectum was comparable to the PD. On average during planning scans, the proximal portion of the cylinder was inserted and angled to the left (+x) and posteriorly (+y), and this was similar during treatment scans. Multiple regression analysis revealed the y insertion angle ($p = 0.018$) and the cylinder treatment length ($p = 0.014$) to be significant predictors of rectal D2cc. There were no significant predictors for bladder dose.

Table: Mean dose ratios and insertion angles

	Bladder		**Rectum**	
	PD (Gy)	DD	PD (Gy)	DD
D2cc	4.40$\pm$0.57	4.61$\pm$0.67	4.75$\pm$0.42	4.66$\pm$0.48
	X Angle		**Y Angle**	
	Plan (^{o})	Actual	Plan (^{o})	Actual
	2.9$\pm$3.7	2.7$\pm$4.4	11.1$\pm$4.6	10.7$\pm$5.3

Conclusions: Interfractional changes in patient anatomy and positioning in combination with differences in cylinder insertion geometry resulted in varying bladder dose but not rectal dose. While a neutral insertion angle has traditionally been used for vaginal brachytherapy, our data suggests that angling the vaginal cylinder anteriorly may reduce rectal dose without significantly increasing bladder dose.
No conflict of interest.

3053 POSTER

Five years follow up study of treating locally advanced cancer of the cervix with hyperfractionated radiotherapy and HDR brachytherapy compared to conventional radiotherapy and HDR brachytherapy

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Background: To compare the clinical outcome at 5 years of treating locally advanced ca cevix with hyperfractionated RT and HDR brachytherapy to conventional RT and HDR brachytherapy.

Materials and Methods: Patients were divided into two arms. Arm A-received hyperfractionated RT, 1.2 Gy bd,6 hours apart,upto 57.6 Gy,along with weekly cisplatin 40 mg/m^2 followed by two sitting of HDR Brachy OF 8 Gy each. Arm B-received 2 Gy per day upto 50 Gy along with weekly cisplatin followed by two sittings of brachy 8 Gy each.
Results: Results were comparable in both arms. Rectal toxicities were lower (18%vs39%) as was bladder complications (26%vs54%) compared to conventional RT. Sexual function was better in hyperfractionated arm (61%vs42%). A subset analysis showed a benefit with hyperfractionated regime in stage IIIB (OS 60%vs50% and PFS 50% vs 40%), lower hemoglobin, younger age compared to the conventional arm.
Conclusions: Hyperfractionated regimen was found to be better than conventional regime in terms of lower toxicities and better quality of life compared to conventional regimen. The advantages seen in the subset populations has to be evaluated with larger randomised control studies. The results of our study was limited by the small sample size.
No conflict of interest.

3054 POSTER

Conservative surgery in granulosa cell tumors: Retrospective series of 22 patients

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The aim of the study was to evaluate fertility and the risk of relapse after conservative surgery for granulosa cell tumor (GCT).
Method: Retrospective study of patients (pts) referred to the Institut Gustave Roussy with a GCT between 1989 and 2011 who underwent conservative surgery (uterus and contralateral ovary in situ).
Results: 22 pts were identified, median age was 28 years (17−41 years). Symptoms at diagnosis included abdominal pain, pelvic mass, vaginal bleeding and amenorrhea. The majority presented with stage I GCT (IA, N = 9; IC (spontaneous or intraoperative rupture), N = 11). There was one stage IIC and one IIIC. Seven (7/22) pts received adjuvant chemotherapy with bleomycin, etoposide, cisplatin (BEP).
Among pts with adult type GCT (N = 16): None of the 9 pts who had complete surgical staging for stage IA has relapsed. Among 6 pts with stage IC, one received adjuvant BEP and has not relapsed, the other 5 did not receive adjuvant BEP and relapsed. 1 patient with stage IIC has recurred despite three cycles of BEP.
Among pts with juvenile type GCT (N = 6): Four of the 5 stage IC pts received adjuvant BEP, 2 relapsed. One stage IC pt did not receive BEP and had a lethal recurrence. The stage IIIC pt received adjuvant BEP and relapsed.
Sites of relapses: ovarian and peritoneal (N = 5) or peritoneal alone (N = 5). Median relapse-free survival at 10 years was 43% (95% CI: 23%-66%), and overall survival 87% (95% CI: 63%-96%). The only bad prognostic factor on univariate analysis was BMI>24. Stage> IA, tumor rupture, age $\geqslant$28 years, lack of adjuvant chemotherapy and juvenile type were not significantly predictive of poor outcome.
21 pts underwent surgery with preservation of the ovary and uterus. Among 11 pts under the age of 36 years, 7 pts had a pregnancy. 2 pts relapsed 6 and 11 years after pregnancy.
Conclusion: Conservative surgery may be possible after complete surgical staging for adult type stage IA GCT. All stage IC must receive adjuvant BEP. The benefit/risk balance of conservative surgery in stage IC GCT must be carefully considered and discussed with the pt. Conservative treatment is not appropriate for $\geqslant$stage II GCT. The role of secondary surgery after pregnancy remains debated.
No conflict of interest.

3055 POSTER

Primary repair of rectovaginal fistulas complicating pelvic surgery by gracilis myocutaneous flap

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Background: Complex rectovaginal fistulas repair are extremely challenging. Various surgical options have been suggested; nevertheless, none had been universally accepted as the procedure of choice. This study discussed a novel surgical technique using gracilis myocutaneous flap interposition.
Patient and Methods: Ten patients had fistulas as a complication post treatment of pelvic malignant tumors and one patient had fistula after resection of rectal endometriosis. Primary treatment was pelvic resection; nevertheless, 6 cases had adjuvant chemo-irradiation, 2 cases had post operative irradiation and 2 patients had adjuvant chemotherapy. Fistulas mean diameter was 2$\pm$0.24 cm (1−3) and 8 patients (72.7%) had their fistulas in the middle vaginal third.
All cases had synchronous diverting stomas and wide debridement of fistulas. According to vaginal defect diameter 5 patients were repaired by single gracilis myocutaneous flaps, 2 cases by simple gracilis muscle and 4 cases by double gracilis myocutaneous flaps.
Results: Patients had a mean follow-up time of 34.8$\pm$5.03 months (12−67) and all patients had definitive healing of their fistulas (100%). Median time to stoma closure was 2 months (1−5). Four women (36.4%) had at least one early postoperative complications including temporary leak (n = 3), vaginal sepsis (n = 1), partial skin paddle necrosis (n = 1) and donor limb deep venous thrombosis (n = 1). Late morbidities were seen in 3 cases (27.3%) including vaginal stricture, anorectal anastomotic stricture and anastomotic tumor recurrence.
Conclusion: Successful repair requires adequate debridement of necrotic devascularized tissues, tissue transposition to the rectovaginal septum and reconstruction of vaginal wall. Gracilis myocutaneous flaps are ideal for this issue.
No conflict of interest.

3056 POSTER

The effectiveness of embolization and chemoembolization in cervix cancer with bleeding complication

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Background: Cervix cancer (CC) is very dangerous disease for women's life and health. The problem of increasing the effect of radial treatment CC patients is very important. The local-spread CC is often complicated by acute bleeding and pain. To control these symptoms we often use surgical ligation of internal iliac artery (IIA). This operation is traumatic and developing of collaterals after it leads to bleeding again.
Material and Methods: One of the modern methods of CC treatment is the selective embolization and chemoembolization of anterior branch of internal iliac artery were performed on 78 patients with CC stage T_{2b} N_{0-1} M_0, $T_{3a,b}$ N_{0-1} M_0. 23 of them had severe form of the disease (profuse bleeding, pronounced pains). Bilateral embolization of anterior branch of internal iliac artery were performed urgently in severe cases. After supporting and medical treatment bilateral embolization with doxorubicin 40 mg/m^2 was performed on 55 patients. After performance antibacterial immuno-potentiative and infusion supporting treatment were used.
Results: Bleeding, decreasing of pains were observed after it.In a short time the regress of tumor (20−50%) was observed and it made possible to do radial therapy. This method of treatment of CC patients is being used in our centre successfully.
Conclusions: The obtained data expressing in full resorption parametrical infiltration, reduction and vanishing be pain, risk of bleeding, that allows here to conduct a course of radial therapy less traumatically, in conditions of a continued regression of a swelling.
No conflict of interest.

3057 POSTER

Cisplatin/taxane or carboplatin/taxane-based chemotherapy in advanced cervical cancer

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Background: Cisplatin (CDDP) + paclitaxel represent the standard first line chemotherapy for advanced cervical carcinoma (CC). Carboplatin (CBDCA)/paclitaxel doublet retains activity, is less toxic and currently compared with CDDP/paclitaxel. This study summarizes the current literature on the efficacy of CDDP/taxane vs. CBDCA/taxane in the treatment of advanced CC.
Material and Methods: PubMed, EMBASE, Web of Science and The Cochrane Library were systematically searched to identify relevant publications. Studies that were conducted in advanced CC patients treated with CCDP/taxane and CBDCA/taxane and reporting objective response rate (RR), progression-free survival (PFS), time-to-progression (TTP) and overall survival (OS) were included. Data on RRs were pooled by using Comprehensive Meta-Analysis software with a random-effects model. Data on PFS/TTP and OS were summarised descriptively.
Results: Eighteen (3 phase III, 7 single-arm and 1 randomized phase II, 6 retrospective and 1 prospective series) studies containing 1,204 advanced CC patients treated with CDDP/taxane or CBDCA/taxane-based chemotherapy were included. Eight studies included CBDCA/taxane arms, 9 CDDP/taxane arms and 1 directly compared CDDP/paclitaxel with CBDCA/paclitaxel. Only 1 out of 18 used a docetaxel-combination, the remaining included a paclitaxel-based combination. The reported weighted median PFS/TTP, median OS and pooled objective RRs were 6.9 months,

12.87 months and 49.3% for CDDP-combinations and 5 months, 10 months and 49.3% for CBDCA-combinations. The difference in PFS/TTP but not in OS was significant in favour of CCDP/paclitaxel chemotherapy (T-test). Response rate were similar with CDDP- and CBDCA-combinations in CDDP-pre-treated patients (43.9 vs 40%). On the contrary in CDDP naive patient RRs were 68.3% and 59.1% for CBDCA-based vs. CDDP-based chemotherapy respectively (p=ns).
Conclusions: CBDCA + paclitaxel represents a valid alternative option for the treatment of advanced CC, with similar RR (about 50%) and OS compared to CDDP + paclitaxel.
No conflict of interest.

3058 POSTER

A single-institution experience of bevacizumab-based therapy in heavily pretreated epithelial ovarian and other Mullerian tract carcinomas

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Background: Recently, bevacizumab (Bev) is considered an active blocker of tumour angiogenesis in epithelial ovarian (EOC) and other Mullerian tract cancers (MTC) such as fallopian tube (FTC), type II endometrial (EC-II), and peritoneal papillary-serous carcinomas (PPSC). Although found to be as active as any salvage chemotherapy (CTx) in platinum-resistant MTCs, the current approval of Bev covers only platinum-sensitive primary and recurrent tumours. We hereby summarise our long-term experience with Bev based systemic therapy (Tx) in patients (pts) with heavily pretreated recurrent MTCs.
Methods: Since 2006, a total of 78 intensively pretreated MTC pts (EOC, n = 69; FTC, n = 2; EC-II, n = 3; PPSC, n = 4) who did not qualify for recruitment into a controlled clinical trial were included in this study with 45 pts (57.7%) being platinum-resistant. Pts had received a median of 4 (range 1−10) prior CTx. In all pts, Bev based Tx was given including Bev monotherapy (group A, n = 19), Bev + metronomic CTx (group B, n = 38), and Bev + conventionally dosed CTx (Group C, n = 21). In all pts, Bev was administered at either 10 mg/kg BW q2w or 15 mg/kg BW q3w. Adverse effects were classified according to the CTCAE Vs 4.03 scale. TTP was calculated from the start of Bev until progression, OS was calculated from the start of Bev until death of any case or loss to follow-up.
Results: The most common adverse effects associated with Bev based Tx were hypertension, proteinuria, headache, inflammation/infection, epistaxis, and subileus. Hypertension which often required adequate treatment was limiting in only case as also were renal toxicity and infection. In the entire population, median TTP was 29.9 wks and median OS was 55.1 wks with no significant difference between platinum-resistant and -sensitive pts. In regard to both TTP and OS, there was a non-significant trend favouring group A (36.0/63.0 wks) and B (29.9/67.7 wks) vs group C (20.3/36.0 wks).
Conclusion: Bev based Tx was active and generally well tolerated in this hard-to-treat population of pts with recurrent MTC. Both TTP and OS were equal or even superior to any conventional CTx used in this setting. Clinical platinum-resistance did not predict a worse clinical outcome. Although this is not a randomised trial, Bev may be preferably given either as single agent or combined with metronomic CTx in pts with heavily pretreated MTCs.
No conflict of interest.

3059 POSTER

CA-125 as a response marker for vintafolide+pegylated liposomal doxorubicin (PLD) vs PLD alone in platinum-resistant ovarian cancer: The PRECEDENT trial

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Background: Vintafolide (EC145), an investigational folic acid/desacetylvinblastine conjugate, binds with high affinity to the folate receptor expressed on most epithelial ovarian cancers. In the randomized, open-label PRECEDENT trial, subjects with platinum-resistant ovarian cancer received vintafolide+PLD or PLD alone. Statistical significance of the primary objective (progression-free survival based on investigator assessment using RECIST v1.0 and prespecified clinical events) was achieved in the ITT population: median 21.7 weeks − vintafolide+PLD (n = 100) vs 11.7 weeks − PLD alone (n = 49) (HR 0.63; 95% CI 0.41–0.96; *P*=.031). An efficacy assessment based on CA-125 response is reported here and compared with overall response rate (ORR; complete response [CR]+partial response [PR]) based on RECIST criteria.
Methods: Women $\geqslant$18 years old with ECOG status 0−2 and exposure to $\leqslant$2 prior systemic cytotoxic regimens were randomized 2:1 to vintafolide (2.5 mg IV tiw, weeks 1 and 3, q 28 days)+PLD (50 mg/m^2 IV day 1, q 28 days) or PLD alone (same dose/schedule). Best overall CA-125 response was assessed in a subset of the ITT population with a baseline CA-125 $\geqslant$2$\times$ ULN and $\geqslant$1 follow-up CA-125 evaluation. CA-125 CR was defined as a return to normal CA-125 levels ($\leqslant$35 U/mL); PR was defined as a CA-125 decrease to $\leqslant$50% of baseline that was still above the ULN.
Results: 60 (vintafolide+PLD) and 26 (PLD alone) subjects were evaluable for CA-125 response. A higher confirmed CA-125 ORR was seen for vintafolide+PLD (21.7%) vs PLD alone (11.5%), as was a higher unconfirmed CA-125 ORR (38.3% vs 19.2%, respectively). CA-125 CR (confirmed and unconfirmed) occurred in 8.3% and 15.0% of vintafolide+PLD subjects, respectively, with no CA-125 CR in the PLD alone arm. In the same population, RECIST confirmed ORR was 21.7% for vintafolide+PLD vs 15.4% for PLD alone, and RECIST unconfirmed ORRs were 36.7% and 19.2%, respectively. One confirmed and 1 unconfirmed RECIST CR were noted in the vintafolide+PLD arm, with no RECIST CR in the PLD alone arm.
Conclusions: CA-125 level changes correlated with RECIST changes in subjects with platinum-resistant ovarian cancer and elevated CA-125 treated with vintafolide and PLD. CA-125 may overestimate CR compared with RECIST in the same population.
Conflict of interest: *Corporate-sponsored research: RW Naumann-Research funding from Endocyte, Inc. E Kutarska-Research funding from Nazwa Sponsora. Other substantive relationships: C Lovejoy-Employment and stock ownership at Endocyte, Inc. KM Anderson and RA Rangwala-Employment and stock ownership at Merck*

3060 POSTER

Combination therapy with Bevacizumab and GEMOX for patients with platinum-resistant recurrent ovarian cancers: A phase II study

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Objective: Combination therapy using gemcitabine with oxaliplatin (GEMOX) showed moderate activity in recurrent ovarian cancers (ROC), however, severe toxicities have been frequently observed. On the other hand, bevacizumab enhances chemotherapeutic efficacy in various cancers. Here we conducted a phase II study to evaluate the effect of weekly low-dose administration of GEMOX in combination with bevacizumab (B-GEMOX) for patients with platinum-resistant ROC.
Methods: Simon's two-stage design was used, and a total number of 25 cases were enrolled in the study. This design yielded a type I error rate of 0.05 and power of 0.8 when the true response rate was 40%. B-GEMOX therapy consisted of 2 mg/kg of bevacizumab, 300 mg/m^2 of gemcitabine, and 30 mg/m^2 of oxaliplatin, three weeks on and one week off, q4weeks. The treatment was continued until development of severe toxicities or progressive disease. Tumor responses were assessed using the Response Evaluation Criteria In Solid Tumors (RECIST) and Gynecologic Cancer Intergroup (GCIG) criteria.
Results: Median number of the B-GEMOX therapy was five cycles. Response was observed in seven cases (41%) by RECIST, and in 2 cases (29%) by GCIG criteria, resulting in overall response rate of 36%. Clinical benefit including stable disease was obtained in 84% of the patients. Median progression-free survival was 4.5 months (range: 2−18+ months). Toxicities were mild and mainly consisted of hematologic, gastrointestinal, and neuropathy, however, there were no non-hematologic toxicities more than grade 1.
Conclusion: Weekly administration of B-GEMOX was active for patients with ROC, and showed mild toxicities. These results warrant further prospective studies for patients with ROC.
No conflict of interest.

3061 POSTER

Adverse event profile by folate receptor status for vintafolide+pegylated liposomal doxorubicin (PLD) vs PLD alone in platinum-resistant ovarian cancer

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Background: Vintafolide (EC145, MK8109), a folic acid/desacetylvinblastine conjugate, binds with high affinity to folate receptors (FRs) expressed in cancers. This exploratory analysis evaluated the incidence of adverse events (AEs) by FR status in the PRECEDENT trial, a randomized open-label study of subjects with platinum-resistant ovarian cancer receiving vintafolide+PLD or PLD alone.
Methods: Women ⩾18 years old with ECOG status 0−2 and exposure to ⩽2 prior systemic cytotoxic regimens were randomized 2:1 to vintafolide (2.5 mg IV tiw, weeks 1 and 3, q28 days)+PLD (50 mg/m^2 IV day 1, q28 days) or PLD alone (same dose+schedule). Patients at centers with ^{99m}Tc nuclear imaging capability underwent SPECT imaging with etarfolatide to identify patients with functionally active FRs. AEs in the safety population (received at least 1 dose of study drug) were evaluated by FR status (FR [100%, all target lesions positive]; FR [0%, all lesions negative]).
Results: 37 patients were FR (100%) (22, vintafolide+PLD; 15, PLD alone), and 19 were FR (0%) (13, vintafolide+PLD; 6, PLD alone). The number of patients reporting at least 1 drug-related AE was generally similar regardless of FR status or treatment arm. One subject in the FR (100%) group and 4 subjects in FR (0%) who received vintafolide+PLD discontinued either vintafolide or PLD during the study due to drug-related AEs.
For the FR (100%) vs FR (0%) groups, the most common drug-related AEs (⩾30% of patients in either group) in the vintafolide+PLD arm were fatigue (54.5% vs 46.2%), constipation (50.0% vs 46.2%), hand–foot syndrome (HFS) (40.9% vs 30.8%), anemia (40.9% vs 30.8%), nausea (36.4% vs 53.8%), stomatitis (36.4% vs 61.5%), rash (36.4% vs 15.4%), peripheral sensory neuropathy (31.8% vs 0%), neutropenia (27.3% vs 30.8%), vomiting (22.7% vs 38.5%), and asthenia (13.6% vs 38.5%).
For the FR (100%) vs FR (0%) groups, the most common drug-related AEs (⩾30% of patients in any group) in the PLD alone arm were HFS (53.3% vs 50.0%), nausea (33.3% vs 33.3%), stomatitis (33.3% vs 50.0%), fatigue (33.3% vs 33.3%), anemia (20.0% vs 50.0%), neutropenia (27.3% vs 50.0%), and leukopenia (13.6% vs 33.3%).
Conclusion: This exploratory analysis suggests that the AE profile appears numerically similar based upon FR status for the vintafolide+PLD and PLD alone groups; however, the small sample size precludes a statistical analysis. Future analyses in larger patient populations are needed to confirm these findings.
Trial number: NCT00722592
Conflict of interest: *Advisory board: TJ Herzog-Consultant J&J, Roche, Morphotek J Symanowski-Consultant Endocyte, Inc. Corporate-sponsored research: E Kutarska-Research funding Nazwa Sponsora B Nguyen and RW Naumann-Research funding Endocyte, Inc. Other substantive relationships: B Nguyen-Employment and stock ownership Endocyte, Inc. RA Rangwala-Employment and stock ownership Merck*

3062 POSTER

Efficacy and safety of generic pegylated liposomal doxorubicin (PLD) in relapsed ovarian cancer

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Background: Currently the innovator product of PLD is not being marketed. Due to drug shortage, even USFDA has permitted the usage of generic formulation. The purpose of this analysis was to evaluate the efficacy and safety of the same formulation in Indian patients.
Methods: We analyzed the case records of the patients of relapsed ovarian or primary peritoneal cancer who started treatment with PLD at our center between May 2011 and October 2012. Starting dose of PLD was 30 mg/m^2 q4 weekly for combination and 40 mg/m^2 q4 weekly for single-agent. Response assessment was done by combined RECIST and CA 125 criteria.
Results: 20 such patients were identified; median age 56 (range 45−71) years. Histology was serous-14, clear cell-2, poorly differentiated-1, transitional-1 and adenosquamous-1. 70% patients received PLD as 2nd line, 20% as 3rd line and 10% beyond 3rd line. 100% patients were platinum and taxane pretreated; 30% received >1 course of platinum and 20% received >1 course of taxane previously. In addition, three patients received gemcitabine and one etoposide. Median interval from last chemotherapy was 8 months; <6 months − 40%, >6−12 months − 40% and >12 months − 20%. ECOG performance status was 0 in 5%, 1 in 85%, 2 in 10%.
Measurable disease on imaging was present in 80% and CA 125 was >ULN in 80%. Three patients underwent surgery for this relapse prior to starting chemotherapy. 40% patient received single agent PLD and 60% received combination with carboplatin. Median Number of cycles received was 6 (range 1−6); 65% received 4−6. Among 18 patients evaluable for response, best overall response obtained was CR in 1 (5.5%), PR in 9 (50%), SD in 1 (5.5%) and PD in 7 (39%). At a median follow-up of 9 months (range, 4−23), 5 (25%) are alive and progression free. Median PFS was 6 months (8 months in platinum sensitive and 3 months in resistant) and median OS not reached; 80% were alive at last follow-up. Nine patients received further chemotherapy after progression. There were 15 Grade 3−4 toxicity events in 8 patients − anemia in 7, neutropenia in 3, thrombocytopenia in 3, mucositis 2. Two patients had to discontinue therapy because of toxicities.
Conclusion: Generic formulation of PLD was effective as therapy for relapsed ovarian cancer, especially in platinum-sensitive. There were more grade 3−4 myelosuppressive events than expected which may be explained by the multiple lines of prior therapy received.
No conflict of interest.

3063 POSTER

Effects of temozolomide combined with bevacizumab in patients with recurrent or refractory uterine leiomyosarcoma (LMS): A preliminary case series

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Background: Treatment modality of patients with recurrent or refractory uterine LMS is mainly systemic therapy, such as anthracycline-based combination, and gemcitabine plus docetaxel, however, the effects are limited, and too toxic. We conducted a preliminary study to evaluate the effects of combination with temozolomide and bevacizumab in patients with recurrent or refractory uterine (LMS).
Material and Methods: From 2009 to 2012, nine patients with recurrent or refractory uterine LMS were treated with weekly bevacizumab (2 mg/kg; days 1, 8, and 15, q4weeks) and temozolomide (80 mg/body, daily) until disease progression or development of unmanageable toxicity. Response and adverse effects were evaluated using the response evaluation criteria in solid tumors (RECIST), and common terminology criteria for adverse events (CTCAE) version 3.0.
Results: One (11%) of 9 patients had complete response (CR) and another case (11%) had partial response (PR) in RECIST evaluation. Four patients (44%) obtained stable disease (SD) more than three months. The response rate (RR; CR+PR) and clinical benefit rate (CBR; CR+PR+SD) were 22% and 67%, respectively. The median progression-free survival was 9.8 months (range: 3−32 months). There were no treatment-related deaths or grade 4 toxicities, and no patient needed dose-reduction due to toxicities.
Conclusions: Chemotherapy with temozolomide and weekly bevacizumab was active and safe in patients with recurrent or refractory uterine (LMS). The present case series suggested that this combination could be a candidate for the treatment not only recurrent LMS, but also first-line therapy for uterine LMS.
No conflict of interest.

3064 POSTER

Response to tamoxifen (T) and letrozole (L) in patients with relapsed high-grade ovarian carcinoma − the Royal Marsden experience

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Background: Hormone treatment is commonly used in ovarian cancer, but the choice of treatment and its role in high grade (HG) ovarian cancer is unclear. It has been suggested that there is a higher response rate to L than T, and that response is associated with platinum sensitivity and ER receptor status. Our aim was therefore to assess the efficacy of T and L in HG ovarian cancer and to explore the factors influencing clinical outcome.
Method: Patients who started T or L for relapsed, confirmed HG ovarian, peritoneal or fallopian tube cancer between 1/6/07 and 1/6/12 were analysed retrospectively. The primary endpoint was response rate (RR, RECIST). Secondary endpoints included clinical benefit rate (CBR), CA-125 response and duration of response. The platinum sensitivity and ER status of the patient were assessed as predictors of response to treatment.
Results: 97 patients were identified (43T, 54L); median age 63 years (20−92); median lines of chemotherapy 3 (1−8); 91% HG serous, 5% endometroid, 4% clear cell/other; 59% platinum resistant, 41% platinum sensitive. ER was positive in 45%, and unknown in 55%. There were no complete responses. 14 patients (6T, 8L) had a partial response, with RR (RECIST) of 14% (T) and 15% (L). A further 22 patients in each group had stable disease for >3 months, giving overall CBR of 65% (T) and 57% (L). All responses were in serous or endometroid cancers. There was no significant difference in RR ($p = 0.99$) or CBR ($p = 0.14$) between T and L. 22 patients (23%) had a CA-125 response (10 T − 23% and 12 L − 22%). There were no differences in response rates between patients with unknown ER status, and known ER positivity ($p = 0.12$); nor by platinum sensitivity ($p = 0.42$). Patients responding to L had longer durations of response than those responding to T (26 vs 11.5 months, $p = 0.03$), but there was no difference in mean duration of disease stability between the treatments (9.6 vs 7.2 months respectively, $p = 0.11$). Hormone treatment was well tolerated, with only 3 patients stopping treatment due to intolerance (all L). 5 patients were diagnosed with either PE or DVT during treatment (3T, 2L, $p = 0.49$).
Conclusion: Within the limits of a retrospective audit, we observed that patients treated with L had a significantly longer duration of response than those treated with T, but the duration of disease stability was equivalent. Endocrine treatment with either T or L is a valid option for patients with ER positive HG ovarian cancer, with equivalent RR and CBR.
No conflict of interest.

3065 POSTER

Lurbinectedin (PM01183) activity in platinum-resistant/refractory ovarian cancer patients: Updated results of an ongoing two stage Phase II study

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Background: PM01183 is a new anticancer agent that acts through DNA minor groove-binding in a wide range of cancer cell lines and orthotopic models, including several platinum resistant (pt-res).
Methods: Pt-res or platinum refractory (pt-ref) ovarian cancer patients (pts) with less than 3 prior chemotherapy (CT)-containing lines, adequate major organ function and performance status (PS) 0−2 are included. The primary endpoint of the study is overall response rate (ORR) (by RECIST v1.1 and/or Rustin criteria). It was designed to reject if true response rate is 8% or less *vs* the alternative of 25% or higher. During the first stage, 22 pts were treated with i.v. PM01183, 7 mg flat dose, q3wk. The second stage is randomizing 60 pts (ratio 1:1) to receive PM01183 (P) or topotecan (T) (standard or weekly regimen according to Investigator's choice). Cross-over to the P arm is allowed for pts who progress to T. The study was not properly powered to detect clinical significant differences across arms.
Results: As of April 2013, 56 pts from both stages (P/T: 41/15) have been included in the analysis. Median age: 59 years; median ECOG: 1; serous histology: 71% pts; pt-res: 59% pts; pt-ref: 41% pts; PFI <3 months: 46% pts; visceral disease: 34% pts; ascites: 23% pts; median advanced lines: 1; prior bevacizumab: 18% pts.
Efficacy results in evaluable pts (both stages) are summarized in the table.

	PM01183 (n = 38)		Topotecan
	1st stage (n = 22)	2nd stage (n = 16)	(n = 15)
OR, n (%)			
CR	0 (0)	1 (6)	0 (0)
PR	§6 (27)	2 (13)	0 (0)
SD	12 (55)	5 (31)	7 (47)
PD	4 (18)	7 (44)	8 (53)
Treatment failure	0 (0)	1 (6)	0 (0)
ORR (%) (95% CI)†	24 (11−40)		0
DCR (%)	68		47
PFS (months)*	3.5		1.4
− Pt-res (n = 16/7/8)**	4.5	5.7	1.4
− Pt-ref (n = 5/8/7)***	3.5	1.3	2.7

§ 2 PRs by Rustin criteria; † $p = 0.0474$; * $p = 0.0769$; ** $p = 0.0287$; *** $p = 0.2501$.

The preliminary PM01183 safety profile confirms prior phase I results, with myelosuppression (neutropenia [Gr 4 65%, FN 15%], thrombocytopenia [Gr 3−4 32.5%]), nausea/vomiting (Gr 3 15/7.5%) and fatigue (Gr 3 37.5%) being the most common drug-related AEs.
Conclusions: PM01183 is an active drug in pt-res/pt-ref ovarian cancer and the study has met its primary endpoint. Toxicity is predictable and manageable. Further studies are warranted. Updated results will be presented.
Conflict of interest: *Advisory board: PharmaMar*

3066 POSTER

Model prediction of mean PFS and OS Time from a phase II trial comparing vintafolide (V) plus pegylated liposomal doxorubicin (PLD), versus PLD alone, in platinum-resistant ovarian cancer (PROC) patients with 100% folate receptor (FR) positive target lesions

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Background: A recent randomized phase II trial (PRECEDENT) has shown that vintafolide plus PLD (V+PLD) resulted in a statistically significant improvement in progression-free survival (PFS) compared with PLD for PROC. Importantly, the observed efficacy was greatest in patients with 100% FR positive tumors, identified by ^{99m}Tc etarfolatide. The median PFS were 24.0 vs. 6.6 weeks for FR(100%) patients treated with V+PLD vs. PLD (HR 0.381; $p = 0.018$). Notably, FR(100%) patients represent a subpopulation in PROC with a worse prognosis when treated with PLD. In addition to median PFS, mean times on PFS, post-progression (post-PD), and overall survival (OS) are meaningful. The objective of this study is to predict mean PFS, post-PD survival and OS for FR(100%) patients treated with V+PLD vs. PLD.
Material and Methods: Parametric Weibull survival models are estimated for FR(100%) subpopulation (n = 37; V+PLD:22, PLD:15) using the PRECEDENT trial data, adjusted for the following pre-specified baseline factors: age (⩾65 vs. <65 years), platinum failure (primary vs. secondary), CA-125 level (⩾200 vs. <200 U/mL), geography (North America vs. Europe), log of the sum of the target lesions longest diameters, log of months since last platinum treatment, and ECOG (1 or 2 vs. 0). The models provide survival probabilities for each patient given the baseline covariates for a given treatment. The mean of each individual's survival probabilities at any time point across all times yields the population survival curve for the treatment. Area under the curve is the mean survival time over a time period. Variance of the mean is estimated using bootstrapping.
Results: The model predictions based on patients' assigned treatment in the trial are very close to the actual mean times calculated from the Kaplan–Meier curves. The models further predict the mean times for a given treatment across all trial patients over 2 years as presented in the table.

Mean time (months)	PFS	(95% CI)	post-PD	(95% CI)	OS	(95% CI)
PLD	2.6	(1.4, 5.7)	6.7	(2.5, 12.4)	9.3	(5.3, 15.4)
V+PLD	6.8	(3.9, 10.9)	7.6	(2.8, 11.5)	14.3	(11.0, 17.6)
Diff	4.1	(−0.8, 8.3)	0.9	(−7.4, 7.4)	5.0	(−2.9, 10.1)

Conclusions: The results suggest there may be a benefit in mean PFS and OS associated with V+PLD. The results will be further evaluated following the ongoing phase III trial (PROCEED). These results may be used for future evaluation of the benefit and cost of V+PLD vs. PLD for decision makers.
Trial number: NCT00722592
Conflict of interest: *Advisory board: TJ Herzog-Consultant J&J, Roche, Morphotek. Other substantive relationships: K Anderson-Employment and stock ownership Merck J Wang-Employment and stock ownership Merck R Xu-Employment and stock ownership Merck*

3067 POSTER

Nuclear translocation of FTS (Fused Toes Homolog) is related with EGFR phosphorylation and radiation resistance of uterine cervix cancer

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Background: Radiation therapy (RT) is the major treatment modality for uterine cervix cancer. However, about one third of the patients especially with locally advanced disease (FIGO IIIB-IVA) suffer from recurrence. Defining the molecular events that contribute to radiation resistance is of critical importance to improve the treatment results. Fused Toes Homolog (FTS) is a member of a group of proteins termed as E2 variants and this group of proteins lacks an active cysteine residue that is required for ubiquitin transfer. Here we evaluated the role of nuclear translocation of FTS in radiation resistance of cervix cancer.
Material and Methods: The expression of FTS in the cervix cancer tissues with patients received curative RT was studied from formalin-fixed paraffin-embedded specimens by immunohistochemistry. The point mutation constructs of FTS were made by using site directed mutagenesis and the change of translocation of FTS and its downstream signaling were studied by transfecting normal FTS and its mutants into the normal and cervix cancer cell lines.
Results: Immunostaining of cervix cancer tissues revealed that FTS was located in the nucleus in the patients with recurrence after RT. In vitro study also revealed that this protein was translocated into nucleus from cytoplasm upon irradiation. Among the six mutants of possible phosphorylated sites of FTS only the threonine into alanine (T190A) mutant failed to translocate into nucleus. The cells transfected with this mutant FTS (T190A) showed decreased phosphorylatation of EGFR, p38 and JNK.
Conclusions: Nuclear translocation of FTS confers radiation resistance on uterine cervix cancer. Threonine residue of FTS at position 190 is essential for its nuclear translocation, which is related with EGFR phosphorylation and its downstream effects.
No conflict of interest.

3068 POSTER

Analysis of the immune status of patients with vulvar cancer

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Background: Immune system analysis in patients with vulva cancer.
Material and Methods: The study was conducted in 127 patients with cancer of the vulva at the age of 31−80 years with stage I−IV, the control of 30 healthy women of identical age. Evaluated the T and B − cell parts of the immune system condition NK cells, macrophages studied indicators of transformation of monocytes and the level of the CIC (circulating immune complexes).
Results: In patients with stage I functional activity in absolute terms, the T-cells were reduced and the mitogen PHA − 0.38±0.08 h109/l. The total number of T cells 0.53±0.07 h109/l significantly reduced in half. Transformation of monocytes into macrophages is depressed − PMTM is 0.48±0.05 h109/l. A high level of circulating immune complexes (CIC) − 36.8±4.1 compared to 25.0±3.3 in healthy stage II to PHA proliferative activity was significantly reduced, RBTL to PHA is 34.0±2.6%, and the data in absolute terms to PHA-0.28±0.05 h109/L was significantly reduced compared with those of healthy women. In patients with stage III-th marked a marked imbalance of the immune system, there was a significant increase in CIC compared with the initial stages, and even more so with women's health indicators. The number of T and B cells was reduced by 30% and 20%, respectively. Contents of monocytes remains at I-th stage, but their functional activity (PMTM) was significantly reduced. With the IV-th stage of cancer of the vulva percentage of T cells at the level of patients with the II-nd and III-th stage, the number of functionally active T cells was significantly reduced from 48.0±4.3% to 27.5±2.4%, the number of LPS-stimulated B cells had the tendency to decrease, and reduced by 20% compared with patients in I-th stage. CIC levels in the blood of patients with Stage IV-2-fold higher than in healthy women, and significantly higher than in patients with I-st and II-nd stage of cancer of the vulva.
Conclusion: The study showed the presence of both quantitative and qualitative immune deficiency in patients with cancer of the vulva, the degree of which is characteristic for each stage of the disease, which requires a special correction.
No conflict of interest.

3069 POSTER

Factors of local cellular immunity in patients with ovarian cancer

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Background: The aim of this work was to study the factors of local immunity in patients with primary ovarian cancer (OC).
Materials and Methods: Investigated the blood and ascitic fluid (AF) 18 patients with generalized OC before treatment. At the time of treatment for patients with medical disease duration ranged from 3 to 18 months., On average, 7±2.2 months. Using flow cytometry BD FACS Canto II in blood and AF were determined percentage of lymphocytes of different subpopulations (CD3 + CD4 +, CD3 + CD8 +, CD19 +, CD16 + CD56 +); in fractions CD3 + CD4 + and CD3 + CD8 + lymphocytes estimated the number of naive T cells (CD45RA + CD62L +) and memory T cells (CD45RA-CD45RO +).
Results: The study showed that the total number of lymphocytes in the AF was significantly higher than in the blood (43.7±11.6 vs 11.7±2.8%; $P < 0.05$). The total number of T-, B-and NK-cells and CD3+CD4+CD8− and CD3+CD4−CD8+ in blood and AF patients had no significant differences, although the blood CD3 + CD4 + cells predominate over the CD3 + CD8 + (immunoregulatory index greater than 1.0), and the AF ratio CD4 +/ CD8 + less than 1.0. A significant difference was found in the studied biological fluids between the levels of naive T cells and memory T cells. Found that the latter are present in high amounts in the AF, and the levels of naive T-cells in it are much lower than in the blood. Thus, the content of T cells with the phenotype of memory cells of CD3+CD4+ lymphocytes in the blood is 68.3±4.7%, and in AJ 89.4±2.5%; maintenance of naive T-cells are respectively 7.1±0.7 and 2.4±0.8% (in both cases, $P < 0.05$). T-lymphocyte memory and naive T cells in a subset of CD3 + CD8 + differences are similar: in blood T cells were found in the number of memory 45.6±7.1, in AJ 73.1±2.7%, and the T-naive in the amount of 21.7±3.4 and 7.2±0.87%, respectively (both $P < 0.05$).
Conclusion: Our data suggest that T-cell memory as a subset of CTL, and of CD3 + CD4 +, have the ability to accumulate in the hearth of tumor growth, and naive T cells predominate in peripheral blood. Establishing specificity of memory cells is not yet possible, we consider it as our future objectives. According to the duration of the disease, they may be associated with tumor process.
No conflict of interest.

3070 POSTER

Viral DNA in patients with cancer of the vulva

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Background: The analysis of HPV DNA and the herpes group of viruses in patients with cancer of the vulva.
Materials and Methods: In 131 patients with cancer of the vulva at the age of 26−82 years I to stage IV disease were determined HPV (Human Papillomavirus) high cancer risk: 16, 18, 31, 33, 35, 45, 51, 52, 56, 58, and 59 types of herpes virus group (HSV type 1.2, cytomegalovirus, Epstein-Barr virus and herpesvirus type 6). Determination of DNA was performed retrospectively by deparafinirovaniya sections and DNA isolation fenolhloroformnym and by adsorption on silica particles. Determination of HPV PCR was performed using quick sets AmpliSens HPV screen and WRC WRC AmpliSens HPV genotype ('InterLabService' Russia).
Results: Of the total group (131 patients) data confirm that the DNA of a virus were detected in 45 (34.35%), including different types of HPV DNA detected in 33 (25.19%), cytomegalovirus − in 2 (1, 5%), Epstein-Barr virus − in 12 (9.16%) and herpes type 6 in 4 (3.05%). In the analysis by age found that in young (26−50 years old) of different types of viruses were identified in 23 of 32 (71.87%), while in the older group, 22 of 99 (22.2%). HPV DNA was detected in 18 of 32 young patients (56.25%), and in the elderly in 15 of 39 (15.5%). Epstein-Barr virus was detected in 5 (15.6%) of the young, and 7 (7.07%) in elderly patients, the herpes virus type 6 detected in 6.25% and 2% of young elderly, cytomegalovirus was isolated only in the elderly 2%. In patients with cancer of the vulva young adults with HPV detected in 62% of HPV type 16, 20.8% − 18 type, 39 and 45 and 56 4% − 8%, 33% noted a combination of 16 and 18 (27, 7%) and

16 and 39 (5.2%). Among the elderly to the presence of HPV type 16 was more common (77.7%), 31 (16.6%) and 52 (5.5%), the combination was observed in 20% (16 and 31) type.
Conclusion: Thus, infection with all types of viruses with cancer of the vulva is for young 71.87%, and 22% for older, more often among patients with a virus found HPV DNA − the young to 56.2%, and 15% in the elderly. Our data confirm the importance of infection, especially HPV in the pathogenesis of cancer of the vulva.
No conflict of interest.

3071 POSTER

Prognostic value and importance of CIP2A as a therapeutic target: Rethinking the use of conventional chemotherapy drugs for the treatment of ovarian cancer

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Background: Epithelial ovarian cancers represent the leading cause of death in women with gynaecologic cancers. The development of acquired resistance to current first-line Taxane and Platinum-based chemotherapy agents is common and a strong motivator for the development of therapeutic approaches that combines targeted drugs and cytotoxics in a more effective manner. The cancerous inhibitor of protein phosphatase 2A (CIP2A) is a novel oncogene overexpressed in many solid human cancers. Recently, CIP2A was found to correlate with reduced survival and parameters associated with high grade disease in many human cancers, including ovarian cancer. Here, we demonstrate that chemo-resistant ovarian cancer cells are sensitized to conventional chemotherapeutic drugs following inhibition of CIP2A.
Methods: A library of conventional chemotherapeutic agents targeting different parts of the human kinome, were screened to identify synthetic lethality with CIP2A depletion in a panel of ovarian cancer cell lines (Hey, Skov-3, Ovcar-8, Ovcar-3 & Caov-3). Gene silencing was done by small interference RNA (siRNA). CIP2A depleted cell lines were developed via lentiviral transduction of cells with shCIP2A. Cell viability and signal transduction analysis was assessed by CTG assay and Western blot. The *in vivo* assessment of CIP2A depletion and treatment with these chemotherapy drugs in xenograft mouse models is in progress. Potential side-effect profiles were determined by examining the consequences of combined CIP2A inhibition and chemotherapy treatment *in vivo* using the CIP2A deficient mouse model.
Results: First-line adjuvant chemotherapy agents, Cisplatin and Paclitaxel, had little effect on the inhibition of cell viability of chemo-resistant ovarian cancer cell lines, consistent with previous reports. The depletion of CIP2A however, significantly sensitized these cell lines to a number of chemotherapeutic agents including Cisplatin and Paclitaxel. We have also identified new therapeutic strategies for the treatment of CIP2A null ovarian cancer cells.
Conclusion: CIP2A is a novel oncogene, previously shown to be a marker of poor outcome in ovarian cancer patients, including the subset of patients currently receiving first-line adjuvant chemotherapy treatment. Our results demonstrate a new therapeutic strategy for the treatment of CIP2A depleted ovarian cancer cells and highlight the potential value of patient stratification based on tumor expression of CIP2A.
No conflict of interest.

3072 POSTER

Molecular analysis of endometrial endometrioid adenocarcinomas based on estrogen receptor, progesterone receptor, and HER2 expression: A proposal for novel classification of endometrioid adenocarcinomas

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Background: Endometrial cancer comprises about 4% of cancers in women worldwide, with a higher incidence in developed countries. The American Cancer Society estimated that endometrial cancer was the fourth most common cancer diagnosed and the eighth leading cause of cancer deaths in women in 2010. And there are two main clinicpathological variants of endometrial carcinoma. type 1 tumor are low grade and estrogen-related endometrial endometrioid adenocarcinomas (EEA). On the other hand, type 2 tumors are non-ECC unrelated to estrogen stimulation. Non-EEA are usually serous and clear cell carcinomas. In recent yaer, status of estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) is key to clinical management in breast cancer. Molecular subtype of breast cancer based on ER, PgR and HER2 plays crucial roles in the treatment. However, in endometrioid adenocarcinoma (EA) which is the same estrogen-dependent tumor, neither such examination nor classification have been considered. In this study, our aim was to examine clinicopathological and molecular pathological findings of EAs according to their ER, PgR, and HER2 expression status in order to propose a comprehensive classification system for EAs.
Material and Methods: 83 EAs cases were analyzed for genetic alteration and immunohistochemistry, usingtumor cell isolated by both conventional technique and the crypt isolation method. Using immunohistochemistry, subtype definitions were as follows: Type A (ER+ and/or PgR+, HER2−), Type B (ER+ and/or PgR+, HER2+), Type C (ER−, PgR−, HER2+), Type D (ER−, PgR−, HER2−). And we examined MSI, methylations, LOH and mutation of *K-RAS*, *BRAF* and *PIK3CA* according to each subtypes.
Results: In immunohistochemistry, subtype were defined as follows: Type A (ER and/or PgR+, HER2−), Type B (ER and/or PgR+, HER2+), Type C (ER/PgR−, HER2+), Type D (ER/PgR−, HER2−). Altough loss of *PTEN* expression was commonly found in all subtypes, the frequency (frq) of *PTEN* expression of Type C was lower than that of others. *K-RAS* mutation was found more frq in Type C, and *PIK3CA* mutation was more common in Type A and B. The frq of LOH-high status in Type C and D was significantly higher than in Type A and B.
Conclusion: The classification of subtypes based on ER, PgR and HER2 in EAs were characterized by each different molecular abnormality and may be helpful to molecular targeted therapy like breast cancer.
No conflict of interest.

3073 POSTER

In situ estrogen metabolism in subgroups of obese women with differing potential risk for developing endometrial cancer

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Background: Enhanced endometrial proliferation correlates obesity to type-I (estrogen dependent) endometrial cancer (EC). Hypothezing that not all obese women develop EC and this is due to differing endometrial proliferation through impaired endometrial estrogenic metabolism, our laboratory previously identified cycling obese women *without EC* with differing endometrial proliferation levels: Obese High Proliferating (O_{HP}) and Obese Low Proliferating (O_{LP}).
Objective: To assess endometrial expression of estrogen metabolic enzymes, 17β-hydroxysteroid dehydrogenase (17β-HSD) type 1 and 2, aromatase, steroid sulfatase (STS) and estrogen sulfotransferase (EST), and the endometrial levels of 17β-estradiol (E2), estrone (E1) and estrone sulfate (E1-S) in the aforementioned subgroups of obese women.
Materials and Methods: The endometrial tissue samples were obtained from from cycling women in the proliferative phase (without type-I EC) with body mass index (BMI) = 18–24.9 kg/m^2 (normal-weight, N, n = 27), BMI $\geqslant$30 kg/m^2 (obese, O_{HP}, n = 28; O_{LP}, n = 15) and obese women with type-I EC (n = 25). Endometrial expression of estrogen metabolic enzymes was measured by immunohistochemistry. Endometrial E2, E1, E1-S levels were determined by radioimmunoassay. Institutional and Health Service Review Boards approved this study before its execution. Informed written consent was obtained before surgery for all patients.
Results: O_{HP} demonstrated increased endometrial expression of 17β-HSD1/17β-HSD2 (30%, $P<0.05$) and aromatase (60.4%, $P<0.05$), and higher endometrial E2 level (26%, $P<0.05$) compared with O_{LP} group. The O_{HP} did not differ from O_{LP} group in endometrial expression of STS and EST or in E1 and E1-S levels. The O_{LP} and normal-weight groups had similar 17β-HSD1/17β-HSD2 ratio, aromatase expression and endometrial E2 levels. Interestingly, obese women with type-I EC possessed similar aromatase and 17β-HSD1/17β-HSD2 expression as O_{HP}.
Conclusions: These data suggest that the 17β-HSD and aromatase pathways may produce higher local concentrations of E2 in the O_{HP} group, and thus explain the higher endometrial proliferation observed in this group. Our data may help identify obese women more susceptible to develop type-I EC, allowing early intervention and a potential reduction in mortality. (FONDECYT 1110232).
No conflict of interest.

3074 POSTER

Integrin alpha(v) beta(3) expression in premalignant and malignant lesions of the uterine cervix

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Cervix cancer has a high prevalence in Brazil, representing 10% of all malignant diseases in women. For the year of 2013 there is an estimative of 17,540 new cases of cervix cancer in Brazil. A high rate of women with locally advanced disease will recur after primary treatment with chemoradiation, and there are only few therapeutic options available for the recurrent setting. Therefore, there is a need to study new therapeutic targets as well as new prognostic factors for cervix cancer. Preclinical studies showed that the expression of several integrins are associated with neoplastic cellular invasion, angiogenesis and carcinogenesis.

Objectives: To evaluate the expression of alpha(v) beta(3) integrin in premalignant and malignat lesions of the uterine cervix and to associate its expression with the outcome of patients with cervix cancer.

Methods: A retrospective cohort study was performed in the Pathology Unit of Hospital Sao Vicente and in the Pathology Institute of Passo Fundo, Southern Brazil. Archives of patients with premalignat or malignant lesions of the cervix diagnosed from 2001 to 2008 were reviewed and their paraffin-embedded blocks were selected. Immunohistochemistry (IHC) was performed with the specific alpha(v) beta(3) (a_Vb_3) mouse monoclonal antibody BV3 (Abcam, Inc. Cambridge, MA) with a dilution of 1:400. Two gynecologic pathologists independently analyzed the results.

Results: It was possible to obtain clinical and pathological data from 146 patients. The interobserver kappa concordance for the IHC results was 0.808 ($p < 0.05$). The a_Vb_3 integrin was expressed in only 22 cases (15.06%). From these positive cases, 45.5% had the diagnosis of premalignant lesion and 54.5% of cervix cancer. There were no differences in disease-free survival for patients with cervix cancer with a_Vb_3 expression compared to those without expression.

Conclusions: There was no association of a_Vb_3 integrin expression with the outcome of patients with cervix cancer.

No conflict of interest.

3075 POSTER

ERBB signaling network in endometrial cancer − determination of clinical significance

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Background: Dysregulation of the ERBB signaling network occurs in many human cancers and is implicated in more aggressive tumor behavior. Data about the family of those four receptor tyrosine kinases in endometrial cancer (EC) are scarce. Results obtained by our team showed *ERBB* gene aberrations to correlate with more aggressive disease characteristics. In order to investigate ERBB family further in the context of EC, we aimed to determine clinical significance of ERBB expression on the protein level.

Material and Methods: The study group included 406 consecutive staged I−IV endometrial cancer patients treated between 2000 and 2010. ErbB1, ErbB2, ErbB3 and ErbB4 protein expression was examined by immunohistochemistry (IHC) on tissue-microarrays (TMA), using the following antibodies: anti-EGFR, clone EGFR113 (Novocastra); anti-HER-2/neu, clone 4B5 (Roche); anti-HER3, clone DAK-H3-IC (Dako); anti-ErbB4, clone HFR1 (Abcam). IHC results were compared with *ERBB1*, *ERBB2*, *ERBB3*, *ERBB4* gene dosages measured by SYBR-Green-based qPCR assay in 107 matching fresh frozen tumor samples.

Results: Out of the studied samples 167 (41%) were classified as ErbB1-positive, 145 (37%) as ErbB2-positive, 143 (35%) as ErbB3-positive and 228 (56%) as ErbB4-positive. Protein expression levels of all the four receptors correlated with each other, with the weakest and strongest correlation for ErbB2 vs. ErbB3 ($p = 0.013$) and ErbB1 vs. ErbB3 ($p<0.00001$), respectively. ErbB2 overexpression correlated with higher stage of the disease ($p = 0.001$) and histology type II ($p = 0.03$) but not with grading. IHC results of ErbB1, ErbB3 and ErbB4 did not reach statistical significance when juxtaposed with the aforementioned characteristics. Higher stage of the disease correlated with gene aberrations of *ERBB2* ($p = 0.004$) and *ERBB3* ($p = 0.00005$) while grading − with *ERBB1* ($p = 0.00005$) and *ERBB3* ($p = 0.03$). Histology type II was associated with amplification of *ERBB1* ($p = 0.00001$) and *ERBB3* ($p = 0.01$). Aberrations of *ERBB4* were not statistically significant. No correlations were found between protein expression levels and gene dosages.

Conclusions: Out of the studied receptors, ErbB2 protein level seems to carry the most useful information. No correlation between protein expression and DNA aberrations has been found. Examined genes, but not necessary their products, play a crucial role in the progression of endometrial carcinoma. Therefore, qPCR should be considered the method of choice in ERBB status determination.

No conflict of interest.

3076 POSTER

[18F]Fluorodeoxyglucose PET and Volumetric CT analysis are early biomarkers of survival in platinum-sensitive relapsed ovarian cancer − a multicentre trial

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Background: The activity of novel agents in relapsed ovarian cancer (OC) is assessed by reduction in tumour size, and increased progression-free (PFS) and overall survival (OS). However, early tumour response (measured by RECIST) correlates poorly with both PFS and OS. To inform future trial design, we evaluated FDG-PET and volumetric CT as early biomarkers of response and predictors of PFS and OS in relapsed OC.

Patients and Methods: This 2-centre trial (MK-0000-143, NCT00959582, sponsor Merck & Co) enrolled women aged >35 with platinum-sensitive (defined as >6 month progression-free interval since prior platinum-based treatment) relapsed OC, scheduled to receive standard-of-care platinum-based chemotherapy. FDG-PET and volumetric CT were performed at baseline, end-of-cycles (EoC) 1, 2 and 6 of chemotherapy. A volumetric CT was performed at week 40. Evaluable patients required $\geqslant$1 lesion with both SUV $\geqslant$2.5 (baseline FDG-PET) and longest diameter $\geqslant$1.5 cm (baseline volumetric CT). Blinded, independent reporting of all images was performed by site investigators and an external imaging CRO. Primary endpoints were 1) concordance of metabolic non-response, defined as <20% decrease in FDG uptake (SUVmean, SUVmax) compared to previous scan, during first 2 cycles of chemotherapy and 2) 40 week PFS rate in EoC1 metabolic responders and non-responders. Secondary endpoints included association between changes in tumour volume and both FDG-PET changes and OS, and the test-retest reproducibility of FDG-PET in relapsed OC.

Results: 43 patients, median age 62, were enrolled. 37 had post-baseline scans and 21 had baseline reproducibility scans. 36/37 have progressed (median PFS 268 days, 40 week PFS rate 0.31) and 21/37 have died (median OS 472 days, 40 and 52 week OS rates 0.94 and 0.66 respectively). The concordance in metabolic non-response rate between EoC1 and EoC2 was 100% (6/6) and 86% (6/7) for SUVmean and SUVmax respectively. There was no significant association between 40-week PFS rate and decreases in SUV parameters at EoC1 and EoC2. By contrast, statistically significant associations between OS and decreases in SUV, tumour diameter and tumour volume at both EoC1 and EoC2 were detected.

Conclusions: In women with relapsed OC receiving platinum chemotherapy, changes in both FDG-PET and volumetric CT after 1 and 2 cycles of treatment are significantly associated with greater OS. These imaging methods may have utility as biomarkers in future trials.

Conflict of interest: *Other substantive relationships: R. Lam and R. Iannone are employees of Merck and Company. P.D. Mozley was an employee of Merck and Company*

3077 POSTER

Tumour-associated inflammatory cytokines are reduced following primary platinum-based chemotherapy in plasma of high-grade serous ovarian cancer patients

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Background: Complete remissions in response to platinum-based first line chemotherapy in patients with advanced stage high-grade serous ovarian cancer (HGSC) are rare. Relapses are frequent even after optimal debulking surgery and chemoresistance ultimately occurs in the majority of FIGO stage IIIC and IV patients. Cancer related inflammation in the microenvironment of peritoneal metastases is tumour-promoting and contributes to chemoresistance. Interleukin 6 (IL-6), tumor necrosis factor α (TNFα) and Interleukin 8 (IL-8) are major components of an autocrine cytokine network in ovarian cancer with paracrine actions on angiogenesis and infiltration of myeloid cells. It is currently unknown how standard chemotherapy influences the production of these cytokines in patients.
Material and Methods: Plasma samples were collected from HGSC patients with ethical permission and informed consent. Inflammatory cytokines (IL-6, TNFα and IL-8) were measured in patients prior to any treatment (chemotherapy or debulking surgery, n = 12) and in patients who had received 3−4 cycles of platinum-based neoadjuvant chemotherapy (n = 21). Inclusive in these were eight patients where matched pre- and postchemotherapy samples were available. Meso Scale Discovery (MSD®) electrochemiluminescence assays were performed to measure the cytokine levels.
Results: Pre-treatment levels of IL-6 and TNFα were significantly elevated compared to controls ($p < 0.05$). After 3−4 cycles of chemotherapy plasma levels of IL-6, TNFα and IL-8 were significantly lower compared to pre-treatment samples ($p < 0.001$, $p < 0.01$ and $p < 0.05$ respectively). Also in the matched pre- and post-chemotherapy samples the mean of the cytokines decreased significantly ($p < 0.01$, $p < 0.05$ and $p < 0.05$ respectively).
Conclusions: Key cytokines of cancer related inflammation are elevated prior to treatment in the plasma of HGSC patients and come down after neoadjuvant chemotherapy closer to values of controls. Correlation to tissue immune cell subsets is warranted to see whether there might be a window of opportunity for immunotherapies to support anti-tumour immune responses.
No conflict of interest.

3078 POSTER

Clinical phase I/IIa study with TERT and survivin double loaded dendritic cell vaccine for patients with advanced ovarian cancer: Focus on safety and immunological proof of concept results

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Background: Ovarian cancer is still characterized by a high unmet medical need with high recurrence and mortality rates after initial good responsiveness to surgery and chemotherapy. Dendritic cells (DC) can be processed to be used as cancer treatment vaccines. Patients at early stages or after successful first line therapy, who carry minimal residual disease (that nevertheless leads to recurrence with high probability) as it is the case for ovarian cancer, seem ideal candidates for the proof of concept of DC treatments.
Material and Methods: Data are presented from the clinical phase I/IIa trial with Eudract no 200800383726, short LRT-I-L01-Ovar, and sponsor Life Research Technologies. For vaccine preparation monocytes were collected via apheresis, matured into DCs and pulsed with two universal tumor associated antigens (uTAA) in our GMP facility. DCs were loaded with TERT and survivin via two different pathways (mRNA and peptide) to elicit $CD8^+$ and $CD4^+$T cells directly. Endpoints of the study were tolerability and safety, immunological and clinical responses. Vaccine specific T cell responses were evaluated by cytokine bead array and intracellular staining assays.
Results: 15 patients with advanced ovarian cancer were enrolled 8 weeks after first-line standard treatment with last patient out Dec 2012. Each patient was vaccinated intradermally on a weekly or fortnightly basis with a maximum of 8 doses of $13*10^6$ double loaded DCs. The majority of treatment related side effects were grade 1 fever and erythema. Overall the therapy was well tolerated. Immune response data is available for 14/15 patients, 1 was withdrawn after the first administration. Highly significant immune responses specific to the vaccine will be presented in detail. The positive response frequency of more than 90% is remarkably high for this kind of treatment and is proven for both uTAAs in CD8+ as well as CD4+ T cells. A clear positive trend in progression free survival is demonstrated compared to matched historical control.
Conclusions: Therapy with our unique double loaded DC vaccine was feasible, safe and well-tolerated by patients. The novel DC-based vaccine was immune stimulatory with high significance and elicited both, long-term and short-term anti-tumor immune responses. Overall these results establish a promising platform for immune therapy for ovarian cancer and all solid tumors in general with the final goal to delay or even prevent recurrent and metastatic disease.
No conflict of interest.

3079 POSTER

Anti-tumour efficacy of the PI3K inhibitor GDC0941, the dual PI3K/mTOR inhibitor GDC0980 and the MEK inhibitor GDC0973 as single agents and in combination in endometrial carcinomas

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Background: The phosphoinositide-3 kinase (PI3K) pathway is commonly activated in cancer, including endometrial cancer (EC) due to mutations at multiple nodes, for example *PIK3CA,* or loss of expression of PTEN. Additionally, we and others have shown that, in EC, mutations in the RAS/RAF/MEK/MAPK pathway and the PI3K pathway frequently co-exist. Here, we examined the hypothesis that interaction between PI3K and RAS/RAF/MEK/MAPK pathway mutations is important in determining responsiveness of EC to therapies targeted to these pathways.
Methods: We used a large panel of genetically defined EC cell lines (n = 16, with diverse genetic backgrounds) to identify the anti-tumour effects (using IC_{50} values derived from viability assays) of a PI3K inhibitor GDC0941, a MEK inhibitor GDC0973 and a dual PI3K/mTOR inhibitor GDC0980 as single agents and in combination. We subdivided 16 endometrial cancer cell lines into 4 groups according to the mutational status of *PIK3CA*, *PTEN*, and *KRAS*: group 1 (n = 2), cell lines with *PIK3CA* mutations only; group 2 (n = 9), cell lines with *PTEN* mutations (+/−*PIK3CA* mutations) and wild type for *KRAS*; group 3 (n = 3) all cell lines with *KRAS* mutations; group 4 (n = 2), cell lines wild type for *PIK3CA*, *PTEN* and *KRAS*.
Results: We observed that the cell lines in groups 1 ($p = 0.02$) and 2 ($p = 0.04$) but not group 4 ($p = 0.77$) are significantly more sensitive to GDC0941 than cell lines in group 3. Group 2 cell lines with *PTEN* mutations without *KRAS* mutations and group 4 cell lines are significantly more resistant to the MEK inhibitor GDC0973 than cell lines in either group 1 ($p = 0.0007$, 0.008, respectively) or group 3 ($p < 0.0001$, =0.002, respectively) (surprisingly, IC_{50} values for GDC0973 were not significantly different between cell lines in groups 1 and 3, p=0.1). Both the combination of the PI3K inhibitor GDC0941 with the MEK inhibitor GDC0973 (CI from 0.03 to 0.19) and the combination of the dual PI3K/mTOR inhibitor GDC0980 with the MEK inhibitor GDC0973 (CI from 0.13 to 0.30) demonstrated significant synergy in cell lines in groups 1 and 2. While both combinations also showed strong synergism in group 3 cell lines also possessing *PIK3CA* or *PTEN* mutations, group 3 cell lines with *KRAS* mutations only demonstrated strong antagonism (CI>10).
Conclusions: Our data suggest that the mutational status of *PIK3CA*, *PTEN* and *KRAS* can be used as biomarkers to select patients for PI3K and RAS/RAF-targeted therapies. Further, the combinations of the PI3K inhibitors GDC0941 and GDC0980 with the MEK inhibitor GDC0973 are promising approaches for the treatment of patients with *PIK3CA*, *PTEN* and KRAS-mutated EC. Surprisingly, *PIK3CA*-mutated group 1 EC cell lines were as sensitive to the single agent MEK inhibitor GDC0973 as group 3 cell lines with *KRAS* mutations.
No conflict of interest.

3080 POSTER

CYP2D6*4 Polymorphism: A prognostic value in advanced ovarian cancer?

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Background: The survival of patients with ovarian cancer (OC) stands at 45 % at 5 years despite advances in surgery and chemotherapy. Pegylated liposomal doxorubicin (PLD), is a nucleolar non-selective class I anthracycline that inhibits both DNA and nucleolar RNA synthesis. This agent is a DNA-intercalating agent that inhibits topoisomerase-II, is widely

applied in advanced stages of the disease, in particular group of patients platinum-resistant.
Cytochrome P450 2D6 (CYP2D6) is an important enzyme involved in the metabolism of innumerous therapeutic drugs and its activity is mainly determined by the presence of genetic polymorphisms, as *CYP2D6*4* polymorphism (rs3892097). Individuals carrying two non-functional alleles of the *CYP2D6*4* polymorphism lack CYP2D6 activity whereas the presence of two functional alleles give rise to a normal enzymatic activity. The aim of this study was to evaluate the influence of *CYP2D6*4* polymorphism as prognostic factor in patients with OC.
Material and Methods: DNA was extracted from peripheral blood of 188 patients diagnosed with advanced OC (FIGO stage III and IV) submitted to chemotherapy. The characterization of *CYP2D6*4* genotypes was genotyped by Taqman® Allelic Discrimination methodology. Overall survival (OS) was the endpoint of this analysis and survival data were analyzed according to CYP2D6*4 polymorphisms' genotypes.
Results: The frequencies obtained for the CC, CT and TT genotypes were 71.28%, 23.40% and 5.32% respectively. The *CYP2D6*4* polymorphism genotypes were grouped as CC genotype and T carrier genotypes. Our results demonstrate that women with advanced OC (stage III and IV) and carriers of the T allele present a decreased overall survival (34 vs 64 months; $p = 0.005$; log-rank test).
Conclusion: CYP2D6 shows great importance in a metabolic level and is greatly studied in the field of translational research. Our results exhibit an association between *CYP2D6*4* and overall survival in patients with advanced stages. LPD plays a central role in the treatment of OC patients platinum-resistant. The interindividual variation in LPD metabolism may have implications on the toxicity and potentially efficacy of the drug, making it critical to understand the pharmacogenetics and pharmacokinetics of the drug. These results could help in the prediction and monitorization of patients, with advanced OC, platinum-resistant and to define the role of this genetic variant in the pharmacogenomic profile of OC.
No conflict of interest.

3081 POSTER

Silver-enhanced in situ hybridization (SISH) for detection of CCNE1/URI amplification in ovarian cancer

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Background: CCNE1, coding cyclin E, is a potential target for ovarian cancer treatment. CCNE1 and URI are part of the frequent genomic amplification site on 19q12 in ovarian cancer, but URI may have more functionality in ovarian tumorigenesis than CCNE1. Purpose of the study was the establishment of a silver-enhanced in situ hybridization (SISH) technique for automated detection of CCNE1/URI. The CCNE1/URI status was further compared with clinico-pathological factors and patient outcome.
Material and Methods: Development and validation of a dual SISH assay for detection of CCNE1/URI copy numbers and Chromosome 19 as a surrogate on ovarian cancer samples using VENTANA BenchMark XT Platform and conventional bright field microscopy. The concordance of the novel probe for SISH was compared with URI amplification status previously assessed by fluorescence ISH (FISH) as well as Cyclin E immunohistochemistry. Dual SISH and Cyclin E immunohistochemistry was applied to a cohort of 136 epithelial ovarian carcinomas.
Results: SISH technique was established for detection of CCNE1/URI amplification and shows a high concordance with known URI amplification by FISH ($p < 0.001$). CCNE1/URI amplification correlates with high Cyclin E expression levels in ovarian cancer ($p < 0.001$). CCNE1/URI amplification was observed in 18% of the ovarian carcinomas and was associated with higher tumor grade and advanced FIGO stage. There was also a trend for a slightly worse survival for the amplified cases.
Conclusion: Our results show that SISH with the novel CCNE1/URI probe is feasible to reliably detect CCNE1/URI amplification. This assay may serve to monitor CCNE1/URI amplification status in patients with ovarian cancer, which may benefit from CCNE1 (Cyclin E) targeted therapies.
Conflict of interest: *Other substantive relationships: The Institute of Pathology (University Hospital Zurich) received research funds from Ventana Medical Systems, Inc.*

3082 POSTER

First evidence and experience of patient-derived xenograft models for endometrial cancer

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Background: Endometrial cancer is the most frequent malignancy of the female genital tract. Treatment modalities are limited for primary advanced and recurrent disease. Development of new treatment strategies is therefore warranted but may be hampered by the lack of representative pre-clinical *in vivo* models. Patient-derived tumor xenograft (PDTX) models appear to have better retention of the morphological and molecular markers of the source tumors, despite serial passages across several generations of mice. In our study, we here present preliminary data on the establishment and characterization of these PDTX models for endometrial cancer.
Materials and Methods: We established PDTXs of different histological subtypes of endometrial cancer. After written informed consent of the patient and within 1 h after surgery, tumor samples were implanted s.c. in NOD-SCID mice (F1 generation). When ~1000 mm^3, tumors were retransplanted in NOD-SCID and/or nude mice. Validation and comparison with the original patient's tumor was performed by histological and genetic analyses.
Results: For engraftment, a current success rate of ~50% is reached, which is comparable to other tumor types. In particular, 18 PDTX models, of different histological subtypes (endometrioid, serous, carcinosarcoma, undifferentiated carcinoma), were initiated, of which 7 were successful (i.e. tumor growth in at least F1-F2). Five PDTX models were categorized as 'failed' since no tumor growth was observed 8 months after implantation. Six other PDTX models were only recently initiated. Tumor growth rate in F1 xenografts was generally slower than in the subsequent generations (F2, F3, . . .). A protocol for re-implantation of cryopreserved xenografts was successfully optimized. Histological analyses showed that general tumor morphology (by H&E staining), proliferation capacity (Ki-67), hormone receptor status (ER, PR) and PTEN status remained similar in F1-F2-F3 xenografts as compared to the original patient tumor. Hotspot mutation profiling showed that mutations present in the original tumor were also observed in the xenograft tumors and no additional mutations in the xenografts were identified. Finally, we successfully evaluated the *in vivo* responsiveness to standard chemotherapy and a PI3K − mTOR inhibitor, BEZ-235, in one of the established models.
Conclusion: We here show first evidence for the establishment of PDTX models for endometrial cancer that can be used for future preclinical drug evaluation.
No conflict of interest.

3083 POSTER

Identifying predictive biomarkers of carboplatin resistance in ovarian cancer

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Background: Ovarian cancer is the most lethal gynecological cancer. Besides surgery, paclitaxel and carboplatin chemotherapy represent the primary treatment option. Platinum resistant cancer recurs in approximately 25% of patients within six months. There is no clinically applicable predictive biomarker of platinum resistance. Our aim was to identify such biomarkers.
Materials and Methods: We have set up a databank of ovarian microarray datasets containing treatment and response information of the patients. For this, we searched GEO and TCGA to identify datasets suitable for the analysis of the effect of the expression change of each gene on therapy response. We performed receiver operating characteristic (ROC) analysis in R for all genes and then ranked them based on the area under the curve (AUC) values. We identified the most promising candidates and compared these to the available literature. Then, eight genes were selected for in vitro functional validation including JRK, CNOT8, RTF1, CCT3, NFAT2CIP, MAP2K1, FUBP1 and CSDE1. We performed gene silencing with simultaneous 48 h carboplatin administration in four epithelial ovarian cancer cell lines (SKOV-3, CAOV-3, ES-2, and OVCAR-3), to evaluate the effect of the genes in carboplatin resistance with MTT viability assay.
Results: We identified 1267 patients in 8 datasets meeting our criteria in GEO and TCGA. The average progression free survival is 24.8 months with 731 progressions. 1152 patients received a platinum-based chemotherapy and 631 received taxol (614 patients received both taxol and platinum). The ROC values of the selected genes were JRK (0.625), CNOT8 (0.610),

RTF1 (0.620), CCT3 (0.620), NFAT2CIP (0.612), MAP2K1 (0.611), FUBP1 (0.608) and CSDE1 (0.605). The expression change of JRK ($p = 0.0002$), MAP2K1 ($p = 0.0117$) and CNOT8 ($p = 0.0036$) were significantly correlated with progression free survival. JRK was not expressed in the cell lines. The silencing of RTF1, FUBP1 MAP2K1, CSDE1 and CNOT8 caused significant sensitization in each cell line. Greatest sensitizing effect (compared to negative control siRNA treated cells) and p values are: RTF1:19.7% p= 5E-07, FUBP1: 31.7% p=3E-03, MAP2K1: 16.9% p=1E-03, CSDE1: 23.3% p=4E-04, CNOT8: 16.7% p=9E-07).
Conclusion: We identified potential biomarkers of carboplatin response on a large patient cohort and in vitro validated the effect. Expression of RTF1, FUBP1 MAP2K1, CSDE1 and CNOT8 correlated to platinum resistance in ovarian cancer.
No conflict of interest.

3084 POSTER

Clinical outcome of BRCA1-associated epithelial ovarian cancer: Significance of the 4153delA and 5382insC mutations

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Background: The impact of the mutations in the *BRCA1* gene on the clinical outcome of epithelial ovarian cancer has been extensively investigated, and despite some conflicting results, most recently published studies have reported higher survival rates for *BRCA1*-associated ovarian cancer patients. Due to the genotype-phenotype correlation effect, carriers of *BRCA1* mutations in different regions of the *BRCA1* gene have different risks for developing breast and ovarian cancer. Moreover, breast cancer patients who are carriers of the 4153delA mutation have a poorer clinical outcome than carriers of the 5382insC mutation. However, the correlation of individual *BRCA1* mutations with the survival rates of epithelial ovarian cancer patients has not yet been fully investigated.
Methods: Ovarian cancer patients carrying the three most prevalent *BRCA1* mutations in Latvia (300T/G, 4153delA and 5382insC) were screened at the Institute of Oncology of Riga Stradins University as part of a nationwide case-control study. Patients who were diagnosed with primary ovarian cancer from 2005–2011 and who underwent mutational analysis before or within 6 months following surgery were included in the study.
Results: Out of 196 patients, 91 had BRCA1 mutations: 4153delA(n = 45), 5382insC (n = 46). The mean estimated survival time was 41.6 months among carriers (36.4 and 46.4 months among 4153delA and 5382insC mutation carriers, respectively), and 36.1 months among non-carriers. The overall survival of the 5382insC mutation carriers was significantly better than both 4153delA mutation carriers($\chi^2 = 4.09$, DF=1, $P = 0.043$)and non-carriers ($\chi^2 = 7.14$,DF=1, $P = 0.008$). The difference in overall survival between the 4153delA mutation carriers and non-carriers was not statistically significant. A multivariable analysis revealed that the 5382insC mutation remains an independent predictive factor of improved survival for epithelial ovarian cancer patients.
Conclusions: Specific mutations within the *BRCA1* gene can have different impacts on the clinical outcome of epithelial ovarian cancer. Further clinical studies are needed to determine the significance of various ovarian cancer treatment options for carriers of individual *BRCA1* mutations located in different parts of the *BRCA1* gene.
No conflict of interest.

3085 POSTER

A redistribution of resistance and sensitivity to platinum according to the observation period after the treatment of epithelial ovarian cancer

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Background: In epithelial ovarian cancer (EOC), platinum-resistant/sensitive relapse is divided into 2 categories: platinum-resistant/sensitive EOC relapse less than 6 months after the completion of the initial treatment and that at 6 months or later following the completion of the initial treatment. This study evaluated the justification for setting the boundary of the treatment-free interval (TFI) at 6 months.
Materials and Methods: Of 405 patients with stage III/IV disease, 107 with relapsed or recurrent disease after attaining a clinical complete response with first-line regimen were assessed retrospectively. The degree of platinum sensitivity was calculated by comparing progression-free survival (PFS) values.
Results: The median TFI in in relapsed patients was 11.5 months. In serous/endometrioid groups treated with platinum after relapse, there were significant differences in PFS between patients who relapsed <6 months and those who relapsed between 6−12 months, and between those who relapsed between 6−12 months and those who relapsed between 12−18 months, and between those who relapsed between 12−18 months and those who relapsed $\geqslant$18 months. There were no significant differences in PFS between patients who relapsed <6 months and those who relapsed between 6−12 months, while there were significant differences in PFS between those who relapsed between 6−12 months and those who relapsed $\geqslant$12 months in clear cell/mucinous adenocarcinoma groups treated with platinum after relapse. PFS of patients who relapsed $\geqslant$12 months in clear cell/mucinous adenocarcinoma groups was significantly shorter compared with that of those who relapsed $\geqslant$12 months in serous/endometrioid adenocarcinoma groups, and similar to that of those who relapsed between 6−12 months in serous/endometrioid adenocarcinoma groups.
Conclusions: It might be rational to classify patients who relapsed <12 months as platinum resistant and patients who relapsed $\geqslant$12 months as platinum sensitive in clear cell/mucinous adenocarcinomas.
No conflict of interest.

3086 POSTER

Living between anxiety and hope: the experiences of women with vulvar intraepithelial neoplasia during their course of illness − a qualitative study

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Background: The vulvar intraepithelial neoplasia (VIN) is a uncommon chronic skin condition which can progress to an invasive carcinoma of the vulva. The most frequent issues affecting women's health were described as occurring symptoms, negative influences on sexuality, changes in the body image and uncertainty concerning the illness progression. Despite this, there is little known about the lived experiences during the course of the illness. Thus, the aim of this study was to describe the lived experiences of women with VIN during the course of illness.
Methods: This study is a secondary data analysis of a foregoing qualitative study. We analyzed eight narrative interviews with women with VIN by using thematic analysis in combination with critical hermeneutics.
Results: A sense of 'hope and fear' was essential for women with VIN during their course of illness. This constitutive pattern reflects the fear of recurrence as well as the trust in healing. The eight narratives showed that women's lived experiences during the course of illness occurred in five phases: 1) 'there is something unknown', 2) 'one knows, what IT is', 3) 'IT is treated and should heal', 4) 'IT has effects on daily life' and 5) 'meanwhile it works'. Furthermore, women's lived experiences were particularly influenced by a feeling of 'embarrassment' and by 'dealing with professionals'.
Conclusion: Current care seems to lack adequate support for women with VIN in order to manage these five occurring phases. Based on our study and the international literature we suggest, that new models of counseling and providing information (such as the WOMAN-PRO II *program*) for women with VIN need to be developed and evaluated.
No conflict of interest.

3087 POSTER

Experimental development of a new antitumor drug for the use in high-dose chemoperfusion treatment

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Background: Nowadays in the Russia morbidity of ovarian cancer is 2.5% of the overall malignancies morbidity and 4.6% of gynecologic tumors. Intraperitoneal chemoperfusion (IPEC) is currently considered as a promising high-technology method of treatment of peritoneal carcinomatosis and tumor ascites. The purpose of the study is development of new antineoplastic drug from group of alkylating agents (ethylenimines)

named dioxadet for the use in high-dose IPEC treatment. It is earlier established that dioxadet is more safety that platinum drugs.
Materials and Methods: Ovarian cancer cells were transplanted intraperitoneally in 90 Wistar female rats. We used dioxadet in doses 1.5 mg/kg for single intraperitoneally injection and 30 mg/kg for normothermal IPEC. In the comparing group we applied cisplatin in doses 4 mg/kg for single intraperitoneally injection and 40 mg/kg for normothermal IPEC. Both drugs were administered 48 hours after the intraperitoneal tumor transplantation. In rats of control group saline solution was administered intraperitoneally (0.5 ml) and in the normothermal IPEC (200 ml). The antitumor effects of the drugs were estimated by median survival time (MST) and increasing life span of rats.
Results and Discussion: In the control group MST was 9.0 days. Single intraperitoneal injection of dioxadet increased MST by 128% (MST=20.5, $p = 0.001$) as well as cisplatin increased MST by 117% (MST=19.5, $p = 0.008$) compared with the control group. In normothermal IPEC dioxadet and cisplatin had the most significant cytostatic effects. Increase of MST after normothermal IPEC with dioxadet was 244% (MST = 31.0, $p = 0.001$) and with cisplatin was 317% (MST = 37.5, $p \leqslant 0.001$) compared with control group. In comparison with normothermal IPEC group without drug (MST = 16.0) increase of MST with dioxadet and cisplatin were 94% ($p = 0.006$) and 134% ($p = 0.002$), respectively.
Conclusion: IPEC enhances cytostatic effects of the drugs; antineoplastic effect of dioxadet is comparable to the effect of cisplatin in normothermal chemoperfusion, while dioxadet has less local and systemic side effects than platinum drugs.
No conflict of interest.

3088 POSTER

Pre-treatment thrombocytosis and prognosis of stage III and IV ovarian cancer

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Background: Thrombocytosis has been found to be an adverse prognostic factor in many types of cancer such as breast, GI and GU. In epithelial ovarian cancer patients across all stages and histologic types pre-treatment thrombocytosis was an independent prognostic factor for overall survival. We investigated if pre-treatment platelet counts provide prognostic information in patients with advanced (stage III and IV) serous ovarian cancer which is the most common clinical presentation and type of ovarian cancer.
Methods: Platelet number on diagnosis of stage III and IV serous ovarian adenocarcinoma was evaluated in 91 patients treated in our hospital and for whom there were complete follow-up data on survival. Survival of patients with normal platelet counts (150–350 $x10^9$/L) was compared with that of patients with thrombocytosis (>350 $x10^9$/L) by x^2 and LogRank tests. Patients with other histologic types of ovarian cancer or earlier stages of disease were excluded.
Results: The median age of the patients was 66 years-old. From the 91 patients, 52 (57.1%) had normal platelet counts (median: 273 $x10^9$/L, range: 153–350) at diagnosis of their disease and 39 patients (42.9%) had thrombocytosis (median: 463 $x10^9$/L, range: 354–631). The median age of the patients with normal counts was 65 years-old (range 27 to 87) and of those with thrombocytosis was 70 years-old (range 41 to 90). In the group of patients with normal platelet counts, 24 of the 52 patients had died with a median survival of 43 months (range: 3–100) and 28 patients were alive at last follow-up with a median follow-up of 32.5 months (range: 1–140). In the group of patients with thrombocytosis, 24 of the 39 patients had died with a median survival of 23 months (range: 4−79) and 15 patients were alive at last follow-up with a median follow-up of 20 months (range: 4−69). Among the 48 patients (24 patients in each group) who had died, the 3 year survival of patients with normal platelet counts was 54.2% and of patients with thrombocytosis was 33.3%. In the entire group of 91 patients there was a statistically significant difference of the overall survival between the two groups (LogRank test $p = 0.02$).
Conclusion: In this retrospective analysis of stage III and IV ovarian cancer patients, thrombocytosis at the time of diagnosis has prognostic value regarding overall survival. Platelets are carriers of VEGF-A, TGF-β and many other active bio-molecules in their granules and their number in circulation may have implications for the amount of these factors in seeding sites, besides the mechanistic support that they provide to circulating tumor cells.
No conflict of interest.

3089 POSTER

Impact of Ki67 expression in prognostic factors and clinical outcome of endometrial carcinoma

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Background: Most decisions regarding the indication of adjuvant radiotherapy in endometrial carcinoma are based on adverse histopathological factors. In the last years there is also an increased interest in relation to the indication of adjuvant chemotherapy in early high risk endometrial carcinoma (GOG 0249 and PORTEC 3 studies are ongoing). Therefore, given the growing importance of adjuvant therapies, there is a need to count on others prognostic markers. Ki67 index is a proliferating cell nuclear marker that could be correlated with adverse factors previously known as well as with clinical outcome in patients with endometrial carcinoma.
Material and Methods: We included patients with endometrial carcinoma of endometrioid type confirmed by histology, stage IA to stage IIIC2 diagnosed between 2006 and 2012. The degree of expression of Ki67 index was evaluated by immunohistochemistry technique. We included the following measuring ranges: 0−10%, 11−49% and $\geqslant$50%. The objectives were to analyze the association between Ki67 expression with histological grade, myometrial invasion, lymphovascular invasion, cervical invasion, patient age and relapse-free survival, using the Pearson's chi-squared test and Fisher's exact test. The analysis of relapse-free survival was performed by log rank test (Mantel-Cox).
Results: 58 patients were included. A significant correlation between Ki67 and histological grade ($p = 0.001$), lymphovascular invasion ($p = 0.029$) and myometrial invasion ($P = 0.025$) was found. We did not found an association between Ki67 and age ($p = 0.303$) and Ki67 and cervical invasion ($p = 0.282$). Median follow-up was 27 months. We found an association between Ki67 and risk of relapse ($p = 0.007$). The analysis of relapse-free survival by log rank test among patients with Ki67 <50% and those with Ki67 $\geqslant$50%, showed a statistically significant difference ($p = 0.003$). Odds Ratio for relapse if Ki67 $\geqslant$50% was 11.04.
Conclusions: An association between Ki67 expression and other adverse histological factors was found. We also found a correlation between high level of Ki67 expression (>50%) and risk of relapse.
No conflict of interest.

3090 POSTER

A phase I study of multiple peptides cocktail vaccine for advanced/recurrent ovarian/cervical cancer

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Background: Despite of improvement in chemotherapy including the molecular targeting agents, advanced or recurrent ovarian cancer (A/ROC) and cervical cancer (A/RCxC) are still incurable. Some tumor associated proteins and tumor related vascular endothelial growth factor receptor 1,2 (VEGFR1, VEGFR2) were found to be candidates as new targets, and their epitope peptides which are restricted human leukocyte antigens (HLA) of A2402 and A0201 have been shown to have the ability to induce specific cytotoxic T lymphocyte (CTL) responses. We conducted a phase I study of these peptides cocktail vaccine (PCV) in patients with A/ROC and A/RCxC in order to evaluate toxicity and immunological response.
Patients and Methods: Cohorts were divided in four groups; such as HLA-A2402 positive A/ROC(A24-Ov), and A/RCxC(A24-Cx), which would cover nearly 60% in patients of Japanese female, and HLA-A0201 positive patients (A02-Ov and A02-Cx) which would cover the rest 20%. Theoretically, 80% of A/ROC and A/RCxC would be covered by theses PCV treatment. The setting of this phase I study was one arm trial according to duplicate Fibonacci method without dose modification. Eligible patients were heavily treated chemo-resistent patients with PS0−2 and normal organ functions. PCV for A24-Ov comprises FOXM1 (Forkhead Box M1), MELK(maternal embryonic leucine zipper kinase, HJURP(Holliday junction recognition protein, VEGFR1 and VEGFR2. As for A02- Ov, PCV comprises hypoxia-inducible protein 2 (HIG2), VEGFR1and VEGFR2. A24-Cx PVC comprises FOXM1, MELK, and HJURP. A02-Cx comprises HIG2 and up-regulated lung cancer 10 (URLC10). Cocktails were made at a dose of 1 mg of each peptide with GMP grade-adjuvant, MONTANIDE ISA51. Vaccination schedule included weekly subcutaneous administration for first 12 weeks, then bi-weekly administration for next 16 weeks, then further vaccination was done monthly for 8 times and 3−6 months as a maintenance step according to patient's need. Pre- and post-vaccination blood samples were obtained from the patients for toxicity assessment and immunological evaluation by ELISpot Assay.

Results: 23 patients were enrolled as for these four cohorts. Only A02-Cx cohort did not reached for 6 patients. A24-Ov, A02-OV, and A24-Cx were completed but A02-Cx has not completed yet and this cohort is going to be terminated. PCV were generally well tolerated with no major adverse events, and most of the patients developed specific CTL responses. Only Grade 1 dermatologic reactions (redness, itching, swelling, induration, pain, scaling) as non-hematologic adverse event by the agents was detected and the trials moved on phase 2 study for more 24 patients in each groups.
Conclusions: PCV for these cohorts of disease were safe and feasible and further patient accrual for phase 2 study is now on going.
No conflict of interest.

3091 POSTER

Impact of relative dose intensity (RDI) on the outcome of patients with metastatic solid tumors: A systematic review

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Background: High RDI has been associated with improved outcomes in various cancers in the curative setting, yet the impact of RDI in advanced/metastatic cancer remains unclear. We performed a systematic literature review to evaluate the impact of RDI on outcomes in patients with metastatic lung, breast, or ovarian cancer receiving chemotherapy (CT).
Material and Methods: PubMed was searched for peer-reviewed English articles published from January 1, 2000 to December 31, 2012 using search terms including RDI, metastatic, breast, lung, ovarian, and cancer. Articles on radiotherapy, stem cell transplantation, and targeted therapy were excluded. Heterogeneity in methods and type of RDI analysis precluded meta-analysis.
Results: 78 studies were identified (lung=33, breast=34, ovarian=11). Overall most trials were phase 2 (lung=19, breast=18, ovarian=1) and involved first-line CT (lung=25, breast=14, ovarian=5). 26 studies (lung=11, breast=11, ovarian=4) estimated RDI. 7 studies analyzed overall survival (OS) as a function of RDI (Table).
Conclusions: The number of clinical trials reporting RDI is insufficient to determine the impact of maintaining planned DI on outcome in metastatic solid tumors.
Conflict of interest: *Ownership: Maureen Reiner, Phuong Khanh Morrow, Holly Watson, and Esteban Abella own stock in Amgen Inc. Advisory board: Jeffrey Crawford has served on advisory boards for Amgen Inc. Corporate-sponsored research: Jeffrey Crawford has received research funding from Amgen Inc. Other substantive relationships: Maureen Reiner, Phuong Khanh Morrow, Holly Watson, and Esteban Abella are employees of Amgen Inc.*

3092 POSTER

Itgbl1 over expression stimulates ovarian cancer cell migration rate

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Introduction: Previously, we performed a microarray analysis of 100 ovarian cancer samples. We found that among serous tumors, two molecular subtypes can be distinguished on the basis of their distinct gene expression profile. Further analysis indicated that these molecular subtypes are correlated with different survival of the patients. One of the genes that were differentially expressed between two subtypes of ovarian cancer was Integrin, beta-like 1 gene (ITGBL1). It codes for a poorly characterized adhesion protein that contains 10 tandem EGF-like repeats similar to those found in the cysteine-rich structure of integrin subunits. ITGBL1 is supposed to be evolutionarily and functionally cognate with integrin β. On this basis this is speculated that this protein may influence adhesion and motility, thus affecting the ability of cancer cell to spread and metastasize. Our aim was to study whether and how ITGBL1 can influence the biology of ovarian cancer cells.
Methods: Microarray analysis of 99 ovarian cancer samples was performed using Affymetrix HGU 133 Plus arrays. ITGBL1 expression in 5 ovarian cancer cell lines (OAW42, SKOV3, OVCAR-3, OVP-10 and ES2) was assayed using semi-quantitative RT-PCR. ITGBL1 coding sequence was amplified from cDNA and cloned in pCRII-TOPO vector than transferred into pLNCX2. Retroviral system was used to obtain cell lines with ITGBL1 overexpression. Wild type and ITGBL1-expressing isogonics cell lines were then used in scratch assay to evaluate the difference in cell proliferation rate and motility.
Results: We checked 5 ovarian cancer cell lines for the expression of ITGBL1 mRNA. Only in the ES2 line ITGBL1 expression was detectable, while 4 other cell lines were negative. Thus we did an attempt to modify these 4 cell lines to obtain overexpression of ITGBL1. We successfully obtained 3 cell lines with overexpression of ITGBL1: SKOV3, OAW42 and OVCAR-3. Than SKOV3/ITGBL1(+) and OAW42/ITGBL(+) cell lines were assayed for cell proliferation and migration rate. The results were analyzed in comparison to the non-modified SKOV3 and OAW42 cell lines. We found that in the scratch assay the scratch area was faster covered with the cells overexpressing ITGBL1 than in the isogenic cell lines that do not express ITGBL1.
Conclusion: It seems that ITGBL1 protein may enhance ovarian cancer cell proliferation and motility. This suggests that ITGBL1 may play an important role in ovarian cancer progression; however this must be further confirmed.
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No conflict of interest.

Table (abstract 3091).

Study	N	CT	Median (95% CI) OS
Lung			
Brunetto 2010, retrospective	169	Platinum[a] (Pl) + vinorelbine (V) or gemcitabine (G)	<90% vs ⩾90% RDI Pl: 62 (34−90) vs 58 (45−70) weeks (wk); $P = 0.4$ V: 51 (45−56) vs 58 (45−72) wk; $P = 0.3$ G: 79 (48–111) vs 76 (49–103) wk; $P = 0.6$
Luciani 2009, retrospective, ⩾70 years	107	V, G, or V+cisplatin	⩽80% vs >80% RDI 7 (3.5–10.4) vs 10 (6.7–13.2) months (mo); $P<0.0001$
Breast			
Loibl 2011, pooled analysis	936	G + epirubicin (E) + paclitaxel (T), 5-FU + E + cyclophosphamide (C), ET, EC, or T + capecitabine (X)	<95% vs ⩾95% RDI 104 (91–129) vs 112 (97–136) wk; $P = 0.407$ <90% vs ⩾90% RDI 103 (86–120) vs 118 (103–138) wk; $P = 0.065$ <85% vs ⩾85% RDI 96 (83–119) vs 118 (103–136) wk; $P = 0.0086$ <80% vs ⩾80% RDI 96 (77–124) vs 116 (103–133) wk; $P = 0.0063$ <75% vs ⩾75% RDI 93 (76–119) vs 113 (103–133) wk; $P = 0.0046$
Battelli 2011, single arm retrospective	41	X or V	Dose intensity (DI) median[b] X: Not reached vs 27.2 mo V: 23.9 vs 32.4 mo
Ovarian			
Fruscio 2011, randomized	285	Cisplatin	Low vs high dose 91% and 92% DI, 32 (21.4–42.6) vs 35 (29.5–40.5) mo; $P = 0.97$
Joly 2000, randomized	195	Pl[a]+C	Low vs high dose[b] Pl: 25 vs 30 mo; $P = 0.3$
Rosenberg 2002, randomized	208	T	Low vs high dose delivered[b] 13.6 vs 14.7 mo; $P = 0.98$

[a]Carboplatin or cisplatin. [b]95% CI and/or *P* value was not specified.

3093 POSTER

Modern approaches to the diagnosis and monitoring of pre-cancer conditions and early forms of cervical cancer

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Background: The incidence of invasive cervical cancer tends to increase in women of reproductive age that makes it necessary to revise the traditional approaches to the diagnosis and monitoring of pre-cancer and early forms of cervical cancer. The purpose of the study was to assess expediency of application HPV test, along with cytology in diagnosis and monitoring of cervical CIN II−III and carcinoma in situ.
Material and Methods: Study was conducted in two directions: 1) correlation of cytologic findings before cone biopsy and histological findings after it were analyzed and compare with data of HPV test; 2) predictive value of HPV-test in estimated risk of residual process or recurrence of severe dysplasia (CIN III) and carcinoma in situ was investigated. 69 patients with cervical severe dysplasia and carcinoma in situ underwent cone biopsy from 2009 to 2011 were enrolled. Cytological study of ecto- and endocervix and HPV test were done before cone biopsy. After operation histological examination of the cone with estimation of resection margin was performed, and then patients were observed with the use of cytology and HPV test.
Results: Mean age was 31.4 years. HPV genotype 16 was found in 33 patients (63.7%), 18 − in 7 patients (14.3%), 31 − in 7 patients (14.3%). The other oncogenic HPV genotypes were detected in isolated cases. Histological examination revealed carcinoma in situ in 40 from 69 patients (57.9%), severe dysplasia (CIN III) − in 8 (11.6%), moderate dysplasia (CIN II) − in 12 (17.4%), and hyperplasia of reserve cells − in 10 (14.5%) patients. Comparison of cytologic and histologic examinations data revealed overdiagnosis CIN or carcinoma in situ in 10 of 69 patients (14.5%), while one patient was overdiagnosis carcinoma in situ. In all 10 cases (100%) with histological diagnosis of hyperplasia of reserve cells HPV test was negative. In two patients with negative cytological data with long-term persistence of HPV type 16 there was detected carcinoma in situ in one case, and CIN II in another. 11 (16%) patients after cone had positive HPV test with negative cytology test in 4. Positive resection margin was revealed in a remote cone in 7 patients. All of them underwent re-conization, with histologically confirmed relapse in 3 cases. At the further monitoring positive HPV test was observed in three patients with negative cytology test.
Conclusions: The combination of cytological and HPV testing methods shows a higher accuracy in the diagnosis of CIN II−III and carcinoma in situ of the cervix comparing to one cytology and in monitoring of patients after cone biopsy.
No conflict of interest.

3094 POSTER

The phase II study of docetaxel and carboplatin combination chemotherapy for advanced/recurrent patients with non-squamous uterine cervical cancer

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Background: Non-squamous cell carcinoma (non-SCC) of the uterine cervix has gradually increased, comprising more than 20% of all uterine cervical cancer. Uterine cervical cancer with non-SCC has a resistance to radiotherapy, suggesting to be associated with worse prognosis compared with SCC. Few prospective studies focusing on this rare disease could conclude the optimal chemotherapeutic regimen, since non-SCC cervical cancer is rare. We conducted this phase II study to evaluate the efficacy and safety of docetaxel (DTX) and carboplatin (CBDCA) combination chemotherapy (DC) for advanced/ recurrent cervical cancer with non-SCC.
Material and Methods: Forty six patients enrolled in this study. The patients were administered DTX at a dose of 60 mg/m^2, followed by CBDCA at a dose based on an AUC of 6. Patients underwent DC chemotherapy until disease progression. The response was evaluated in 41 patients based on RECIST criteria 1.0 and toxicity grade was determined in 46 patients by NCI-CTC version 3.0.
Results: Median age and cycles of DC chemotherapy were 55 years old (range: 25−77), and 5 (range: 1−12). The response rate (RR) and disease control rate (DCR) were 56% and 83%, with 5 patients achieving complete response, 18 partial response, 11 stable disease, 7 progressive disease. The most frequent grade 3 and grade 4 hematological toxicity was neutropenia, with 36 patients (78%) having grade 4 neutropenia and 4 patients (9%) having grade 3 neutropenia. Grade 3 febrile neutropenia was observed in 6 patients. Nineteen patients (41%) had more than grade 3 anemia, and 18 patients (39%) showed more than grade 3 thrombocytopenia. The non-hematological toxicities were mainly grade 1 or 2 in severity. With regard to grade 3 non-hematological toxicities, 8 patients had infection, 7 nausea or anorexia, 2 diarrhea, and 1 vomiting, fatigue or allergic reaction to DTX. Only one patient had grade 4 allergic reaction to DTX.
Conclusions: DC chemotherapy had good RR and DCR to advanced/ recurrent uterine cervical cancer with non-SCC, suggesting to prolong overall survival. DC chemotherapy might be also tolerated, although DC chemotherapy showed high incidence of hematologic toxicities, especially neutropenia.
No conflict of interest.

3095 POSTER

A prospective study of ERCC1 protein expression and gene polymorphisms in locally advanced cervical squamous cell carcinoma patients treated with cisplatin-based concurrent chemoradiotherapy

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Background: Excision repair cross-complementation group 1 (ERCC1) expression and some polymorphisms of the gene could predict treatment efficacy in patients with different types of tumors receiving platinum-based treatments. The purpose of this study is to correlate ERCC1 gene polymorphism and protein expression by immunohistochemistry (ICH) with recurrence free survival (RFS) and overall survival (OS) in locally advanced cervical squamous cell carcinoma patients who have undergone cisplatin-based concurrent chemoradiotherapy (CRT).
Methods: Sixty-six patients with locally advanced cervical squamous cell carcinoma treated with radical CRT from a cooperative group were evaluated. This group studied the polymorphism that causes a single nucleotide change C to T at codon 118 -becoming AAC on AAT- resulting in a decreased ERCC1 gene expression carrying a loss of DNA repair activity, using quantitative real-time PCR in blood samples. ERCC1 protein expression was determined in pre-treatment tumor tissues by IHC. The association of ERCC1 status with clinicopathological characteristics (age, hemoglobin, grade, FIGO stage) and treatment outcome were analyzed.
Results: Thirty-three patients (50%) were homozygous for AAC codon (C/C genotype), 17 (26%) were homozygous for AAT codon (T/T genotype), and 16 (24%) were heterozygous (C/T genotype). Thirty-eight percent of patients were ERCC1 negative or low expression by IHC, whereas 62% were positive. There was a significant association of C/C genotype and positive ERCC1 by IHC (p 0.003). No significant correlation between ERCC1 expression, codon 118 polymorphism and clinicopathological characteristics was observed. No difference was observed between C/C or non C/C genotypes in terms of RFS or OS. Positive ERCC1 expression by IHC was related to worse RFS (p 0.04).
Conclusions: C/C genotype was associated to high expression of the protein but without impact on RFS or OS. ERCC1 expression by IHC has been shown to be a biomarker for RFS in cervical squamous cell carcinoma patients treated with CRT.
No conflict of interest.

3096 POSTER

Elevated platelet count as a marker of aggressive disease in patients with ovarian cancer

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Background: Ovarian cancer is the leading cause of death from gynecological cancers in the United States. Over 70% of patients present with advanced disease. Cho et al showed that the proliferation of ovarian cancer cells increased significantly upon coincubation with platelets (Blood 2012;120:4869). The same investigators, alongside the laboratory analysis, also reviewed epithelial ovarian cancer patients from four cancer centers and found that increased platelet count was associated with a worse overall survival. However the study had 92% patients with advanced stage III/IV disease with 97% high grade tumors suggesting a more sicker and hence, skewed patient population (NEJM 2012;366:610). We undertook this study to see the effect of thrombocytosis on our ovarian cancer patient population in a public hospital setting.

Methods: All patients with a diagnosis of ovarian cancer from January 2006 to December 2011 were identified from the tumor registry of our hospital. All charts were retrospectively screened for histologic identification of the epithelial origin of the tumor, platelet count at diagnosis (before any surgical procedure), age at diagnosis, tumor grade, FIGO stage and survival at one year. Patients with non-epithelial histology, iron deficiency, other inflammatory disorders, known platelet disorder and ones with incomplete records were excluded. Statistical analysis was done using the relative risk calculator and student t-test.
Results: A total of 188 patients were screened of which 136 met the inclusion criteria. The ethnic mix was 32% african-americans, 23% hispanics, 33% caucasians and 12% asians. Stage III/IV disease was seen in 71% of all patients. Fifty-eight patients had elevated platelet counts at diagnosis (Group A) and 78 had normal platelet counts (Group B). The average age was 53 years for both groups. High grade 3 tumors were seen in 44 of 50 patients (88%) in group A compared to 37 of 60 patients (62%) in group B ($p < 0.001$) with low grade 1 tumors seen in only 3 (6%) group A and 12 (20%) group B patients. Stage III/IV disease was seen in 53 (91%) patients in group A compared to 44 (56%) in group B ($p < 0.001$). Only 3 (5%) patients had stage I cancer in group A compared to 27 (35%) in group B. At one year only 75% patients were alive in group A compared to 96% in group B ($p = 0.003$, CI 0.67–0.92).
Conclusion: Our data from a non-referral public hospital confirms that an elevated platelet count at diagnosis in patients with ovarian cancer is associated with a higher grade and higher stage of the cancer and a significantly worse one-year survival.
No conflict of interest.

3097 POSTER

Treatment with the trifunctional antibody catumaxomab followed by systemic chemotherapy: Results of a subgroup analysis from a phase III study in patients with relapsed ovarian cancer and malignant ascites

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Background: Malignant ascites (MA) can compromise quality of life in patients with relapsed ovarian cancer (OC). The trifunctional antibody catumaxomab has been approved for intraperitoneal (ip) treatment of patients with MA due to EpCAM-positive carcinomas where standard therapy is not available or no longer feasible. The safety and efficacy of catumaxomab in MA patients was confirmed in a 2nd phase III trial (CASIMAS, NCT00822809) comparing a 3-h ip infusion with and without prednisolone premedication (Sehouli, ESMO 2012). In order to investigate the value of catumaxomab in the entire treatment algorithm of ovarian cancer, a subgroup analysis was performed on OC patients with regard to subsequent chemotherapy after treatment with catumaxomab (post-catumaxomab CTX).
Materials and Methods: OC patients in both treatment arms were pooled. The efficacy parameters time to next puncture (TTPu), puncture-free survival (PuFS) and overall survival (OS) were evaluated in relation to post-catumaxomab CTX.
Results: 42/109 (39%) patients with MA due to OC received post-catumaxomab CTX, which included a platinum-containing regimen in 19 patients (17%). 21/109 (19%) received >1 post-catumaxomab CTX regimens. Patients with any post-catumaxomab CTX compared with those without CTX had significantly prolonged OS (median 273 vs 81 d, HR 0.24, $p < 0.0001$) and PuFS (median 138 vs 43 d, HR 0.46, $p = 0.0002$). The difference in TTPu was not significant (223 vs 110 d, HR 0.68, $p = 0.1788$). Patients with >1 post-catumaxomab CTX compared with 1 post-catumaxomab CTX had significantly prolonged OS (480 vs 167 d, HR 0.20, $p < 0.0001$). The difference between the groups with >1 and 1 post-catumaxomab CTX in PuFS (153 vs 123 d, HR 0.64, $p = 0.1804$) and TTPu (153 vs 169 d, HR 1.52, $p = 0.3600$) was not significant. Patients who received platinum-containing post-catumaxomab CTX had significantly prolonged OS compared with those who received post-catumaxomab CTX without platinum (462 vs 169 d, HR 0.32, $p = 0.0026$). The difference between the groups with and without platinum in PuFS (153 vs 123 d, HR 0.76, $p = 0.4448$) and TTPu (153 vs 229 d, HR 1.68, $p = 0.2373$) was not significant.
Conclusions: The data indicate that patients with MA due to OC who are able to receive CTX after catumaxomab treatment have significantly prolonged OS compared with patients who could not receive CTX. Further trials have been initiated to identify the best patient population to receive catumaxomab followed by subsequent CTX.
Conflict of interest: *Advisory board: Fresenius Biotech GmbH. Corporate-sponsored research: Fresenius Biotech GmbH. Other substantive relationships: Employee Fresenius Biotech GmbH*

3098 POSTER

UK guidance on diagnosis of ovarian cancer: Its impact on services in an acute general hospital

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Introduction: The UK National Institute for Health and Clinical Excellence (NICE) recommended in April 2011 that women with symptoms suggesting epithelial ovarian cancer (EOC) should have measurement of CA125 with ultrasound (U/S) examination of the pelvis for those with values 35 IU/ml or greater. Airedale General Hospital (AGH) provides diagnostic services for gynaecological cancer for about 200,000 people. We have monitored the demand for services and analysed the outcome of patients found to have elevated CA125 values in the year following publication.
Methods: The records of the biochemistry laboratory were scrutinised to identify CA125 measurements requested from primary care. The radiological and clinical pathology records of patients with values exceeding the defined cut-off were futher scrutinised to identify tests done and their outcomes.
Results: There were 486 requests to AGH laboratory for CA125 from primary care November 2010 − April 2011 compared with 1,314 in May–October 2011, an increase of 170%. 117 (8.9%, 95% CI 7.4–10.4%) post-April results were 35 IU/ml or more. Among requests from primary care practices known routinely to refer patients to AGH clinical services we identified 84 patients with elevated CA125 in the first six month period (May-October 2011). Among these, no follow-up test could be identified from hospital imaging records in 7 (8.3%, 2.4–14.2%)) patients. EOC was diagnosed in 7 (8.3%, 3.4–16.4%) cases, CA125 range 144–6645 IU/ML. Other cancers were diagnosed in 5. Nonmalignant pathology was found in 17 and 37 had U/S examinations, 11 of whom had repeat imaging, without an abnormality being identified. Five patients had chronically elevated stable CA125. In the second period (November 2011 to April 2012) there were 34 elevated measurements. One (2.9%, 0.1–15.3%) was not followed up, EOC was diagnosed in 5 (14.7%, 5.0–31.0%) CA125 range 268–2344.7 IU/ml. Other cancer was diagnosed in 5 cases, nonmalignant pathology was found in 16 and 5 had U/S with no abnormality detected. Two cases with chronically elevated CA125 were detected. In the first period 13 EOCs and 9 in the second period were diagnosed by other routes.
Conclusion: Primary care doctors have responded to NICE guidance with increased CA125 measurements. Most elevated values have been followed up. The impact of this on EOC diagnosis is not yet apparent; those that were diagnosed by this route had markedly elevated CA125 values. There were fewer elevated CA125 measurements in the second six months but the number of diagnoses of all types did not change; possibly primary care doctors are getting used to the system. The most common cause of raised CA125 is benign gynaecological pathology. Unexplained elevated CA125 levels will be a clinical dilemma in coming years.
No conflict of interest.

3099 POSTER

Cancer in pregnancy: To treat or not?

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Background: Cancer in pregnancy accounts for ~1 in 1000 pregnancies. Studies show that cytotoxic agents are safe from the second trimester. Long-term follow up has not shown increased malformations or malignancies in children exposed to chemotherapy in utero. There is no evidence of worse outcomes among women diagnosed in pregnancy.
Material and Methods: We retrospectively identified women diagnosed with cancer in pregnancy over a 25-year period. Medical records were reviewed for demographics, diagnosis, gestation, timing of treatment and outcomes. We assessed if all cancers need to be treated in pregnancy or if treatment could be safely deferred to allow normal delivery.
Results: Twenty-five women were diagnosed with cancer in pregnancy and referred to medical oncology.
Of twenty-five women, sixteen (64%) received chemotherapy during pregnancy. These included thirteen cases of breast cancer, one Ewing's

sarcoma, one ovarian cancer and one small cell of cervix. All sixteen women received Doxorubicin/Cyclophosphamide. There were fifteen live births and no abnormalities seen in children who received chemotherapy in utero. At a median follow-up of six years eleven mothers (69%) are disease free and four (25%) have recurrent disease. Of nine mothers who did not receive chemotherapy in pregnancy, seven received chemotherapy immediately post-partum. Six (86%) were diagnosed in early pregnancy (median gestation 13 weeks). There were three cases of Hodgkin's lymphoma, two breast cancers and one ovarian cancer. At a median follow-up of 12 years, all mothers remain disease free. There were no abnormalities seen in these children.

Conclusions: We did not identify any adverse outcomes in mothers or infants exposed to chemotherapy during pregnancy. We identified a cohort of patients that do not need immediate treatment during pregnancy. In selected cases, it is safe and appropriate to delay chemotherapy until delivery of the baby. There were no adverse outcomes to mothers due to delayed treatment and no adverse outcomes to babies not exposed to chemotherapy in utero. A multi-disciplinary team is essential to individualize treatment planning.

No conflict of interest.

Table: Characteristics of 25 patients

Median age (range)	33 (20−42)
Gestation at Dx (range)	14 (6−36)
Tumour type	
Breast	15
Hodgkin's	3
Ovarian	3
Soft Tissue Sarcoma	2
Small Cell Cervix	1
Ewing's	1

3100 POSTER

The impact of survival on ovarian cancer and non ovarian cancer-specific health care charges during ovarian cancer treatment

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Background: Treatment charges typically increase during the last year of life in women with ovarian cancer, but it remains unknown if charges differ between patients who die while receiving treatment compared to those who survive. The objective of this study was to assess the mean charge per patient in those diagnosed with ovarian cancer by survival status.

Materials and Methods: Women $\geqslant$18 years with a diagnosis of ovarian cancer, identified by ICD-9 code (initial diagnosis defined as index date), treated at the Huntsman Cancer institute (HCI) from 2002–2010 were identified using the University of Utah Enterprise Data Warehouse. The HCI Tumor Registry was used to determine stage at diagnosis. Cause and date of death were captured from the Utah Population Database. Ovarian cancer-related (OCR) and non-OCR charges were identified using ICD-9 codes and were assessed from index date until death or the end of the study period. Patients who died were matched to survivors based upon the Kaplan–Meier probability of survival at the time of death or end of the study period. A generalized linear model (GLM) with gamma distribution and log link function was then used to examine charges by survival status, while adjusting for baseline characteristics including stage, demographics, year of diagnosis, cancer treatments, and comorbidities.

Results: A total of 228 matched patients were included in the analysis. When compared to survivors, patients who died were significantly older (mean age: 63 vs. 54, $p < 0.001$) and fewer were white (68% vs. 86%, $p < 0.001$). Additionally, more deceased patients were diagnosed with stage IV disease (40% vs. 19%, $p < 0.005$) and fewer with stage I (8% vs. 18%, $p = 0.03$) than survivors. Mean unadjusted OCR charges ($55,885 vs. $56,832; $p = 0.89$) and non-OCR charges ($84,131 vs. $74,624; $p = 0.49$) were not significantly different between deceased patients and survivors. However, results from the GLM indicated deceased patients had significant increases in mean OCR charges ($18,072; $p = 0.03$) and non-OCR charges ($43,945; $p < 0.001$). Being older and being diagnosed at worse stage were the primary factors driving up the mean OCR charges.

Conclusions: When adjusting for confounders, women with ovarian cancer who died had significantly higher OCR and non-OCR charges. Though cancer stage, comorbidities, and other potential confounders were included in the analysis, patients who died may have had more aggressive disease leading to increased heathcare utilization.

No conflict of interest.

3101 POSTER

Mean platelet volume could be a prognostic biomarker for monitoring ovarian cancer

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Background: Epithelial ovarian cancer (EOC) accounts for 3.6% of all cancers among women all over the world, and is leading cause of death from gynecologic cancer. After initial treatment with debulking surgery and taxane and platinum based chemotheraphy, most patients will relapse; outcomes of patients are still unsatisfactory with a 5-year survival of only %20−40 Recently new studies showed that inflammatory markers and blood cells may have relation with epithelial ovarian cancer. It has been shown that mean platelet volume (MPV) is a sign of inflammation in hepatocellular carcinoma and pancreatic adenocarcinoma; also elevated platelets, neutrophils and lymphocytes or neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were reported in EOC.

The aim of this study is to determine whether MPV would be a useful inflammatory marker for predicting prognosis and tumor burden in EOC patients.; also to examine the importance of preoperative PLR and NLR in our study subjects.

Material and Methods: We retrospectively investigated 113 EOC patients who underwent surgery at 19 Mayis University Hospital between 2005 and 2012. Patients with hypertension, hematological and renal disease, heart failure, chronic infection, hepatic disorder and other cancer were excluded from the study. Complete blood count data were collected before and after surgery from recorded computerized database.

Results: Preoperative MPV levels were significantly higher compared to postoperative values(mean 8.27 ± 0.10 vs 7.61 ± 0.09 $p = 0.000$). But we did not find statistically significant relationship between MPVlevels and TNM stages, grade, OS, PFS and CA125 levels. On the other hand smilar to MPVand CA125, NLR values also significantly decreased after the surgery (mean 3.49 ± 0.18 vs 2.49 ± 0.11 $p = 0.000$). The decrease in PLR values were statistically nonsignificant ($p = 0.06$).

Conclusions: Our data suggests that MPV could be a promising and easily available biomarker for the diagnosis and monitoring of EOC patients at low-cost compared with other modalities.

No conflict of interest.

3102 POSTER

Malignant transformation of ovarian mature cystic teratoma

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Background: Mature cystic teratoma MCT is not a rare occurrence, accounting for about 20% of ovarian tumors, but malignant transformation of MCT is infrequent, the risk of transformation is estimated to be between 0.17−2%.

Material and Methods: The objective of this study is to determine clinicopathologic factors affecting survival in this rare tumor. From January 2000 to December 2009, 03 patients with malignant transformation arising in ovarian MCT were treated at department of pediatric surgery, and national institute of oncology in Rabat. Symptoms, signs, stage, mode of therapy, and results of follow-up were reviewed retrospectively.

Results: There were 03 cases of the malignant transformation of ovarian MCT out of 34 cases of MCT. Their ages were 47, 35 and 60 years. Histologically, 2 cases were squamous cell carcinoma and one adenocarcinoma. Abdominal pain and palpable abdominal mass were the most frequent complaint. As for the stage of disease, 2 cases were in stage IA, and the other was in stage IIIC. All the patients had surgery, and adjuvant chemotherapy. 2 patients in stage IA survived until the period of follow-up median of 74 months. Patient in stage IIIC died 4 months from the surgery.

Conclusions: We reported in our experience supports the use of radical surgery and adjuvant chemotherapy, but the prognosis of MCT is highly dependent on age, stage, and optimal treatment.

No conflict of interest.

Proffered Papers Session (Sat, 28 Sep)
Head and Neck Cancer

3151 ORAL

Very accelerated radiotherapy or chemoradiotherapy for N3 head and neck squamous cell carcinoma: Pooled analysis of two GORTEC randomized trials

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Background: The optimal management of inoperable N3 head and neck squamous cell carcinoma (HNSCC) remains controversial. The outcome of patients treated with very accelerated radiotherapy (VART) or different schedules of concomitant chemoradiotherapy (CRT) within two phase III trials was analyzed.
Materials and Methods: Data of 179 patients with N3 HNSCC from two randomized trials (GORTEC 96−01 and GORTEC 99−02) were pooled. Patients received either VART: 64.8 Gy in 3.5 weeks (1.8−2 Gy BID) or one of the 3 following CRT regimens: 1) Conventional CRT: 70 Gy in 7 weeks + 3 cycles of 4 days of carboplatin−5FU; 2) Moderately accelerated CRT: 70 Gy in 6 weeks + 2 cycles of 5 days of carboplatin−5FU; 3) Strongly accelerated CRT: 64 Gy in 5 weeks + cisplatin (days 2, 16, 30) and 5FU (days 1−5, 29−33) followed by 2 cycles of adjuvant cisplatin−5FU. Analyses were performed using Cox models stratified for trial.
Results: Median follow-up was 13.3 and 5.2 years for GORTEC 96−01 and GORTEC 99−02, respectively. Overall survival (OS) at five years was 13.8%. No significant difference was observed between CRT versus VART in terms of OS (hazard ratio (HR): 0.93, 95% confidence interval: 0.67–1.29, $p = 0.68$), locoregional progression (HR: 0.70, 0.44–1.11, $p = 0.13$), or distant progression (HR: 0.86, 0.53–1.39, $p = 0.53$). OS was worse for patients with T3−4 tumors versus early T stage (11.0% versus 25.7%, HR: 1.66, 1.11–2.50, $p = 0.015$) and those with initial performance status WHO $\geqslant 1$ versus 0 (10.1% versus 16.9%, HR: 1.49, 1.06–2.10, $p = 0.023$). The oropharyngeal primary site was associated with higher risk of distant metastasis (77.4% versus 28.7%, HR: 3.24, 1.83–5.74, $p < 0.0001$).
Conclusions: The outcome of N3 HNSCC remains poor despite recent efforts for treatment intensification and without difference between CRT and VART. Early T stage patients with good performance status could benefit from further investigation. Different treatment strategies are probably needed for oropharyngeal cancer compared with others sites.
No conflict of interest.

3152 ORAL

Association of XPF and HPV among squamous cell head and neck cancer tumors: Biomarker analysis of ECOG 3303

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Background: In locally advanced head and neck cancer (LA-SCCHN) HPV+ tumors have a better prognosis than HPV−. An understanding of treatment resistance is required, especially for HPV− LA-SCCHN. XPF and ERCC1, components of nucleotide excision repair, are potential biomarkers of cisplatin (C)/radiation (RT) resistance. E3303 is a phase II trial to study the safety and efficacy of RT, C and cetuximab (C225) for LA-SCCHN.
Materials and Methods: Archival pre-treatment tissues were obtained and HPV16 DNA was detected by in situ hybridization (Dako GenPoint). For immunofluorescent IHC analysis, sections were incubated with XPF ab (1:100, ab 17798, Abcam), ERCC1 ab (1:5000 HPA0297731, Sigma) and a wide-spectrum rabbit cytokeratin ab (Dako Z0622) to create tumor mask. Prolong Gold mounting medium (P36931; Molecular Probes) containing 4,6-Diamidino-2-phenylindole (DAPI) defined nuclear staining. Staining intensity was measured using HistoRx PM-2000 image analysis, with AQUA algorithms. Data were analyzed based on the median cut point for nuclear staining of XPF, and quartiles for ERCC1. Time-to-event distributions were estimated by the Kaplan–Meier method and compared using the log-rank test. Cox's proportional hazards models were used to estimate hazard ratios (HR) and test for significance for overall survival (OS) and progression free survival (PFS). All p-values were two-sided with type I error rate at 0.05.
Results: Analysis of XPF, ERCC1 and HPV was conducted in 31, 32 and 29 of 69 patients. Median XPF AQUA score was 159.9 (58–660); ERCC1 was 930.5 (101.7–3557). Incidence of XPF/HPV: HPV+/XPF high (H) = 2, HPV+/XPF low (L) = 7, HPV−/XPF H = 14, HPV−/XPF L = 3. Thus, HPV+ tumors were more likely to be XPF L ($p = 0.01$); a 2-way interaction between HPV and XPF in PFS was noted ($p = 0.0597$), but not with HPV and ERCC1. XPF was not a predictor for PFS after controlling for sex, race, ECOG performance status, weight loss (<5% vs. $\geqslant$5%), primary site (oropharynx vs. non-oropharynx), smoking, and HPV (HR (L vs. H)=2.71, 95% CI=(0.39, 18.96), $p = 0.31$). For HPV− median PFS was 15.7 months (m) (XPF H) vs. 7.7 m (XPF L). For HPV+, the 25th percentile PFS was 15.3 m (XPF L)(95% CI=(11.4, NR) and 11.1 m (XPF H) (95% CI=(11.1, NR).
Conclusions: Among LA-SCCHN treated with C/C225/RT, HPV+ disease is more likely to be XPF L; this subgroup has an improved PFS. Future research should further study DNA repair mechanisms and treatment resistance in HPV− SCCHN.
No conflict of interest.

3153 ORAL

A cancer specific enteral nutrition formula improves nutritional status and functional performance in patients with head and neck cancer undergoing chemoradiotherapy

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Background: The aim of this study was to investigate the influence of cancer-specific enteral nutrition (EN) high in fat, protein, eicosapentaenoic- (EPA) and docosahexaenoic acid (DHA) from fish oil on body composition, nutritional and functional status in head and neck (H&N) cancer patients undergoing chemoradiotherapy (CRT).
Material and Methods: Subgroup analysis restricted to patients with H&N cancer (n = 102), derived from a larger prospective, randomized, controlled, double-blind, multicenter study (NCT01025167) of oesophageal- (n = 9) and H&N cancer (n = 102) recruited from ten radiooncological centers in Germany. Patients either received standard EN (control group, n = 51) or metabolically adapted, cancer-specific EN (Supportan®) high in fat, protein, EPA + DHA, low in carbohydrates (experimental group, n = 51) via percutaneous endoscopic gastrostomy (PEG) for $\leqslant$14 weeks. Primary endpoint was the change in body cell mass (BCM) directly following CRT (week 7) and after follow-up (week 14) as compared to the baseline value. Secondary endpoints included additional parameters of body composition, anthropometric parameters, nutritional status (Kondrup Score, Subjective Global Assessment (SGA)) and functional status, inflammation (TNF-α, IL-6) and quality of life.
Results: Patients receiving experimental nutrition lost only -0.75 ± 0.64 kg BCM, compared to -2.82 ± 0.73 kg BCM in the control group ($p = 0.0407$) after follow-up. For objectively measured parameters of nutritional status, such as body weight, BMI, fat-free mass, and skinfold thickness, a tendency towards smaller decreases during the study period was observed in the experimental vs. control group. In the experimental group the Kondrup score of impaired nutritional status (-0.47 ± 0.15 vs. 0.02 ± 0.16; $p = 0.0320$) and overall SGA-rating ($p = 0.0145$) improved significantly at follow-up.
A significant difference ($p = 0.0227$) between the trial groups was observed in the Karnofsky index due to higher improvement rates in the experimental group after CRT. The significantly attenuated increase in IL-6 after CRT in the experimental group compared to the control group (5.29 ± 3.74 vs. 17.33 ± 4.08 pg/mL; $p = 0.0338$) suggests an anti-inflammatory effect of Supportan®.
Conclusions: Cancer-specific enteral nutrition high in fat, protein, EPA and DHA may be advantageous in patients with H&N cancer by reducing losses

in BCM and counteracting the deterioration of parameters of nutritional and functional status during and following CRT.
No conflict of interest.

3154 ORAL

Progressive, metastatic medullary thyroid cancer: Baseline symptoms and disease characteristics among patients enrolled in the EXAM trial

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Background: The symptomatology and disease burden in patients with progressive, metastatic medullary thyroid cancer (MTC) are not well characterized. Patients in the EXAM trial (NCT00704730) placebo arm had short median progression-free survival (4.0 months). Therefore, we analyzed the baseline characteristics of all patients enrolled in the EXAM trial to define the study population and characterize the disease burden and symptomatology in patients with progressive MTC as a reference for future clinical research.
Material and Methods: In the EXAM trial, 330 patients with MTC and radiographic evidence of disease progression ($\leqslant$14 months between reference and screening scans) by mRECIST were randomized to cabozantinib or placebo. Patient baseline symptoms (CTCAE v3.0) and disease characteristics were collected and analyzed descriptively.
Results: At baseline, 312 (94.6%) patients had measurable disease (independent radiology review); most (87.0%) had metastatic disease at $\geqslant$2 sites/organs, including lymph nodes (79.1%), liver (66.4%), lungs (54.5%), and bone (50.9%). Median age was 55 years (20−86), mean bodyweight was 73.4 kg ($\pm$18.5), 67.0% were male, 89.4% were white, and 92.4% were thyroidectomized. The median interval between the initial diagnosis of MTC and randomization was 3.9 years (0.07–48.4), and the median interval between diagnosis of metastatic disease and randomization was 2.0 years (0.04–33.7). Overall, 39% of patients had prior systemic anticancer therapy and 20.6% had prior tyrosine kinase inhibitor therapy (10.3% vandetanib). The most frequent patient-reported baseline symptoms were mainly grades 1 or 2 and included pain 46.1% (54% grade 1, 38% grade 2, 5% grade 3, <1% grade 4), diarrhea 39.7% (63% grade 1, 28% grade 2, 5% grade 3), fatigue 25.8% (79% grade 1, 17% grade 2), dysphonia 23% (73% grade 1, 5% grade 2, 1% grade 3), dyspnea 16.1% (70% grade 1, 17% grade 2, 2% grade 3), cough 12.1% (78% grade 1, 15% grade 2), dysphagia 9.1% (80% grade 1, 10% grade 2, 3% grade 3), anorexia 7% (78% grade 1, 9% grade 2, 9% grade 3), weight loss 5.5% (50% grade 1, 33% grade 2, 6% grade 3), and flushing 4.2% (86% grade 1, 14% grade 2).
Conclusions: MTC is often considered an indolent disease. However, our baseline data indicate that patients with radiographic evidence of progressive MTC have a substantial disease burden and high incidence of disease-related symptoms.
Conflict of interest: *Advisory board: PS: Has received honoraria for advisory functions from Exelixis. Board of directors: EC: Has received honoraria for consulting services from Exelixis. FB: Is employed by Exelixis. SS: Has received honoraria for consulting services from Exelixis.*

3155 ORAL

Association between tumor BRAF and RAS mutation status and clinical outcomes in patients with radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC) randomized to sorafenib or placebo: sub-analysis of the phase III DECISION trial

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Background: We recently reported that treatment of RAI-refractory DTC patients with sorafenib reduced the risk of progression or death by 42% compared to placebo in the randomized, phase III trial DECISION. A number of genetic abnormalities have been implicated in the etiology of DTCs. We examined BRAF and RAS mutations as possible prognostic biomarkers and as predictors of sorafenib efficacy in RAI-refractory DTC patients.
Methods: In DECISION, patients with locally advanced/metastatic RAI-refractory DTC progressing in the preceding 14 months were randomized 1:1 to sorafenib 400 mg bid po or placebo. Placebo patients were allowed to receive sorafenib upon progression. Archived tumor samples were analyzed for 238 mutations in 19 common oncogenes (Sequenom OncoCarta 1.0).
Results: Tumor mutation data was available from 256 patients (61.4% of the study population); 126 in sorafenib arm and 130 in the placebo arm. Demographics of the genetic subgroup were similar to the overall study population. BRAF and RAS mutations were detected in 30.1% and 19.5% of patients, respectively, and were well balanced across arms. Other point mutations occurred in less than 5% of patients, with 47.3% of patients having no detectable mutations. Placebo patients with mutant (m) RAS tumors had worse PFS outcomes vs wild-type (wt) RAS (HR = 1.78, p = 0.03), whereas placebo patients with mBRAF tumors had better PFS outcomes vs wtBRAF (HR = 0.53, p = 0.01); no significant difference in OS was observed with either mutation. Both wtBRAF (n = 92) and mutant (n = 34) patients treated with sorafenib had improved PFS vs placebo (n = 87 and 43, respectively) (wtBRAF: HR = 0.54, p < 0.001; mBRAF: HR = 0.47, p = 0.02; interaction p-value=0.68). Similarly, sorafenib-treated patients benefited independently of RAS mutation status in terms of PFS prolongation (wtRAS: sorafenib n = 102, placebo n = 104, HR = 0.60, p = 0.004; mRAS: sorafenib n = 24, placebo n = 26, HR = 0.45, p = 0.037; interaction p-value=0.39). Although the number of events were small, mBRAF patients treated with sorafenib appeared to have a better OS compared to placebo (HR = 0.32, p = 0.03). No difference in OS was seen with regards to RAS mutation status.
Conclusion: These exploratory analyses suggest that mutant RAS and mutant BRAF were negative and positive prognostic factors, respectively, for PFS in RAI-refractory DTC patients and that patients benefited from sorafenib treatment in terms of PFS prolongation independent of BRAF and RAS mutation status.
Conflict of interest: *Ownership: None. Advisory board: Brose − Bayer HealthCare Pharmaceuticals, Onyx Pharmaceuticals. Sherman − AstraZeneca, Bayer, Eisai, Exelixis. Smit − Bayer HealthCare PharmaceuticalsSchlumberger − Astra Zeneca, Bayer, Eisai, Exelixis, Genzyme. Board of directors: None. Corporate-sponsored research: Brose − Bayer HealthCare Pharmaceuticals Sherman − Genzyme, Pfizer. Schlumberger − Genzyme. Other substantive relationships: Chung − employee of Bayer HealthCare Pharmaceuticals. Molnar − employee of Bayer HealthCare Pharmaceuticals. Jeffers − employee of Bayer HealthCare Pharmaceuticals. Pena − employee of Bayer HealthCare Pharmaceuticals.*

Poster Session (Sun, 29 Sep)
Head and Neck Cancer

3156 POSTER

Biomarkers of radioresistance in head and neck squamous cell carcinoma and their relation to cancer stem cell

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The development and growth of a tumor have been attributed to the existence of cancer stem cells (CSCs), or tumor progenitor cells, which have been discovered for many types of cancer including head and neck squamous cell carcinoma (HNSCC). Radiotherapy plays a key role in the management of head and neck squamous-cell carcinomas (HNSCC). The evidence continues to accumulate that current anti-cancer therapy fail to achieve long-lasting cancer cures because they do not eliminate CSCs, which are protected by multiple intrinsic and extrinsic mechanisms. The number of CSCs and their radiosensitivity vary between tumors, which affects their radiocurability. Therefore, the objective of this study is the investigation of novel HNSCC CSC-related biomarkers to benefit individualized radiotherapy.
In a first step we created radioresistant cancer cell lines, which have been exposed to minimum 40 Gy given in small clinically relevant fractions of 2 or 4 Gy. Their radioresistance was verified in radiobiological 3D in vitro assays in comparison to the non-irradiated parental cell lines. Comparative analysis of stem cell marker expression and assessment of in vivo tumor growth were performed in order to elucidate putative CSC-related biomarkers, which expression correlates with cell radioresistance. Next, we used the aldehyde dehydrogenase (ALDH) activity as an already

known cancer- and stem cell feature to ascertain its role in the development of radioresistance. For this purpose, we investigated and characterized the ALDH positive and ALDH negative populations within the above mentioned radioresistant and non-irradiated cancer cells.
Our study suggests a highly dynamic regulation of the stem cell marker expression after irradiation stress. Irradiation of cancer cells increased the tumor progenitor populations that can be defined by classical stem cell markers including ALDH activity, CXCR4, CD133, ABCG2, and led to activation of PI3K/AKT and epithelial–mesenchymal transition (EMT) signaling pathways, which were increased with increasing number of radiation fractions. Analysis of radiation-induced DNA double-strand breaks using immune fluorescent staining of γH2AX revealed an initial quick DNA damage response to irradiation in ALDH positive cell population as compared to negative or total population. Moreover, our in vivo studies suggest that high ALDH activity defines tumorigenic and radioresistant cell subsets only within the parental non-irradiated cell lines.
Our studies revealed ALDH activity is indicative of HNSCC progenitor cells with increased radioresistance. Our finding suggests that radioresistant properties of cancer progenitor population may be dynamic in nature and can be differently employed throughout the course of radiotherapy. Thus, different therapeutic strategies and different predictive biomarkers may be required at the different stage of tumor treatment.
No conflict of interest.

3157 POSTER

Association of MSH2 IVS1+9G>C and EXO1 K589E polymorphisms with inherited risk of head and neck squamous cells carcinoma

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Background: The MSH2 and EXO1 are fundamental proteins involved in mismatch repair (MMR) system that contribute to DNA stability. The proteins are encoded by the polymorphic *MSH2* and *EXO1* genes. The C and A variant alleles of the *MSH2* IVS1+9G>C and *EXO1* K598E polymorphisms promote lower DNA repair than the respective G and G wild alleles, and seems to be involved on the onset of cancer. Since the roles of the above-mentioned polymorphisms in the risk of head and neck squamous cells carcinoma (HNSCC) are unclear, we aimed to analyze this issue in the present study.
Materials and Methods: Genomic DNA of 212 HNSCC patients and 212 controls was analyzed by the polymerase chain reaction and enzymatic digestion. The differences between groups were analyzed by the logistic regression model. Power analysis (PA) was used to verify the effect of sample size on the results obtained in the study.
Results: Patient's and control's samples were in Hardy–Weinberg equilibrium for *MSH2* (χ2= 0.81, P = 0.37; χ2= 2.11, P= 0.15) and *EXO1* (χ2= 0.02, P = 0.88; χ2= 1.89, P = 0.17) loci. The frequency of *MSH2*GC+CC combined genotype was higher in patients than in controls (83.5% *versus* 66.0%, P = 0.012, PA= 92%). Carriers of the C variant allele were at 2.10-fold (95% CI: 1.18–3.74) increased risk for HNSCC development than those with the wild genotype. An excess of the *EXO1*AA genotype was seen in patients when compared to controls (15.5% *versus* 9.0%, P= 0.028, PA= 88%). Individuals with the homozygous variant genotype were at 2.47-fold (95% CI: 1.10–5.53) increased risk for HNSCC than those with the remaining genotypes. Moreover, the frequency of *MSH2*GC+CC + *EXO1*GA+AA combined genotype was higher in patients than in controls (50.9% *versus* 35.4%, P = 0.037; PA>99.0%). Carriers of the variant alleles of the above-mentioned genes, when combined, were at 2.78-fold (95% CI: 1.06–7.26) increased risk for HNSCC than those with the respective wild genotypes. Similar frequencies of the distinct genotypes of the *MSH2* IVS1+9G>C and *EXO1* K598E polymorphisms were seen in patients stratified by clinical aspects and tumor biological features.
Conclusion: Our results suggest, for the first time, that *MSH2* and *EXO1* polymorphisms alone or combined, are important inherited risk factor for HNSCC. We believe that healthy carriers of variant alleles of both genes deserve additional recommendations for disease prevention and early diagnosis.
No conflict of interest.

3158 POSTER

Mesenchymal phenotype is associated with increased cell migration and cisplatin resistance in head and neck squamous cell carcinoma cell lines

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Background: We previously identified three head and neck squamous cell carcinoma (HNSCC) subtypes which were significantly associated with patient clinical outcome. The poor prognosis subtype presented mesenchymal features indicative of having undergone epithelial–mesenchymal transition (EMT). The purpose of this study is to study the relationship between the mesenchymal phenotype and response to cisplatin or cell migration in HNSCC cell lines.
Methods: We determined E-cadherin, N-cadherin and Vimentin protein expression in six HNSCC cells lines. We determined cisplatin sensitivity by XTT assays. For the migration assays, cells were deprived of FBS (12 h.), incubated in 24-well transwell plates (48 h.) and stained with crystal violet. We analyzed the gene expression profile of the cell lines using the HG-U133Plus2.0 array. Gene expression analysis was performed using Bioconductor. Probe sets with a FDR value lower than 0.05 were identified as differentially expressed.
Results: We identified two different morphologies and patterns of growth in HNSCC cell lines. UM-SCC-74B and SCC9 showed a fibroblast-like morphology and scattered growth, while UM-SCC-22A, UM-SCC-22B, SCC25 and Fadu grew forming cell colonies and depicted epithelial features. Western Blot and immunocytochemistry analysis showed a high Vimentin and N-Cadherin expression in UM-SCC-74B and SCC9. In addition, these two cell lines did not express E-Cadherin. This expression pattern was consistent with EMT. In contrast, UM-SCC22A and UM-SCC22B cell lines maintained E-Cadherin expression. Fadu and SCC25 expressed both epithelial and mesenchymal markers. We identified 93 genes differentially expressed by comparing the expression profiles between cells with mesenchymal and those with epithelial phenotype. Genes differentially expressed were associated with EMT (VIM, ZEB2, FGFR2 and FGFBP1), cell polarization (DAAM1), the secretory pathway (Rab38 and SRGN1) and differentiation (SPRR1A, SPRR3, SPRR1B, KRT6, S100A8 and S100A9). The cell lines with mesenchymal phenotype showed higher migration capacity than those with epithelial phenotype. SCC9 showed the highest resistance to 48 h of treatment with cisplatin.
Conclusion: Mesenchymal phenotype was associated with increased cell migration and cisplatin resistance in HNSCC cell lines. This could explain the poor rates of response and high recurrence rates, observed in patients having tumors that display mesenchymal features, after cisplatin-based chemotherapy.
No conflict of interest.

3159 POSTER

Role of IKBB, a NFKB inhibitor, as putative tumour suppressor candidate in nasopharyngeal carcinoma

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Background: Nasopharyngeal carcinoma (NPC), endemic in southern China and Southeast Asia, was ranked 4th as the most common new malignancy in Hong Kong. Inactivation of tumour suppressor genes (TSGs) through the loss of chromosomal regions is frequently reported in NPC, including chromosome 14. NFkB inhibitor, IkBB, a major isoform of inhibitor of kB, is a putative TSG candidate identified by our previous chromosome 14 microarray analyses. To date, the role of IkBB as a TSG is still largely unknown. In this study, we aimed to study the role of IKBB as a putative TSG candidate in NPC.
Material and Methods: Gene expression of IKBB in NPC tumour and matched normal tissue samples was determined by qPCR. Using a tetracycline-inducible system, IkBB-expressing clones were obtained for further phenotype and functional studies. Wound healing and HUVEC tube

formation assays were performed to study the inhibitory effect of IKBB on cell migration and angiogenesis fin NPC cell lines, respectively.
Results: The gene expression level of IkBB is down-regulated in approximately 40% of the NPC patient samples (n = 36), as observed by qPCR analysis. After 24 hours, stable IkBB-expressing clones (−DOX) show <50% of wound closure in average. Similarly, HUVEC tube formation is disrupted by IkBB, as compared to the vector-alone control (+DOX).
Conclusions: Down-regulation of IkBB in the majority of NPC patients indicates that IkBB may play an essential role as a TSG in NPC. Interestingly, our preliminary results on both wound healing and HUVEC tube formation assays demonstrate that IkBB exerts its tumour suppressive functions through inhibition of cell migration, proliferation, and angiogenesis. However, further investigation is warranted for further elucidation of the molecular and biological mechanisms of candidate TSG IkBB in cancer, specifically in NPC.
No conflict of interest.

3160 POSTER

The FASL −844C/T polymorphism is associated with inherited increased risk for head and neck squamous cell cancer

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Background: Fas ligand (*FASL*) is a member of the Tumor Necrosis Factor (TNF) super family and acts in cell apoptosis. The extracellular region of *FASL* binds to CD95 (*Fas*) and typically induces apoptosis in activated cells expressing *Fas*. The *FASL* −844C/T polymorphism, in the promoter region of the gene, impairs apoptotic signal transduction and is associated with the onset of tumors. We aimed in this study to analyze the role of the *FASL* −844C/T polymorphism in the head and neck squamous cell cancer (HNSCC) risk.
Material and Methods: Genomic DNA from peripheral blood of 268 consecutive HNSCC patients (aged 27−92 years; 248 males, 20 female, 227 Caucasians, 41 non-Caucasians) and 268 healthy subjects, matched to patients by gender and race, were genotyped using the polymerase chain reaction and enzymatic digestion. The differences between groups were analyzed by the logistic regression model. Power analysis (PA) was used to verify the effect of sample size on the results obtained in the study.
Results: Patients' and controls' samples were in Hardy–Weinberg equilibrium for *FASL* −844C/T ($\chi^2 = 0.031$, $P = 0.860$; $\chi^2 = 3.14$, $P = 0.076$) locus. The frequencies of the *FASL* CT and *FASL* TT genotypes were higher in patients than in controls (48.9% *versus* 44.0%, P = 0.008, PA = 99%, 31.0% *versus* 22.4%, $P = 0.002$, PA = 99%; respectively). Carriers of these genotypes were at a 2.22-fold (95% CI: 1.23–4.04) and 2.74-fold (95% CI: 1.45–5.20) increased risks for HNSCC development than those with the remaining genotypes. The frequency of *FASL* CT+TT combined genotype was also higher in patients than in controls (79.8% *versus* 66.4%, $P = 0.001$, PA = 99%). Carriers of the T variant allele were at a 2.45-fold (95% CI: 1.44–4.18) increased risk for HNSCC than those with the wild genotype. No differences in frequencies of the distinct genotypes were seen in patients stratified by clinical aspects and biological features of the tumor.
Conclusions: Our data suggest, that *FASL* −844C/T polymorphism alter consistently the risk for HNSCC. We believe that healthy carriers of the variant allele of the above-mentioned gene should receive additional recommendation to avoid smoking and alcohol consumption and to adhere to periodic follow-up for HNSCC prevention and early diagnosis.
No conflict of interest.

3161 POSTER

Inherited risk for head and neck squamous cell carcinoma and tumor suppressor gene MCC c.*5077A>G polymorphism

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Background: The mutated in colorectal cancer (*MCC*), a tumor suppressor gene, regulates negatively cell cycle progression. The *MCC* c.*5077A>G (rs7033) polymorphism may be related with the onset of tumors, but the role of the distinct alleles in gene expression is still unknown, as well as its role in head and neck (HN) squamous cell carcinoma (SCC). We aimed in this study to investigate whether this polymorphism would be an inherited risk factor for HNSCC.
Material and Methods: Genomic DNA of 150 HNSCC patients (27−85 years; 134 males, 16 females; 133 caucasians, 17 non-caucasians; 109 pharynx, 27 larynx, 14 oral cavity) and 150 controls matched to patients by age, gender and race were analyzed by TaqMan® genotyping assays. Significant differences between groups were evaluated by logistic regression model. Power of analysis (PA) was used to verify the effect of sample size on the results obtained in the study.
Results: HNSCC patient's and control's samples were in Hardy–Weinberg (HW) equilibrium for *MCC* c.*5077A>G locus ($\chi^2 = 3.8$, $P = 0.05$; $\chi^2 = 1.7$, $P = 0.19$). The frequencies of isolated *MCC* AA and combined AA+AG genotypes were higher in patients than in controls (59% *vs* 45%, $P = 0.02$, PA=79%; 98% *vs* 93%, $P = 0.04$, PA=73%; respectively). Carriers of the isolated and combined genotypes had a 1.9-fold (95% CI:1.13–3.25) and a 5.8-fold (95% CI:1.09–31.21) increased risks for HNSCC than others, respectively. The *MCC* AA genotype was also more common in male patients than in female patients (62% *vs* 31%, $P = 0.02$, PA=66%). The frequency of the genotype in male patients was also higher than that found in controls (62% *vs* 45%, $P = 0.001$, PA=98%). Male individuals with *MCC* AA genotype had a 2.6-fold (95% CI:1.45–4.76) increased risk for HNSCC than others. Additionally, the frequency of *MCC* AA genotype was similar in patients with pharynx SCC (PSCC) than in those with other types of HNSCC (61% *vs* 51%, $P = 0.16$, PA=21%). The samples of PSCC patients were in HW disequilibrium for *MCC* c.*5077A>G loci ($\chi^2 = 6.2$, $P = 0.01$). The frequency of the isolated *MCC* AA genotype was also higher in PSCC patients than in controls (61% *vs* 45%, $P = 0.009$, PA=87%). Carriers of the AA genotype had a 2.2-fold (95% CI:1.21–3.88) increased risk for PSCC than others.
Conclusions: Our results suggest, for the first time, that *MCC* polymorphism is an important inherited risk factor for HNSCC. We believe that healthy individuals with *MCC* AA genotype should receive additional care for HNSCC prevention and early diagnosis.
No conflict of interest.

3162 POSTER

Recurrent genomic alteration and high risk HPV with impact on prognosis in oropharyngeal cancer

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Objectives: The whole picture of chromosomal alterations in oropharyngeal cancer and their prognostic implications have not been well studied. We aimed to identify chromosomal changes and high risk HPV infection associated with prognosis in oropharyngeal cancers.
Methods: For this purpose, we analyzed copy number alterations in the discovery set of 32 oropharyngeal cancers using oligoarraycomparative genomic hybridization and validated the recurrently altered regions (RARs). High risk HPV in situ hybridization was performed to detect HPV infection.
Results: The positive rate of high risk HPV in situ hybridization was 28.1% (9/32). A total of 10 RARs were defined in the discovery set. Among them, gains on 16p11.2 and 17q12 showed significant associations with high risk HPV infection ($P = 0.019$ and $P = 0.019$, respectively). There was statistical significant association between gains on 16p11.2 and 17q12 with high risk HPV positivity and the disease-specific survival in patients with oropharyngeal cancer (p = 0.001).
Conclusion: Our findings will help to elucidate molecular mechanisms underlying tumorigenesis of oropharyngeal cancer with high risk HPV infection and to develop clinical tool for predicting prognosis of oropharyngeal cancer.
No conflict of interest.

3163 POSTER

Expression of Bmi-1 and ZEB1 in tongue squamous cell carcinoma and epithelial dysplasia

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Background: The Epithelial–mesenchymal transition (EMT), the crucial event for the invasion and progression of epithelial carcinogenesis, induces stem-like properties epithelial cells. However, the relationship between EMT in the carcinogenesis process of squamous cell carcinoma is not reported in most. Expression of Bmi-1 which is the stem cell line marker and ZEB1 which is the EMT inducer were studied on the role in the carcinogenesis process of tongue squamous cell carcinoma using immunohistochemistry.
Material and Methods: Sixty five tongue tissue specimens (33 carcinoma and 32 dysplasia) formed the materials of this study. We compared the expressions of Bmi-1, ZEB1, vimentin, E-cadherin with clinicopathologic parameters.
Result: By the immunohistologic examination, Bmi-1 was highly expressed in tumor cells at the invasive front compared with normal stratified squamous epithelia, demonstrated a significant correlation Between Bmi-1 expression and INF (Kruskal-Wallis H-test, p = 0.024).

Elevated levels of Bmi-1 were accompanied by downreguration of E-cadherin and the expression of vimentin at the invasive front, demonstrated a significant negative correlation between Bmi-1 and E-cadherin expressions (x^2-test, $p = 0.016$). Elevated levels of ZEB1 were found in tumor cells at the invasive front of advanced tongue carcinoma compared with normal stratified squamous epithelia, demonstrated no significant correlation Between ZEB1 and Bmi-1 expression.
Conclusions: As a result of this study, Bmi-1, ZEB1 and E-cadherin fulfilled the role which was important for EMT and invasion in tongue squamous cell carcinoma, and it was indicated to be concerned to various carcinogenesis process.
No conflict of interest.

3164 POSTER

The role of tumor markers and clinico-laboratories result in prognosis of relapse oral squamous cell carcinoma

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Background: The most common malignancy of the oral cavity is squamous cell carcinoma (SCC). The prognosis of treatment is limited by recurrent disease or lymph node metastasis. Secondary to, chemotherapy, surgery and radiotherapy, anatomical structures are often severely changed and make early diagnosis of renewed tumour growth by clinical and radiological examination difficult. The aim of this study was to estimate prognostic importance of value of serum tumour markers (CEA, SCC-Ag), performances of peripheral blood (WBC, ACN, PLT) characteristics, histological type of the tumour, tumour size in relation to the appearance of lymph node metastases and relapse in oral SCC.
Material and Methods: In the prospective study 133 cases of oral SCC were analysed. They were diagnosed from 2009 to 2011 in City clinical oncology centre, Saint-Petersburg, Russia. All patients were treated by standard protocol: the first phase was 1−3 cycles neoadjuvant chemotherapy (PF regime ± Cetuximab®). In the second phase all patients were conducted the radical surgical treatment. The third phase contained a post-surgery radiotherapy. All patients were examined by standard programs: vital signs, height, weight, BSA, ECOG status, physical examination, ECG, ultrasound examination and standard and special clinical pathology. The standard laboratories tests were WBC, ACN and PLT; the special tests were CEA and SCC-Ag which were detected with enzyme-linked immunosorbent assay (ELISA) and time-resolved fluoroimmunoassay (TRFIA). CEA and SCC-Ag were detected the first time before neoadjuvant chemotherapy, the second time before surgical treatment, the third time before radiology and in the end of radiology treatment. The level of WBC, ACN and PLT were taken from routine schedule. The data about localisation, histological type were taken from patient's medical files. All cases were followed up for 23±2.7 months. The follow-up period started from confirmed diagnosis to progressive disease.
Results: The earliest and latest recurrence occurred, respectively 5 and 26 month after radical treatment. The average recurrence time (PFS) was 16.4 months after radical complex treatment. The recurrence rate of oral cavity SCC, age, TNM staging, tumour's histological type and localisation, laboratory tests were taken into account for statistical analysis. There was statistically significant difference in level of serum tumour markers, level of WBC, ACN and PLT among the patients with and without disease relapse.
Conclusion: From the results, combination of high level of CEA and serum SCC-Ag, increasing counts of WBC, ACN and PLT, poorly differential histological type and localisation in the tongue and mouth floor was associated with poor prognosis. This complex of activities will apply practically as prognostic factors for the appearance of the disease relapse during and after complete treatment. Thereby, comprehensive analysis of complex common and special factors is recommended to predict early recurrence of oral SCC.
No conflict of interest.

3165 POSTER

The epidemiological factors in prognosis of recurrent HNSCC

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Background: The role of viral infection in relapse of HNSCC now is very discussed by many authors. Knowledge of epidemiology factors would give us the chance of real prognosis of the running of HNSCC and choosing correct scheme of complex treatment for each patient.
Material and Methods: In the prospective study 86 cases (group A) of oral SCC were analysed. They were diagnosed from 2010 to 2012 in City clinical oncology centre, Saint-Petersburg, Russia. All patients were treated by standard protocol for complex treatment: the first phase was 1−3 cycles neoadjuvant chemotherapy (PF regime). During the second phase all patients were conducted the radical surgical treatment. The third phase contained a post-surgery radiotherapy. All tumour tissues were studied for detection of expression of HPV6, 11, HPV 16 and HPV 18, EBV, CMV and HSV I and II before the treatment using real-time PCR (qPCR) analysis. Treatment response, progression free survival and their correlation with expressions of genes were obtained for all patients. The control group (group B) contained 35 healthy volunteers.
Statistical differences were considered significant if 'p' was <0.05.
Results: EBV was identified in 59.28% tumour samples (group A) and in 20% intact mucosa in group B. Frequency of occurrence HPV 6, 11, HPV 16 and HPV 18 was 6.8% in group A with HNSCC and in 40% cases in control group. CMV was identified in 3% cases in group with HNSCC and wasn't registerd in control group B. HSV I and II was registered in 2% patients in group A and 1% healthy volunteers.
Conclusion: Our preliminary results suggest, evaluation of EBV. HPV 6, 11, HPV 16 and HPV 18, CMV, HSV I and II before the planning of complex treatment of patients with HNSCC are appropriate for definition of disease prognosis and give possibility to provide individual treatment scheme for each patient. This complex of activities will apply practically as prognostic factors for the appearance of the disease relapse during and after complete treatment. Thereby, comprehensive analysis of complex common and special factors is recommended to predict early recurrence of oral SCC.
No conflict of interest.

3166 POSTER

10 year follow-up of high-dose intra-arterial cisplatin and concomitant radiation (RADPLAT) for advanced head and neck cancer

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Background: The RADPLAT randomized phase III trial compared intra-arterial (IA) to intravenous (IV) cisplatin-based chemoradiation for advanced stage IV head and neck cancer. In the IA regimen higher doses of cisplatin reached the tumor while the addition of IV sodium thiosulfate neutralized systemic exposure of cisplatin, thus minimizing the risk for toxicity. With 10 years of follow up data now available for the last patients, long term differences in late toxicity, locoregional control, overall and disease free survival can be assessed.
Material and Methods: This trial included 237 patients with inoperable squamous cell carcinoma of the oropharynx, oral cavity or hypopharynx, stage IV (T3-T4, any N, M0); WHO 0−1 and adequate laboratory parameters. Patients were randomly assigned to either radiotherapy (RT) + IA cisplatin or RT + IV cisplatin. The RT regimen consisted of a dose to the primary tumor and all nodal areas of 46 Gy in 23 fractions (fx), 5 fx/week, followed by a boost of 24 Gy in 12 fx to all involved areas including the primary tumor (total dose 70 Gy). A 3D conformal technique was used for all patients. Chemotherapy comprised cisplatin 150 mg/m^2 IA on days 1, 8, 15 and 22, followed by sodium thiosulfate 12 g/m^2 IV or cisplatin 100 mg/m^2 IV on treatment days 1, 22 and 43.
Results: Median follow-up was 90 months. Among 237 patients, 57 recurred locally, 35 regionally and 80 loco-regionally. There were 32 new primary tumors, 65 distant metastases (all as first events) and 154 deaths. No significant difference was found between treatment arms in locoregional control, survival or late toxicity. 95% of the recurrences occurred within 3 years. In multivariable analyses, increasing age and T-stage were linked with poorer severe-toxicity free survival ($p = 0.007$ and $p = 0.053$, respectively). The risk of developing any severe toxicity was 45% ($p = 0.037$), 67% ($p = 0.010$) and 73% ($p = 0.028$) lower in the 2nd, 3rd and 4th year after treatment, respectively, compared to the 1st year. Toxicities developing more than 3 years after treatment were found to have median

durations between 1 and 3 years, while those developing earlier ended after less than a year.
Conclusions: After 10 years of follow-up of the RADPLAT trial, we conclude that IA cisplatin is not superior to IV cisplatin. Therefore, IV cisplatin treatment remains the standard of care. The combination of the highest risk of severe late toxicity in the 1st year post treatment and the timing of (loco)regional recurrences indicates 3 years of follow up to be sufficient.
No conflict of interest.

3167 POSTER

Efficacy and toxicity of docetaxel/cisplatin/5-fluorouracil (TPF) induction chemotherapy followed by two schedules cisplatin-containing concomitant chemoradiotherapy (CRT) in patients with locally advanced head and neck cancer (LAHNC): The CONDOR study

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Background: TPF induction chemotherapy (ICT) has been associated with survival benefit compared to cisplatin/5-fluorouracil. However, hardly any data are available on TPF ICT followed by standard cisplatin-containing concomitant CRT. The aim of this multicentre phase II study was to evaluate the feasibility (>90% of the planned RT) of TPF followed by cisplatin-containing CRT schedules.
Material and Methods: Pts with LAHNC, PS 0−1 were included. They were treated with 4 TPF courses (T 75 mg/m^2, P 75 mg/m^2 and F 750 mg/m^2 day 1−5) and thereafter randomized between P 100 mg/m^2 on days 1, 22, 43 combined with conventional RT (arm A) or P 40 mg/m^2 weekly combined with accelerated RT (arm B). Based on power analysis for feasibility 70 pts were needed. Interim analysis for safety was planned.
Results: Between Dec 2008 and Dec 2011 65 pts were included; 2 were ineligible and 1 withdrew consent. 81.5% of pts was male, median age was 56 yrs and PS was 0 in 79%, primary site: oral cavity (23%), oropharynx (57%), hypopharynx (12%), larynx (8%). Six (10%) of the 62 pts were not randomized after TPF, due to death (1), toxicity (3) or PD (2). 27 pts were randomized to arm A and 29 to arm B. 96.4% of the pts received the total planned irradiation dose. However, only 22% of pts in arm A and 41% pts in arm B, received the total planned cisplatin courses during CRT due to toxicity. Grade 3−4 toxicity during CRT consisted of: dehydration (26% vs 14%), dysphagia (26% vs 24%), mucositis (22% vs 57%) and rise in serum creatinin (19% vs 3%) in arm A vs arm B. After the second interim analysis the low rate of pts tolerating cisplatin during CRT was reason to terminate further inclusion of pts in the study.
Response after TPF was CR in 4 pts (6.5%), PR in 34 pts (54.8%), SD in 19 pts (29.2%), PD in 2 pts (3.2%). The RR twelve weeks after end of CRT is shown in the Table. After a median follow up of 23 months (0−49) 2 years OS and DFS survival was equal in both arms (Table).
Conclusions: Cisplatin-containing concomitant CRT after induction TPF is not feasible with the used schedules. Although after induction TPF only 32% of the pts completed the planned concomitant treatment, OS and DFS compared favorable relative to other schedules employing concomitant CRT or TPF containing regimens in LAHNC.
No conflict of interest.

	Total pts (62)	Arm A (27)	Arm B (29)	
RR after TPF	61.3% (CR: 6.5%; PR 54.8%)			
RR 12 weeks after CRT		81.5% (CR: 62%; PR 23%)	72.4% (CR: 55%; PR 17%)	ns
OS (2 yrs)	70%	77%	76%	ns
DFS (2 yrs)	63%	69%	68%	ns

3168 POSTER

Phase I trial of nab-paclitaxel (A), cisplatin (P) and 5-fluorouracil (F) induction chemotherapy (IC) followed by concurrent chemoradiotherapy (CCRT) in patients (pts) with locoregionally advanced squamous cell carcinoma of head and neck (LA-SCCHN): final results

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Background: Sequential therapy (IC followed by CCRT) has been evaluated in the treatment of LA-SCCHN, with triplet IC (docetaxel, P and F) shown to be superior to PF doublet. The final results of a study evaluating 130nm albumin-bound paclitaxel (A) in SCCHN are presented here.
Methods: A phase I trial to determine maximum tolerated dose, recommended phase II dose (RP2D), and assess the safety and preliminary efficacy of APF as IC for 3 cycles followed by concurrent carboplatin (Cb) (AUC 1.5 weekly) with radiation therapy (RT) (70 Gy/35), was conducted using a 3+3 design in previously untreated LA-SCCHN pts. Dose-limiting toxicities (DLT) included: standard hematologic and non-hematologic toxicities, treatment delays, inability to complete $\geqslant$95% of RT and skin/mucosal toxicity related to RT were assessed from day 1 of IC to 8 weeks after completion of CCRT.
Results: 17 pts were enrolled at 3 dose levels: M:F = 14:3; median age = 54 yrs (range 44−65 yrs); ECOG 0:1 = 5:12; oropharynx p16 positive/negative/unknown = 11/2/4; T1/2/3/4 = 2/4/5/6; N2a/2b/2c/3 = 1/3/7/6. 15 pts were DLT evaluable (1 withdrew consent, 1 PD after cycle 1 of IC). Dose level 1 was considered toxic despite 1/3 DLT since both pts without DLT missed d8 of cycles 2 and 3; dose level −1A was evaluated as intermediate between dose levels 1 and −1. Common Gr 3/4 adverse events (no. of pts) were: lymphopenia (12), stomatitis (10), neutropenia (7), dysphagia (4) and hyponatraemia (4). Best response to IC include: partial response 10 pts (63%) stable disease 5 pts (31%), progressive disease 1 pt (6%). At median follow-up of 12.3 months, 2 deaths were observed: 1 due to disease relapse and 1 due to intercurrent illness. Median progression-free survival has not been reached, 2-year PFS rate = 73% (95% CI, 38−91%).
Conclusion: The RP2D of APF was: A 100 mg/m^2 IV d1+d8, P 75 mg/mg^2 IV d1 and F 1000 mg/m^2/d CIV x 96 hrs d1−4, Q3W, for 3 cycles prior to CCRT.
Study APF-001; clinicaltrials.gov identifier NCT00731380; Sponsored by University Health Network, Toronto, Canada.
No conflict of interest.

Dose level	Induction regimen	No. of DLT/ No. of evaluable pts	DLT descriptions
1	A 75 mg/m^2 d1+d8, P 100 mg/m^2 d1, F 1000 mg/m^2/d $\times$ 96 hrs, Q3W $\times$ 3 cycles	1/3	Febrile neutropenia; inability to receive 95% of RT; received <6/7 doses of Cb due to Gr3 stomatitis
−1	A 75 mg/m^2 d1+d8, P 75 mg/m^2 d1, F 1000 mg/m^2/d $\times$ 96 hrs, Q3W $\times$ 3 cycles	1/6	Received <6/7 doses of Cb due to Gr3 stomatitis and prolonged neutropenia
−1A	A 100 mg/m^2 d1+d8, P 75 mg/m^2 d1, F 1000 mg/m^2/d $\times$ 96 hrs, Q3W $\times$ 3 cycles	1/6	Gr3 stomatitis during IC

3169 POSTER

A phase II study of nimotuzumab and CDDP concurrent with radiation in locally advanced squamous cell carcinoma of the head and neck (SCCHN) [NCT00702481]

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Background: Nimotuzumab is a humanized monoclonal antibody (MAb) to EGFR. Concurrent cisplatin with radical radiotherapy (RT) is standard treatment for locally advanced SCCHN where it is unresectable or for

organ-preservation. We explored the combination of nimotuzumab with concurrent CDDP and RT in these patients (pts).
Materials and Methods: Patients with locally advanced stage III/IV SCCHN were eligible for study if: age >18, ECOG 0−1, SCC, normal organ function. CDDP 100 mg/m^2 on days 1, 22, and 43 was given with RT (70 Gy over 35 fractions). Nimotuzumab was given as a flat dose of 200 mg weekly on weeks 1 to 8 of treatment. Pts were followed up for RECIST response, progression free survival and toxicity. Using Simon's minimax 2-stage design with a type I error of 5%, power of 80%, target response rate of 70% and no further interest rate of 50%, a total of 37 patients were required. The combination would be considered for further study if 24 or more responses of 37 were reported. Analysis was by intention-to-treat (ITT).
Results: Thirty seven patients were recruited. The median age was 57 (29−68). Most were Chinese (76%) and all ECOG 0−1. The ratio of oropharynx/non-oropharynx was 19 (51%):18 (49%). Majority of pts had stage IVA disease. Per protocol treatment was completed in 76% of pts. Twenty-nine pts were evaluable for response, 3 pts withdrew from study, 1 early death from undiagnosed Fanconi's anemia, 4 pts did not have post-treatment scans (2 unconfirmed PR). By ITT, the response rate was CR: 43%/PR: 30% (ORR = 73%), PD: 5%. Pts with oropharynx Ca had significantly higher 1-year PFS rate than non-oropharynx (90% vs 42%, P = 0.019). Major G3/4 toxicities were limited to mucositis, dysphagia, and hyponatremia. One G5 toxicity from febrile pancytopenia occurred in 1 pt with undiagnosed Fanconi's. Acneiform rash typical of EGFR MAb was limited to G1/2 severity. Thirteen patients with non-oropharynx cancer were referred with organ-preservation intent. Of these, 11 completed treatment and the ORR was 77% (CR/PR). Seven pts relapsed. Three pts who had locoregional relapse underwent successful salvage surgery.
Conclusions: This combination is tolerable and acneiform rash was distinctly minimal. Pts with oropharynx Ca had significantly better 1-yr PFS than non-oropharynx Ca. This combination is being evaluated in a phase 3 randomized controlled study as adjuvant therapy following surgery for resectable disease (NCT00957086).
No conflict of interest.

3170 POSTER

Comprehensive genotyping of the receptor tyrosine kinase pathway using semi-conductor sequencing in HPV+ and HPV− oropharyngeal cancers (OPC)

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Background: Recently, HPV was recognized as an important etiological and prognostic factor in OPC. At this moment treatment of locally advanced OPC consists of concomitant CRT or cetuximab-RT in elderly or non-fit patients. In OPC no predictive marker for response to EGFR inhibition is known. Therefore genotyping is of utmost importance, but is often hampered by the small amount of tumour material available. The aim of this study is to assess the feasibility of testing actionable mutations in multiple genes of the receptor tyrosine kinase (RTK) pathway in small amounts of formalin fixed paraffin embed (FFPE) material and to determine the frequency of these mutations in HPV+ and HPV− OPC.
Materials and Methods: We included the archival material of 50 OPC, 25 HPV+ and 25 HPV-, all treated with concomitant CRT between 2003 and 2010. We assessed mutations in the RTK-pathway using an in-house developed gene-panel that targets 90 genetic regions in 22 genes using the AmpliSeq technology (Life Technologies). The single multiplex PCR requires only 10 ng input DNA. 8 samples were pooled and sequenced on an Ion 316 chip using the Ion PGM 200 sequencing kit protocol. Data were analysed using SeqNext software package 4.0.1 (JSI). All variants were confirmed by Sanger sequencing.
Results: So far 12 HPV- and 9 HPV+ samples OPC have been successfully analysed. As expected we identified a *TP53* mutation in almost all HPV− samples (11/12), while no *TP53* mutations were detected in the HPV+ samples. We only identified 1 mutation in the RTK-pathway, i.e. in *FGFR3* in an HPV+ patient, and 1 incidental mutation in *FBXW7* in an HPV− patient. We are currently expanding the series and re-analysing the data for gene deletions and/or amplifications.
Conclusion: We developed an assay to identify mutations in the RTK pathway with high sensitivity by semiconductor-based sequencing. As only small amounts of FFPE material are sufficient for reliable analysis, this test opens new possibilities to investigate small biopsies of primary tumours and metastases even when only archived clinical material is available. This is of special importance for head and neck cancer pts, of which we do have a limited amount of archival material, especially in those patients, which are not surgically treated. In the near future we will test HPV+ en HPV− OPC patients to investigate if we can detect mutations that can predict responsiveness to EGFR inhibition.
No conflict of interest.

3171 POSTER

Radiotherapy, gemcitabine, and cetuximab (RAGE) in patients (pts) with locoregionally advanced squamous cell carcinoma of the head and neck (LA-SCCHN): A feasibility study

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Background: Concurrent chemoradiation (CCRT) is the standard treatment for inoperable LA-SCCHN. Gemcitabine and cetuximab are potent, synergistic radiosensitizers. The aim was to study the feasibility of the gemcitabine, cetuximab, and radiotherapy (RT) combination in SCCHN.
Material and Methods: Eligible were patients with SCCHN who qualified for definitive CCRT. Cetuximab 400 mg/m^2 was started 1 week before (RT). Gemcitabine 10 mg/m^2 and cetuximab 250 mg/m^2 were administered weekly for the duration of RT (32 fractions, 5 fractions/week, up to 69.12 Gy, simultaneous integrated boost technique). Induction chemotherapy prior to RAGE was allowed. During RAGE, toxicity was scored weekly according to NCI-CTC version 4.
Results: 17 patients (15 male) were treated between April 2010 and June 2012. Median age: 60 (range: 47−72). Tumor sites: hypopharynx: 7; oropharynx: 5; supraglottis: 2; maxillary sinus, tongue, unknown: each 1. Stage: T2N1: 2; T2N2b: 2; T3N2b: 4; T1N2b, T1N3, T3N0, T3N2c, T3N3, T4N1, T4N2b, T4N2c, recurrence after prior surgery and RT: each 1. In 13 patients, RAGE was preceded by induction chemotherapy: 6 x weekly carboplatin (AUC 2)/paclitaxel (70 mg/m^2): 2; TPF: 10 (4 cycles: 9; 2 cycles + weekly carboplatin/paclitaxel: 1 [stop TPF for renal toxicity]); 4 x docetaxel, 5-FU, carboplatin: 1. Median duration of RT: 44 days (range: 42−50). Duration of RT was $\leqslant$47 days in 16 patients, 50 days in 1. 17/17 received planned RT dose. Gemcitabine and cetuximab dose intensity was >98%. Toxicity during RAGE is shown in table (maximum grade; number of patients).

Grade	1	2	3	4
Radiodermatitis	1	5	9	2
Mucositis		1	16	
Weigth loss	3	2	9	

9 patients needed temporary tube feeding or parenteral nutrition, 9 needed hospitalization(s) (16 episodes, median duration: 13 days). 15 needed opioids. 1 patient (T3N2b hypopharynx) required a partial colectomy followed by prolonged tracheal intubation for a bowel perforation (diverticulitis) 9 days after the end of RAGE (which was preceded by 4 x TPF). He required a laryngectomy for laryngopharyngeal dysfunction 12 months after RAGE (no tumor in specimen). 1 patient (T3N3 at diagnosis) was rendered tumor-free by salvage lymphadenectomy. 2 patients had persistent unresectable local disease at the end of RAGE. Lung metastases developed in 2 (1 with persistent local disease), a local recurrence in 1. Median follow-up for surviving patients is 21 months (range: 8−35). 12 patients are alive without evidence of SCCHN disease, all feeding-tube independent. No toxicity-related deaths.
Conclusions: With adequate support, the concomitant administration of cetuximab, gemcitabine and RT in SCCHN patients is feasible, both with and without induction chemotherapy, without treatment interruptions, with patients receiving >98 % of planned cetuximab and gemcitabine dose, and 100 % of planned RT dose.
Conflict of interest: *Advisory board: Jan B Vermorken participated in advisory boards of Merck-Serono, Amgen, Genentech, and Boehringer-Ingelheim. Corporate-sponsored research: The project was funded by an unrestricted grant from Merck Serono*

3172 POSTER

A phase II randomized study to compare short course palliative radiotherapy with short-course concurrent palliative chemotherapy plus radiotherapy in advanced and unresectable head and neck cancer [interim analysis]

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Background: Head and neck cancer is the commonest cancer in India. Locally advanced and unresectable disease constitute one third of cases. Treatment for this group is not very well defined and has poor results.
Materials and Methods: Patients with locally advanced and unresectable squamous cell carcinoma of oral cavity, oropharynx or hypopharynx were randomized either to arm A [Short course palliative RT alone(4 Gy/#/day on 5 consecutive days, to a total of 20 Gy in the first schedule)] or arm B [short course concurrent palliative CTRT]. RT was identical in both arms. In arm B, cisplatin was given as i.v. bolus at 6 mg/m^2/day along with RT. Patients in both the arms were taken for further radical treatment [FRT] only if they had atleast a PR both clinically and radiologically. Patients eligible for FRT were given RT at 2 Gy/#/day with a total radiobiological equivalent dose of 70 Gy, in both the arms. In arm B, concurrent Cisplatin was given at a dose of 40 mg/m^2/week along with RT. Response and toxicity assessment was done at 4 weeks; and proportion of patients eligible for FRT, OS and PFS was compared between the treatment arms.
Results: Enrollment started in March 2012 and is ongoing. Of 100 planned patients, 53 patients who have completed 6 months of follow-up are included in this interim analysis. Median age for the whole cohort was 55 years [range, 27−74 years]; 44 patients were male. 26 patients were randomized to arm A and 27 to arm B. At 4 weeks, 8 patients [32%] in arm A and 16 (59%) in arm B had either CR or PR and 17 (68%) in arm A and 11 (41%) in arm B had SD or PD ($p = 0.045$). 7 patients (27%) in arm A and 16 (59%) in arm B were taken for FRT ($p = 0.027$), At 1 month, significant symptom relief was noted for pain ($p = 0.029$) and trismus ($p = 0.049$) in arm B. At 1 week, grade 3/4 toxicities were not significantly different between both arms and no grade 3/4 toxicity was noted at 1 month. At a median follow-up of 8.5 months, median OS was 5.4 months for arm A and 6.9 months for arm B and estimated OS at 6 months was 44.5% and 55.6% respectively ($p = 0.292$). Median PFS was 2.6 months (95% CI, 2.2−3.1) for arm A and 8.8 months (95% CI, 3.0–14.6) for arm B and estimated PFS at 6 months was 28.1% and 60.9% respectively ($p = 0.012$).
Conclusion: Compared to palliative RT alone, concurrent low dose CTRT improves PFS for advanced and incurable HNSCC with tolerable toxicity profile.
Clinical trial registry number: CTRI/2012/06/002717
No conflict of interest.

3173 POSTER

Toxicity and efficacy of concomitant chemoradiotherapy with weekly cisplatin for locally advanced head and neck carcinoma

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Background: This retrospective study reports on the acute toxicity, relapse pattern and survival of (patients) pts treated with weekly cisplatin concomitant with accelerated radiotherapy (AR) as primary treatment for locally advanced head and neck carcinoma (LAHNC).
Material and Methods: Between 2003 and 2010, 106 pts with LAHNC of the oral cavity (n = 12), oropharynx (OPC) (n = 53), hypopharynx (n = 34) and larynx (n = 7), median age 57 yrs, male 76.4%, stage III 17.9% and stage IV 82.1% were enrolled in this protocol in our institute. Treatment consisted of cisplatin 40 mg/m^2 weekly concomitant with AR with concomitant boost up to a dose of 68 Gy over 5.5 weeks. IMRT was used in 30 pts. Acute toxicity was recorded based on the CTC v3.0. HPV analysis was performed using p16 immunohistochemistry and PCR.
Results: AR was given as planned without interruptions in 97.2% of pts; 60.4% received all 6 cycles and 89.6% received at least 5 cycles of cisplatin. Overall dermatitis was seen less in pts treated with IMRT ($p = <0.05$); dermatitis grade 3 was present in 53.6% of pts treated without IMRT and 26.7% with IMRT (ns). Grade 3 mucositis was observed in 86.8% of the pts treated without IMRT vs 76.7% treated with IMRT (ns). The majority of pts (78.7%) were temporary feeding-tube dependent, median 9.0 weeks during and directly after treatment, the prevalence of tube feeding at 12 months was 3.7%. Only 1 pt developed a grade 1 nephrotoxicity. Gastro-intestinal toxicity of cisplatin was mild. There was 1 toxic death due to sepsis. The median follow-up was 34 months (range 2−92 months). The 3-year loco-regional control (LRC), DFS and OS were 70%, 51% and 61% and 5 yrs LRC, DFS and OS were 64%, 38% and 48%, respectively. In 50 of the 53 pts with OPC HPV status could be determined; PCR and p16 were positive in 11 pts. OS after 3 and 5 yrs was 81% and 67% in HPV + pts and 72% and 55% in HPV − pts (ns).
Conclusion: Weekly cisplatin 40 mg/m^2 concomitant with AR with concomitant boost is feasible and associated with a high level of compliance. LRC and survival rates in this series of predominantly HPV− LAHNC pts, are at the upper percentile of what is reported in literature using cisplatin 100 mg/m^2 (day 1−22−43) concomitant with conventional RT. We suggest that LAHNC pts with renal impairment are treated preferably with weekly cisplatin 40 mg/m^2, as renal toxicity with this schedule is infrequent.
No conflict of interest.

3174 POSTER

Nimotuzumab with induction chemotherapy and chemoradiation in patients with advanced head and neck cancer: A pilot study

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Background: Head and neck squamous cell carcinoma (HNSCC), is a common malignancy in the Indian population. In locally advanced disease, chemoradiation is the standard of care. Although induction chemotherapy has been much studied, no clear benefit has been identified apart from laryngeal preservation. A few randomised trials have demonstrated improved response rate, disease free survival, and overall survival with induction chemotherapy. Nimotuzumab is a humanized monoclonal antibody targeting EGFR receptors and has been demonstrated to be safe and effective when combined with chemotherapy and/or chemoradiotherapy. We evaluated safety and efficacy of administrating Nimotuzumab with chemotherapy to target EGFR over expression in patients with HNSCC in usual health care setting.
Material and Methods: The present study was an open label single arm study, with a retrospective analysis of results. Patients of age 18 years and above with histologically confirmed advanced HNSCC were included in the study. Informed consent was obtained from all the patients. The patients were treated with three cycles of induction chemotherapy consisting of modified TPF regimen along with Nimotuzumab (200 mg IV) on day 1, followed by radiotherapy for a dose of 66 Gy along with concurrent weekly Cisplatin (30 mg/m^2) and Nimotuzumab (200 mg) throughout the course of radiation. Patients were evaluated based on RECIST criteria, four weeks after completion of radiotherapy.
Results: Sixteen patients were included this study. Mean age of the patients was 54±11 yrs. Most common subsite of cancer was oral cavity in 69% (n = 11), followed by pharynx in 19% (n = 3). Four patients had metastasis at the time of presentation. Six patients (37.5%) had a complete response, six patients (37.5%) had progressive disease and four patients (25%) were lost to follow up. The combination chemotherapy with Nimotuzumab was well tolerated. Addition of Nimotuzumab to TPF regimen was not associated with added toxicity.
Conclusions: Addition of Nimotuzumab to induction chemotherapy and chemoradiation may be a promising alternative to concurrent chemoradiotherapy in HNSCC due to the known overexpression of EGFR receptors. The results of this study need further evaluation in a larger study setting.
No conflict of interest.

3175 POSTER

Predicitve factors of cisplatin completion/discontinuation in concurrent chemoradiotherapy to locally advanced head and neck cancer patients

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Background: Concurrent chemoradiotherapy (CCRT) with cisplatin (CDDP) is a standard therapy for locally advanced head and neck cancer

patients, but some patients have intolerance to high dose density of CDDP. Predictive factors for CDDP completion/discontinuation need to be investigated for making appropriate treatment decisions.
Material and Methods: We retrospectively analyzed non-metastatic head and neck cancer patients treated with CCRT with CDDP (80 mg/m^2 per 3 weeks) from November 2005 to April 2012 in our institute. Radiation therapy was performed as three-dimensional radiotherapy or intensity-modified radiotherapy (IMRT).
Results: A total of 164 patients received CCRT, of which 89 (54 %) were Stage 4. Primary sites were as follows; oral cavity 7, oropharynx 52, hypopharynx 53, larynx 14, nasopharynx 30, paranasal sinus/nasal cavity 3, and unknown primary 5. IMRT was performed to 54 (33 %) patients. Median follow-up time was 19 months (range 1−69 months); 1-year overall survival (OS) and progression free survival (PFS) were 90 % and 78%. Non-Stage 4 and high creatinine clearance (>70 ml/min) were associated with longer OS in Cox proportional hazard model (p = 0.004, hazard ratio 5.923; p = 0.001. hazard ratio 4.167, respectively). As for CDDP treatment cycles, 75 (46 %) patients completed 3 cycles of CDDP, 69 (42 %) patients received 2 cycles, and 20 (12 %) patients received only 1 cycle because of adverse events. The main reasons for CDDP discontinuation were infection (24 patients) and renal dysfunction (18 patients). In logistic regression analysis, male sex, younger age (<61 years) and high body mass index (BMI) (>25) were associated with 3 cycles completion of CDDP statistically significantly (p = 0.002, odds ratio 6.622; p = 0.006, odds ratio 2.602; p = 0.035, odds ratio 2.655, respectively).
Conclusions: In CCRT to head and neck cancer patients, infection and renal dysfunction were the main reasons for CDDP discontinuation. Sex, age and BMI could be predictive factors of CDDP continuation.
No conflict of interest.

3176 POSTER

Quality of life of elderly patients receiving weekly carboplatin and paclitaxel chemotherapy plus cetuximab first line for metastatic squamous cell carcinoma of the head and neck

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Background: A phase III trial demostrated that Cetuximab is the first agent to improve survival when added tho platinum-based chemotherapy for metastatic squamous cell carcinoma of the head and neck. The safety and tolerability of a combination of weekly Paclitaxel and Carboplatin and the epidermal growth factor receptor (EGFR) monoclonal antibody Cetuximab for the first line treatment for metastatic squamous cell carcinoma of the head and neck in elderly population were investigated.
Patients and Methods: Patients >70 years of age with histologically confirmed metastatic squamous cell carcinoma were enrolled. Other eligibility criteria included: measurable disease (using RECIST), Karnofsky performance status (KPS) >60% and adequate hematologic, hepatic and renal functions. Patients receiving Paclitaxel (80 mg/mq), Carboplatin AUC 2 and Cetuximab (400/250 mg/mq) weekly. Treatment was continued for a maximum of six cycles of chemotherapy. After six cycles, patients in the who had at least stable disease received cetuximab monotherapy until disease progression or unacceptable toxicity. The European Organisation for Research and Treatment of Cancer QoL Questionnaire-Core 30 (QLQ-C30) and QLQ-Head and Neck 35 (QLQ-H&N35) module were used to assess QoL.
Results: From September 2010 to September 2012 were evaluated 40 patients with metastatic squamous cell carcinoma of the head and neck. Patients were scheduled to complete the questionnaires at screening or baseline, on day 1 of every cycle. The analysis of the responses to the questionnaires from patients shows that the pattern of chemotherapy used provides excellent control of symptoms related to the disease. Common grade 3/4 adverse events were acne-like rash (18%), asthenia (20%) and neutropenia (10%).
Conclusion: This analysis shows an important clinical benefit of chemotherapy regimen proposed in the population included in the study. Relevant results in terms of overall survival, PFS, in response rates and disease control.
No conflict of interest.

3177 POSTER

Weekly cisplatin concurrently with radiotherapy in head and neck squamous cell carcinoma: A retrospective analysis of a tertiary institute

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Background: The widely used regimen in locally advanced head and neck squamous cell carcinoma (HNSCC) of combined radiation and 100 mg/m^2 of cisplatin every three weeks on day 1, 22, and 43 causes severe toxic effects. To limit toxic effects alternative schedules are being used, including once weekly cisplatin dose of 40 mg/m^2. Here, we report the cumulative dose, compliance and the acute toxicities of weekly cisplatin given concurrently with radiation in HNSCC patients in a single tertiary institute.
Methods: Retrospective review of data of HNSCC patients treated with concurrent weekly cisplatin and radiotherapy between January 2012 and January 2013 in St James's Hospital, Dublin. Toxicities were defined according to the common terminology criteria for adverse events (CTCAE) Version 4.0.
Results: 52 patients with squamous cell carcinoma of the oropharynx (73%), larynx (19%), or hypopharynx (8%) were treated with concurrent standard radiotherapy and weekly 40 mg/m^2 of cisplatin for 6 consecutive weeks in the study period. 19 (36.5%) patients had stage IV disease and 33 (63.5%) had stage III. Treatment was given as radical chemoradiation or adjuvant chemoradiation in 35(67%) and 17 (33%) patients respectively. Cumulative dose of 200 mg/m^2 or more was reached in 37 (71%) patients. 22 (42.3%) patients completed 6 cycles of cisplatin. Commonest adverse effects were mucositis, neutropenia, and renal toxicity in a decreasing order of frequency. Grade 3 and 4 mucositis occurred in 22 (43.3%) and 12 (23%) patients respectively. Grade 3 and 4 neutropenia occurred in 6(11.5%) and 3 (5.7%) respectively. No grade 3 or 4 renal toxicity occurred in the study cohort. Death occurred in one patient due to neutropenic septicemia.
Conclusion: Weekly cisplatin at 40 mg/m^2 combined with radiotherapy is a feasible option in the treatment of locally advanced HNSCC. Adverse effects are generally manageable; however it might affect treatment completion. Due to lack of strong comparative data from large phase III trials with three weekly cisplatin, each center will continue to develop its own experience in selecting the ideal regimen for different patients' populations.
No conflict of interest.

3178 POSTER

Neoadjuvant chemotherapy in 13 patients with locally advanced poorly differentiated thyroid carcinoma − a phase 1/2 study

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Background: There is a paradigm that chemotherapy is ineffective in thyroid carcinoma. The aim of our study was to find out if neodjuvant chemotherapy before thyroid surgery had effect on the size of primary tumor in patients with poorly differentiated thyroid carcinoma.
Patients and Methods: Altogether 13 patients (8 women, 5 men; median age 61 years) with poorly differentiated thyroid carcinoma were treated with neoadjuvant chemotherapy from 1986–2005 at our institute. Papillary and follicular poorly differentiated carcinoma was diagnosed in 5 and 8 patients, respectively. Tumor diameter was from 4.5−18 cm (median 9 cm). Regional and distant metastases were detected in 6 and 8 patients, respectively. Eight (61%) patients had pT4 tumor. Chemotherapy consisted of Vinblastine, Vinblastine with Adriamycin or Vinblastine with Cysplatin in 11, 1 and 1 cases, respectively.
Results: Altogether, 29 (range 1−5) cycles of chemotherapy were given. Tumor size decreased for more than 50% in 5 patients (=38%). Chemotherapy was effective in follicular and papillary thyroid carcinoma in 37.5% and 40%, respectively. Total thyroidectomy, lobectomy and neck dissection was performed in 10, 3 and 5 cases, respectively. R0 resection was done in 8 cases and R1 resection in 5 cases. Eight patients had postoperative external beam irradiation of the neck and upper mediastinum. Distant metastases were diagnosed in two patients during follow-up of 7–189 (median 118) months. Seven patients died of distant metastases, one of other causes, while five patients are alive. The 5-year and 10-year cause-specific survivals of the patients were 77% and 46%, respectively.
Conclusions: Neoadjuvant chemotherapy may decrease tumor size for more than half in 38% of patients with poorly differentiated thyroid carcinoma.
No conflict of interest.

3179 POSTER

25-year experience with primary major salivary gland carcinoma at a single institution in Japan

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Background: Salivary gland cancers (SGC) are rare neoplasms which account for less than 5% of all cancers of the head and neck. The major histological subtypes mucoepidermoid carcinoma (MEC), acinic cell carcinoma (AcCC) and adenoidcystic carcinoma (AdCC) together account for about 60% of cases, but SGC encompass a wide spectrum of histologies with varied biologic behavior. Further, geographic variation in subtype frequency is present.
Patients and Methods: We retrospectively reviewed 150 Japanese patients (pts) with malignant SGC from medical records between 1987 and 2012. Thirteen pts with metastatic salivary tumors and 9 who received initial treatment at other institutions were excluded, leaving 128 pts with primary major SGC for analysis. Clinical and pathological information was corrected from medical records. Histology was re-evaluated using the WHO classification (2005) and re-staging with UICC 7^{th}.
Results: Pts consisted of 81 men and 47 women (median age 62 years, range 5 to 88). Primary tumor sites were the parotid gland (74%) and submandibular gland (25%). 40% of pts had pain and 27% had facial paralysis at initial diagnosis. 56% of pts presented with a stage IV tumor, and 89% received surgery as initial treatment. Neck dissection and postoperative radiation were carried out for 68% and 40%, respectively. Locoregional recurrence was observed in 22%, and distant metastasis in 30%. Incidence of subtypes was MEC (24%), AdCC (19%), carcinoma ex pleomorphic adenoma (EXPA, 15%), adenocarcinoma (ADE, 11%), squamous cell carcinoma (SCC, 11%), salivary duct carcinoma (SDC, 9%) and AcCC (7%). On follow-up (median 42 months), overall 5-year survival rate was 75%, and that of subtypes was 86%, 80%, 60%, 62%, 91%, 67%, and 100%, respectively. Although univariate analysis revealed that high grade SGC, T4 disease, node positivity, Stage III/IV, pain, and facial paralysis had statistically significant poorer survival, multivariate analysis suggested that T4 disease (HR: 7.29, 95% CI: 2.33–22.80, p = 0.001) and node positivity (HR: 4.20, 95% CI: 1.35–13.11, p = 0.013) were dependent prognostic factor for survival.
Conclusion: This is one of the largest clinicopathological reports of major SGC from Japan. The incidence of histological subtypes in our institution differed slightly from those reported previously, in particular a higher rate of SDC and lower rate of AcCC, but prognosis and prognostic factors were closely similar.
No conflict of interest.

3180 POSTER

Adenoid cystic carcinoma of head and neck: A single institutional analysis of 73 cases treated with multimodality approach

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Background: Adenoid cystic carcinoma (ACC) accounts for less than 5% of head and neck (H&N) cancers. These are usually locally invasive tumors with propensity for perineural invasion, osseous involvement, local and distant failure.
Materials and Methods: Medical records of 73 patients of ACC of H & N region from 1995–2011 were retrieved from the departmental archives and analyzed for demographic profile, clinical presentation, disease site, stage, treatment modalities and survival outcome. Patients were retrospectively staged as per AJCC (2010) TNM classification. Disease free survival (DFS) was estimated by Kaplan Meier method. SPSS version 12.0 was used for statistical analysis.
Results: Median age at presentation was 35 years (range 12−73 years) and male: female ratio was 34:39. Primary disease site was sino-nasal in 23 (31.5%) patients, lacrimal gland in 14 (19.1%) patients, salivary gland in 25 (34.25%; 15 major & 10 minor salivary glands) patients and others in 11 patients. AJCC T stage was T4, T3, T2 and unknown in 15%, 23%, 55% and 7% of patients, respectively.10 patients had clinical and 8 patients had pathological node positive disease.15 (20.5%) patients had either intracranial or skull base extension. 57 (78%) patients were treated with surgery followed by radiotherapy (60−64 Gray at 2 Gray per fraction) and concurrent chemotherapy (cisplatin 40 mg/m^2 weekly) was used in 8 of these patients. 3 patients underwent surgery alone. 9 patients (lacrimal gland ACC) had surgery followed by adjuvant chemotherapy (3−6 cycles of cisplatin and doxorubicin). 4 patients with advanced disease received palliative radiotherapy (20−30 Gray/ 5−10 fractions/ 1−2 weeks). 17 (24.64%) patients had margin positive disease and all of them received post-operative radiotherapy.
Median follow up duration was 20 months (range 12–211 months). In the evaluable patients (N = 61), 15 (24.5%) patients failed locally, 8 (13.11%) patients had distant metastasis and 2 patients failed at both site. 2 year and 4 year DFS was noted to be 73% and 44% respectively. On univariate analysis (Log rank test), skull base/intracranial extension at presentation (HR 4.16, 95% CI 1.35–12.79; p = 0.0001), lymph node involvement (HR 2.81, 95% CI 0.56–13.99; p = 0.04) and treatment modality (others versus surgery and postoperative radiotherapy, HR 2.41, 95% CI 0.83–6.97; p = 0.01) were significant predictors of DFS. Other factors viz age ($\leqslant$45 years and >45 years; P = 0.64), sex (P = 0.54), T stage (T2&T3 versus T4; P = 0.11) and margin positivity (P = 0.95) did not correlate significantly with DFS.Treatment modality (HR 3.40, 95% CI 1.29–8.91; p = 0.01) and skull base/intracranial extension (HR 5.10, 95% CI 1.89–13.69; p = 0.001) continued to have significant impact on DFS on multivariate analysis(Cox proportional hazard regression method).
Conclusion: Surgery followed by postoperative radiotherapy remains the treatment of choice for ACC of H&N cancers. Lymph node involvement and skull base/intracranial extension confers poor prognosis. The risk of recurrence due to margin positivity seems to be negated by the use of postoperative radiotherapy.
No conflict of interest.

3181 POSTER

Prognostic factors of head and neck sarcomas in a tertiary care centre

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Background: Head and neck sarcomas are rare heterogeneous group of tumors. Due to lack of guidelines, rarity and different biologic behavior, treatment of these tumors is challenging. However few prognostic factors had been made out and described in this study.
Materials and Methods: Retrospective analysis of head and neck cancer database of Department of Surgical Oncology, BRA IRCH, AIIMS (1992–2010) was performed and 45 cases of histologically proven head and neck sarcomas[HNS] were identified. Spectrum of head and neck sarcomas, their treatment patterns and prognostic factors were analyzed.
Results: HNS constituted 4% [45 /1118]of head and neck cancers. Median age was 41 years with slight male predilection [M-28, F-17]. Out of 45 cases 12 were skeletal sarcomas and 33 were of soft tissue origin. Dermatofibrosarcoma [n = 10] was the major sub type of soft tissue sarcoma followed by malignant peripheral nerve sheath tumor[n = 6] and synovial sarcoma[n = 4]. Osteosarcoma[n = 8] and chondrosarcoma[n = 4] were the major histological variants among skeletal sarcomas. Median size was 7 cm [range 1.5 cm to 30 cm]. Thirty eight cases were deep and 7 were superficial in location. All patients underwent radical surgery and R 0 resection could be achieved in 33 patients. Twenty three patients required reconstruction using flaps. In 5 borderline resectable cases, pre-operative chemotherapy and radiotherapy was used. Twenty six received post-operative radiotherapy and 14 received chemotherapy. During follow up 11 [24.44%] recurrences were detected with local recurrence being more common [n = 9, 20%] than distant recurrence[n = 4, 8.8%]. Similar survival seen in soft tissue sarcoma and bone sarcoma. Deep tumors, margin positive resections and large tumors [>5 cm] are found to be poor prognostic factors.
Conclusion: HNS is a rare and heterogenous disease entity comprising a diverse group of histopathological variants involving a complex anatomical head and neck sites. Optimal outcomes can be achieved by using radical surgery in combination with chemotherapy and/ or radiotherapy especially for deep tumors, margin positive resections and large tumors [>5 cm].
No conflict of interest.

3182 POSTER

Second primary malignancies after radioiodine in thyroid cancer patients and the association with radioiodine dosage: A nationwide population-based study

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Background: Radioactive iodine (RAI) is widely used in the diagnosis and treatment for thyroid cancers, and increased risk of second primary malignancies (SPM) in thyroid cancer patients has been reported. However, dose-response correlation between RAI and SPM is lacking, so the potential risk of SPM caused by RAI still cannot be determined. Therefore, we investigated the risk of SPM among thyroid cancer patients and the association between RAI dosage and cancer development using a nationwide population-based dataset.
Material and Methods: We recruited patients with newly diagnosed thyroid cancer aged 20 years or older without antecedent cancer from the Taiwan National Health Insurance database between 1997 and 2006. Standardized incidence ratios (SIRs) of cancers were calculated to compare the cancer incidence of thyroid cancer patients to the general population. The association of RAI dosage and cancer development was estimated using time-dependent analysis.
Results: After a median follow-up of 7.9 years, 617 SPM developed among 13,018 patients of thyroid cancer (79.3% females; n = 10,317), with a follow-up of 102,527 person-years. The median age of all thyroid cancer patients was 44 years, and the percentages of each age-of-diagnosis groups were 37.3% (n = 4,860), 43.6% (n = 5672), 17.4% (n = 2264), and 1.7% (n = 222) at age 20−39, 40−59, 60−79, and ⩾80 years, respectively. The SIR for all cancers was 1.46 [95% confidence interval (CI), 1.35–1.58], and increased with the duration of follow-up: 1.08 (95% CI, 0.69–1.61) at 0.5−1 years, 1.28 (95% CI, 1.12–1.46) at 1−5 years, and 1.47 (95% CI, 1.31–1.65) at ⩾5 years. The increased risks of SPM of lung and hematologic malignancies were significant in all patients [SIRs, 2.1 (95% CI, 1.70–2.58) and 2.83 (95% CI, 2.11–3.72)], in male patients [SIRs, 1.81 (95% CI, 1.20–2.62) and 2.67 (95% CI, 1.42–4.56)], and in female patients [SIRs, 2.26 (95% CI, 1.75–2.88) and 2.89 (95% CI, 2.05–3.97)]. The increased SPM that only observed in male patients included prostate (SIR, 2.47; 95% CI, 1.55–3.74) and bladder (SIR, 2.65; 95% CI, 1.37–4.63). The increased SPM that only observed in female patients included head and neck (SIR, 1.78; 95% CI, 1.07–2.78), colon and rectum (SIR, 1.42; 95% CI, 1.09–1.82), and breast (SIR, 1.46; 95% CI, 1.22–1.74). As a time-dependent covariate with a 2-year latency period, RAI significantly increased risk of hematologic malignancies (age- and sex-adjusted hazard ratio, 1.005; 95% CI, 1.002–1.007, *P*=.001) with a clear dose-response correlation (shown in the table). This effect was not seen in other SPM.
Conclusions: Our study finds an increased SPM risk among thyroid cancer patients receiving RAI, and the significantly increased SPM risks of lung and hematologic malignancies are observed in both genders. RAI increases the risk of hematologic malignancies with a clear dose-response effect.
No conflict of interest.

RAI dosage	Hazard ratio	95% CI	*P* value
100 mCi	2.959	1.047–5.358	0.041
200 mCi	5.455	1.813–16.408	0.003
300 mCi	10.823	3.253–36.007	<0.001

3183 POSTER

Pre-treatment EBV DNA differentiates different stages of undifferentiated carcinoma of the nasopharynx

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Background: Nasopharyngeal carcinoma of undifferentiated type (NPC) is endemic in Southern China including Hong Kong. Previous meta-analysis showed that concurrent chemoradiation conferred a better survival for stage III or above disease than radiotherapy alone. EBV DNA is the most accurate tumour marker for diagnosis and treatment response monitoring of NPC. We investigated if pre-treatment EBV DNA correlates with different stages of NPC in a prospective cohort of Chinese population.
Material and Methods: A total of 228 out of 249 consecutive patients with untreated histologically confirmed NPC had pre-treatment serum EBV DNA taken which was analysed by RT-PCR. The results were compared among different stage stratification according to AJCC 7th edition by independent sample t-tests.
Results: The distribution of stage of NPC in our patients was as follows: I=14 (6.1%); II=24 (10.5%); III=109 (47.8%), IVA/B=63 (27.6%) and IVC=18 (7.9%) patients. Overall sensitivity of EBV DNA was 91.7%. EBV DNA sensitivity for stage I, II, III, IVA/B and IVC were 35.7%, 87.5%, 93.6%, 100% and 100% respectively. Table 1 showed the mean EBV DNA for every stage of NPC. EBV DNA of stage IVC disease was higher than stage IVA/B (p = 0.053), which was higher than stage III (p = 0.026), which was higher than stage II (p = 0.019), which in turn was higher than stage I disease (p = 0.008). There was no difference in EBV DNA between stage IVA (16437 copies/ml) and IVB (62902 copies/ml, p = 0.202). When stratifying NPC into locally advanced vs early-stage disease, Stage III to IVB has higher EBV DNA (20327 copies/ml) than stage I to II (mean 1749 copies/ml, p = 0.012). Within stage III disease, there was no difference in EBV DNA between T3N0 (9417 copies/ml, 8 patients) and non-T3N0 disease (7852 copies/ml, 100 patients, p = 0.839).
Conclusions: Pre-treatment EBV DNA enabled us to differentiate different stages of newly diagnosed NPC. However it may not be sensitive enough for stage I disease.
Acknowledgment: This study was supported by SK Yee Medical Foundation (Project number 210212).
No conflict of interest.

Table 1. Pre-treatment EBV DNA among different stages of NPC

	Stage distribution of NPC patients according to AJCC classification 7th edition (N = 228)				
	I (n = 14)	II (n = 24)	III (n = 109)	IVAB (n = 63)	IVC (n = 18)
EBV DNA (copies/ml, mean)	26	2753	7968	41513	4449256
		p = 0.008	p = 0.019	p = 0.026	p = 0.053

3184 POSTER

Cochrane review: Effectiveness of psychosocial interventions for patients with head and neck cancer

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Background: A diagnosis of head and neck cancer, like many other cancers, can lead to significant psychosocial distress. Patients with head and neck cancer can have very specific needs, due to both the location of their disease and the impact of treatment, which can interfere with basic day-to-day activities such as eating, speaking and breathing. There is a lack of clarity on the effectiveness of the interventions developed to address the psychosocial distress experienced by patients living with head and neck cancer. The objective of this systematic review was to assess the effectiveness of psychosocial interventions to improve quality of life and psychosocial well-being for patients with head and neck cancer.
Methods: Electronic searches were conducted in the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ICTRP; and additional sources for published and unpublished trials up to 17 December 2012. Two review authors independently selected trials, extracted data and assessed the risk of bias, with mediation from a third author where required.
Results: Seven trials, totalling 542 participants, met the eligibility criteria. Studies varied widely on risk of bias, interventions used, and outcome measures reported. From these studies, there was no evidence to suggest that psychosocial intervention promotes global quality of life for patients with head and neck cancer at end of intervention (MD 1.23, 95% CI −5.82 to 8.27) as measured by the EORTC QLQ-C30. This quality of life tool includes five functional scales, namely cognitive, physical, emotional, social and role. There was no evidence to demonstrate that psychosocial intervention provides an immediate or medium-term improvement on any of these five functional scales. From the data available, there was no significant change in levels of anxiety (SMD −0.09, 95% CI −0.40 to 0.23) or depression following intervention (SMD −0.03, 95% CI −0.29 to 0.19). At present, there is insufficient evidence to refute or support the effectiveness of psychosocial intervention for patients with head and neck cancer.

Conclusion: Evidence for psychosocial interventions is limited by the small number of studies, methodological shortcomings and difficulties with comparability between types of intervention, and a range of outcome measures used. Future good quality research is required in this field and should target those in need of psychosocial intervention, in order to guide service development.
No conflict of interest.

3185 POSTER

Gastrostomy use and weight loss in patients treated for head & neck cancer

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Background: National guidance recommends gastrostomy placement prior to treatment for head & neck cancer if it is likely to cause problems with eating. We collected data on practice and outcomes in our centre.
Materials and Methods: Clinical data was collected retrospectively on all 66 patients with head and neck cancer that required gastrostomy placement at Cambridge University Hospitals between January 2010 and December 2011.
Results: The age range of patients was 38−76 (median 57), while 47 were male and 19 female. The majority (52/66−79%) received radiotherapy with concomitant chemotherapy for oropharyngeal squamous cell carcinoma (SCC). Percutaneous Endoscopic Gastrostomy (PEG) was placed, using the push method, for all but one patient (who underwent a Radiologically Inserted Gastrostomy procedure). In all but one case gastrostomy was performed prior to commencing radiotherapy.
91% of patients used their gastrostomy for feeding. 74% of patients had their gastrostomy removed less than 6 months after treatment and 91% were removed within 12 months. 44% of patients lost 5−10% of their starting weight during treatment and 33% lost over 10%. 30% of patients were admitted during treatment but only 10% of these admissions were primarily due to problems with nutrition. Possible gastrostomy site infections were recorded in 26% of patients. Staphlococcous aureus (53%) and pseudomonas (6%) were the commonest causal pathogens identified.
Conclusions: The main indication for head & neck cancer patients to require feeding gastrostomy was elective placement prior to concomitant chemoradiation for Oropharyngeal SCC. Despite tube placement most patients lost weight and gastrostomy site infections were not uncommon. Almost a third of patients required a hospital admission during treatment but not usually primarily due to nutrition problems. Average time on PEG feeding was short with the few patients requiring nutrition via their gastrostomy beyond one year after treatment. Ongoing further work will collect comparable data from other centres in our network.
No conflict of interest.

3186 POSTER

Impact of aprepitant on emesis control, dose intensity (DI) and recurrence free survival (RFS) in head and neck cancer patients (HNC) receiving high dose cisplatin chemotherapy

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Background: The standard of care for locally advanced HNC patients consists of three cycles of high dose cisplatin (>75 mg/m^2) administered concurrently with radiation. The intent of treatment is the prolongation of RFS. However, poorly controlled emesis can compromise maximum DI, which could affect disease control. In this observational study, the impact of aprepitant therapy on emesis control, DI and RFS is described.
Methods: A retrospective analysis of 192 HNC patients treated within the British Columbia Cancer Agency was conducted. Within this sample, 141 patients received aprepitant prophylaxis compared to 51 patients who did not. RFS was evaluated using Kaplan–Meier methods and adjusted Cox proportional hazard models. To control for selection bias, a propensity score analysis was incorporated into the Cox regression models.
Results: Patients between groups were comparable with respect to mean age (56.3 vs. 58.1), male gender (82.3% vs. 86.3%), tumour location and number of metastatic sites (median = 1). However, more patients in the aprepitant group had surgically resectable disease (31.2% vs. 15.7%) and had a better performance status (PS 0/1 = 87.9% vs. 76.4%). Less emesis was reported in aprepitant patients (21.3% vs. 28.0%) and they were more likely to complete three full cycles of high dose cisplatin (OR = 2.3, p = 0.03). The propensity score adjusted Cox regression analysis suggested a reduced risk for disease recurrence in patients who received aprepitant (HR = 0.47, [95% CI: 0.17 to 1.28]). However, there was no indication by the magnitude of the 95% CI that a difference existed in overall survival between groups (HR = 1.29, [95% CI: 0.36 to 4.6]).
Conclusion: In this observational study, aprepitant antiemetic therapy contributed to improved emesis control, enhanced DI and was associated with a reduction in disease relapse. These findings warrant further investigation in a larger sample of patients.
No conflict of interest.

3187 POSTER

Metabolic therapy with iodine-131: Removal of the radioisotope and duration of the radiation protection recommendations

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Background: The aim of this paper is to analyze the length of the radiation protection recommendations that are delivered to the patient at the time of radiologic discharge, taking into account the treatment duration, radiopharmaceutical dose, time of admission, the dose rate measured at one meter and family environment among others.
Material and Methods: We have available data for more than 100 patients treated in our hospital, both thyroid cancer or hyperthyroidism during the years 2011 and 2013 and with activities ranging from 100 to 200 mCi.
We consider here the value of the measured dose rate at one meter in two different times: the day of discharge and the tracking day (performed to search for thyroid remnants or metastasis). In this regard, we analyze the removal of radioisotope based on the remnant radiation and, therefore, it is possible to adapt the radiation protection recommendations taking into account the new measurement.
Results: Applying discharge criteria of patients and measures for the radiation protection of the public after treatment with iodine 131 metabolic Radiological Protection Forum in the health, based on the IAEA-63, we get a noticeable difference in the duration of restrictions of 8.3±4.1 for 100 mCi, 10.7±4.1 for 150 mCi and 11.1±4.4 for 200 mCi days if we consider measures to discharge or subsequent tracking.

	Mean difference (days)	Standard deviation (days)
100 mCi	8.3	4.1
150 mCi	10.7	4.1
200 mCi	11.1	4.4
Complete	10.2	4.3

Conclusions: This study demonstrates the usefulness of monitoring patients when they come to the hospital to make the tracking, greatly reducing the time to follow the radiation protection recommendations to avoid unnecessary exposure of other people, the time to return to work, going to shows, traveling by public transport, etc.
In the same way, the duration of the recommendations appear to be almost independent of the administered dose.
It seems clear that the values of the recommendations adopted in Spain from the 'Safety Report Series No. 63' IAEA, can be optimized if updated measurements of the dose rate and therefore the time duration of the radiation protection recommendations considered.
No conflict of interest.

3188 POSTER

A proposed new model of follow-up for patients with head and neck cancer

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Background: Over two million people are living with cancer in the United Kingdom, of which 51,000 live in Northern Ireland. The number of cancer survivors is growing by over 3% per year. If this trend continues there will be 4 million cancer survivors by 2030, adding to the ever increasing demands on time and resources within the NHS.
Traditionally, most patients experience the 'one size fits all' medical approach to clinical follow-up with the focus on monitoring for signs and symptoms of recurrence. There is much debate over the efficacy of this practice as patients themselves detect many recurrences between scheduled follow-up visits.
Aim: Implement and evaluate a new model of follow-up clinic, which will incorporate the completion of UWQOLv4 and PCI on touchscreen computer.

Objectives:
- To evaluate the patients' satisfaction with the new follow-up clinic
- To examine the impact of using a HRQOL questionnaire and problem concern checklist at follow-up clinic on QOL and empowerment
- To explore the feasibility of using touch screen assessments in routine follow-up clinics from the clinician's perspective.

Methods: A mixed methodology of both quantitative and qualitative approaches will be used.

A − First post-treatment visit − baseline:
i. Informed consent
ii. Consultation in its current format
iii. After consultation completion of:
  – UWQOLv4 & PCI
  – Exit Interview Checklist
  – Patient Enablement Instrument

B − Second post-treatment visit − intervention:
i. Prior to consultation completion of UWQOL & PCI
ii. Information used to focus consultation
iii. After Consultation completion of
  – Exit Interview Checklist
  – Patient Enablement Checklist
  – Patient satisfaction with new model of follow-up care

Evaluating process of care will include the review of clinical letters to ascertain the type and number of onward referrals and a proforma to collate information on the detection of HNC recurrence.

Clinicians' perspectives One-to-one semi-structured interviews focusing on suitability of using touchscreen computers in the routine follow-up, quality of the information gathered and clinical relevance of information.

No conflict of interest.

3189 POSTER

Locally advanced nasopharyngeal carcinoma in the Algerian West: Outcomes and prognostic factors in a cohort of 180 cases

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Background: The objective of this study was to analyze the clinical and therapeutic aspects, long-term outcome and determine the prognostic factors of locally advanced nasopharyngeal carcinoma (LANPC) in the west of Algeria.

Patients et methods: This is a study including 180 patients who had histopathologically confirmed LANPC treated in our department between 2002 and 2005. Survival rates were estimated using the Kaplan–Meier method. Univariate and multivariate analyses were performed using the Cox proportional hazards regression models.

Results: There were 123 males and 57 females with a mean age of 39.9±1.1 years (Range 12−73). Stage III, IVA and IVB (UICC2002) were 62, 56 and 62 respectively. 87 patients received induction chemotherapy platinum-based (with docetaxel, 5 fluorouracil or epirubicin) followed by radiotherapy (CT/RT) and 93 concomitant chemo-radiotherapy (CCRT). 8-years locoregional control (LRC), disease free survival (DFS) and overall survival (OS) rates were: 82% (±3%), 57.6% (±3.7%) et 77% (±3.6%), respectively. In univariate analysis, age>40 years ($p = 0.03$), T3−4 ($p = 0.04$) showed poor prognosis for LRC; stage IV ($p = 0.03$) for DFS; age >40 years ($p = 0.05$), stage IV ($p = 0.01$) and CT/RT ($p<10^{-3}$) for OS respectively. In a multivariate analysis, independent prognostic factors were: age (>40 years vs ⩽40 years) [$p = 0.07$] and Tumor (T3−4 vs T1−2) [$p = 0.09$] for LRC; Stage (IV vs II/III) for DFS ($p = 0.06$) and OS ($p = 0.07$), Treatment (CT/RT vs CCRT) for OS ($p = 0.001$).

Conclusion: The therapeutic results of our series seem satisfactory, however an optimization of the association of the chemotherapy and the radiotherapy in concomitant is necessary to have a better therapeutic index especially for the patients aged >40 years and stages IV of disease.

No conflict of interest.

3190 POSTER

Nasopharyngeal carcinoma in young patients in the Algerian West: About 92 cases

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Background: The objective of this study was to discuss the clinical feature, long-term outcome and determine the prognostic factors of nasopharyngeal carcinoma (NPC) in young patients (paediatric patients and young adults), in the west of Algeria.

Patients and Methods: Data were collected from 92 patients ⩽40 years diagnosed with NPC and treated at our department between 2002 and 2005. Survival rates were estimated using the Kaplan–Meier method. Univariate and multivariate analyses were performed using the Log rank test and Cox proportional hazards regression models respectively.

Results: There were 57 males (62%) and 35 females (38%). The mean age was 26.4±0.8 years (Range12−40). We have found: 3 T1 (3.3%), 31 T2 (33.7%), 34 T3 (37%), 24 T4 (26.1); 16 N0 (17.4%), 19 N1 (20.7%), 24 N2 (26.1%), 33 N3 (35.9%). Stage II, III and IV (UICC2002) were 7.6%, 37% and 55.4% respectively. It was undifferentiated carcinoma in 94.6% of cases and WHO type1 or 2 in 5.4%. 40 (43.5%) patients received induction chemotherapy platinum-based (with docetaxel, 5 fluorouracil or epirubicin) followed by radiotherapy (CT/RT) and 52 (56.5%) concomitant chemo-radiotherapy (CCRT). After a median follow-up of 72 months (range 10–106), 37 patients (40.2%) developed recurrences (locoregional and/or distant metastasis). 8-years locoregional control (LRC), disease free survival (DFS) and overall survival (OS) rates were: 89% (±3.5%), 58.9% (±5.2%) and 81.9% (±5.1%), respectively. Only treatment (CT/RT, CCRT) have an influence on OS in univariate ($p = 0.02$) and multivariate analysis ($p = 0.07$ − HR: 0.571).

Conclusion: This study shows that the NPC in patient 40 years old or younger, in the Algerian west is diagnosed at advanced stage with acceptable long term outcome. Another therapeutic sequence associated to the concurrent chemoradiotherapy seems necessary to improve our results.

No conflict of interest.

3191 POSTER

Serum alkaline phosphatase predicts survival outcomes in patients with nasopharyngeal carcinoma and bone metastasis

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Background: Bone metastasis is a frequent event of nasopharyngeal carcinoma (NPC) with a potential for complications such as pain, hypercalcaemia and pathologic fractures. The diagnosis and follow-up of bone metastatic patients usually relies on skeletal X-ray and bone scintigraphy which are time-consuming and costly. This study aims to evaluate whether serum alkaline phosphatase (S-ALP) has a clinical value in predicting clinical response and survival outcome for patients with NPC and metastatic bone disease.

Material and Methods: S-ALP level were measured at baseline and then before every cycle of treatment in 416 NPC patients with bone metastasis admitted to Zhejiang Cancer Hospital between January 2000 and December 2011. Correlations of pre-treatment and post-treatment S-ALP levels to treatment efficacy were analysed using the Chi-Square test. Survivals were analysed using the Kaplan–Meier method and were compared using the log-rank test. Univariate and multivariable analyses were performed using the Cox proportion hazards model.

Results: Patients with elevated values of pre-treatment S-ALP (>110IU/L) had significantly worse progression-free survival ($P<0.001$) and overall survival ($P<0.001$) than those with normal values of pre-treatment S-ALP (⩽110IU/L). Patients with elevated values of post-treatment S-ALP had worse progression-free survival ($P<0.001$) and overall survival ($P<0.001$) compared with those with normal values of post-treatment S-ALP. Patients with normal values of pre-treatment and post-treatment S-ALP showed the the most favourable prognosis. The Cox multivariate analysis identified that only pre-treatment S-ALP level (HR=1.794,P<0.001)and post-treatment S-ALP level (HR=2.657,P<0.001) were independent prognostic factors for overall survival.

Conclusion: S-ALP appears to be a significant independent prognostic index in NPC patients with bone metastatic involvement, which could reflect the short-term treatment response of palliative chemotherapy as well as the long-term survival outcomes.

No conflict of interest.

3192 POSTER

Institutional experience of RADPLAT for advanced maxillary cancer

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Background: Originally devised by Robbins et al. RADPLAT or intra-arterial chemotherapy for head and neck squamous cell carcinomas using cis-diamminedichloroplatinum (CDDP) with concurrent radiotherapy has led to participation of some Japanese facilities in this new treatment. While there have been some reports on feasibility and efficacy of this treatment,

the regimen of RADPLAT is yet to be established. The purpose of the present study was to evaluate our modified RADPLAT in terms of its feasibility and short-term the efficacy.
Methods: Between 2008 and 2012, we treated 20 patients (18 male and 2 female with a median age of 66 years old; range 55−78) with T4 (15 patients with T4a, 5 patients with T4b) squamous cell carcinoma of maxillary antrum. Eight patients (two N1 patients, five N2b patients, and 1 N2c patient) had lymph node metastasis. The treatment consisted of intra-arterial infusion of CDDP(150–200 mg/body, weekly for 7 weeks) combined with simultaneous intravenous administration of sodium thiosulfate (30−40 g/body) and concurrent radiotherapy (70 Gy, 2.0 Gy/fraction, daily for 5 days over 7 weeks).
Results: Apart from one patient, in whom radiotherapy was interrupted for 14 days because of the Great East Japan Earthquake, full-dose irradiation could be performed in 19 patients without interruptions. Seven IA infusions of CDDP was possible as planned, whereas in some cases fewer infusions were conceded sufficient because there was anticipated effect on the tumor. All in all, RADPLAT was feasible in 17 patients (85%). There were three patients who did not attain the planned IA infusions. The reasons for the failure were that lung metastasis was found during the treatment in one patient and the remaining two ejected the treat ment because of the patient's social problem or the fatigue and lassitude related to RADPLAT. Average total dosage of CDDP was 1236 mg. Maximum CDDP dosage per infusion was ranging from 109 mg/m^2 to 148 mg/m^2. Major adverse events (grade 3 or higher) were only mucositis and nausea. No grade 4 toxicity was observed. The rates of grade 3 mucositis were 45%(9 patients). Grade 3 nausea was observed in six patients (30%) The complete response (CR) rate was 85%. At a median follow-up of 1.1 years (range, 0.2 to 4.6 years), the estimated 1-year and 2-year locoregional tumor control rates are 72% and 63%, respectively.
Comclusions: Despite being a single-institution experience, the results of the current study suggest that our intensive treatment regimen of RADPLAT for advanced maxillary cancer is feasible and efficacious.
No conflict of interest.

3193 POSTER

The evaluation proinflamatory cytokine levels in thyroid papillary carcinoma

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Background: Cytokines are secreted or membrane-bound proteins that regulate the growth, differentiation and activation of immune cells. The cellular alterations that give rise to cancer provoke changes in local cytokine expression. Cancer-related inflammation recently has been proposed as a major physiological hallmark of malignancy and has important value in diagnosis, treatment, and prognosis. The aim of this study was to investigate pro-inflammatory cytokine levels IL-1β, IL-6, IL-8 and Neopterin levels in thyroid papillary carcinoma (TPC) patients before and after treatment.
Material and Methods: Thirty-nine female TPC patients before treatment and 31 female TPC patient's after treatment sera were recruited for the study. TPC was diagnosed by fine needle aspiration biopsy. TPC patients had a bilateral total thyroidectomy operation and serum IL-1β, IL-6, IL-8 and Neopterin levels were evaluated before and 20 days after the operation with ELISA.
Results: There were no significant differences on Nepterin levels between the before and after treatment ($P > 0.05$). However, IL-1 β and IL-8 levels were detected statistically importantly high after treatment but IL-6 serum levels were significantly decreased in patients after treatment.
Conclusions: Assessment of serum IL-6, IL-8 and IL-1 β levels can be performed in patients with TPC. They can be considered as both diagnostic and prognostic biomarkers.
No conflict of interest.

3194 POSTER

Analysis of the solitary pulmonary nodule on FDG-PET/CT in patients with head and neck cancers

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Background: This study was conducted to determine the accuracy of FDG-PET/CT for characterization of solitary pulmonary nodules (SPNs) in the patients with head and neck cancer.
Material and Methods: A total of 457 patients with head and neck cancer except thyroid cancer and lymphoma treated at Kangdong Sacred Heart Hospital from January 2009 to December 2012 and performed FDG-PET/CT as initial staging work up or follow-up exam. were screened. We retrospectively analyzed the 40 patients who had SPNs. Thirty of them had squamous cell carcinoma, 4 adenoid cystic carcinoma (ADCC), and 6 other type of malignancy.
Results: Ten patients were assumed to have solitary metastasis; 5 confirmed by biopsy, 5 aggravated by follow-up exam. Five of them had squamous cell carcinoma, 4 adenoid cystic carcinoma, and 1 adenocarcinoma. One patient had another malignancy in the lung. The median value of the SUVmax for malignancy was 2.95 (0.4−8.2). Ten of them had hypermetabolic SPNs and one non-hypermetabolic lesion (ADCC). Three of metastatic squamous cell cancer were performed resection and have been alive for 9, 25.5, 31 months without recurrent tumor. Among benign SPNs, 4 patients had pulmonary tuberculosis; 2 confirmed by biopsy, 2 by laboratory test. All of them had hypermetabolic SPNs. The median value of the SUVmax was 3.9 (3.4−9.3). Twenty three had other benign inflammatory SPNs, however 14 patients had hypermetabolic SPNs (median SUVmax. 2.8, range 1.6−8.1). There was no significant difference in SUVmax between malignant and benign hypermetabolic SPNs ($p = 0.773$).
Conclusions: FDG-PET/CT was not sensitive and specific, and not the best method to identify the SPN in the patient with malignancy. There was no significant difference in SUVmax between the malignant SPN and benign inflammatory SPN in the FDG-PET/CT. Early tissue diagnosis or careful follow-up exam could help in relevant treatment.
No conflict of interest.

3195 POSTER

Esthesioneuroblastoma: The 15-year experience of a Cancer Institute

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Background: Esthesioneuroblastoma (ENB) is a cancer originating from olfactory neuroepithelium, with an estimated incidence of 4 cases per 10 million individuals. ENB displays wide range of biologic activity from indolent growth to a highly aggressive behaviour capable of fast widespread metastization. Etiology, optimal staging system and treatment modalities vary according to different authors. The prognosis depends on the extension of the disease at diagnosis. We present a series of patients (pts) from a single cancer center.
Material and Methods: 15-year (1998–2012) retrospective cohort analysis was performed on pts with histologically confirmed ENB, followed at the Instituto Português de Oncologia de Lisboa. The Kaplan–Meier analysis was used to estimate and compare survival and progression rates.
Results: 17 pts were evaluated with a median age of 60 years (range 18−83), 9 males and 8 females. The median time between the first symptom and the definitive diagnosis was 6 months. 10 pts were treated with surgery and radiotherapy, 3 with radiotherapy, 2 with surgery, radiotherapy and chemotherapy, 1 with chemotherapy and 1 with surgery alone. The median follow-up and overall survival was 11.6 months (range 1.7 to 160 months) and 79.1 months, respectively. According to the modified Kadish staging system, 7 pts were in the low risk group (A-B) and 10 pts in the high risk group (C-D). Among the high risk pts, median overall survival was 10.5 months (95% confidence interval 6.35–14.64); only one patient from the first group died (median overall survival not reached), $p < 0.052$. All ($n = 8$) except one of the pts died within the first year of follow-up. The median overall progression free survival was 31.3 months and was worse for the high risk group (9.5 months, 95% confidence interval, 3.49–15.64, $p < 0.053$).

Conclusions: ENB is an uncommon malignant tumour. An accurate and rapid histological evaluation allows for an early staging and is the key for planning the combined modality therapy. The presented results could gain more statistical significance with a higher sample size.
No conflict of interest.

3196 POSTER

DAHANCA 9 − a randomized multicenter study to compare accelerated normo-fractionated radiotherapy with accelerated hyperfractionated radiotherapy in patients with primary squamous cell carcinoma of the head and neck

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Background and Aim: Based on the experience from the DAHANCA 5 trial, which showed the benefit of the hypoxic sensitizer Nimorazole, and the DAHANCA 6&7 trial, which demonstrated superiority of accelerated fractionation, the study was designed to evaluate in an randomized trial if the use of accelerated hyperfractionated radiotherapy (to a higher total dose) was feasible and superior to normo-fractionated accelerated fractionation. Both regimes being supplemented with the hypoxic radiosensitizer Nimorazole.
Patients and methods: Pts with squamous cell carcinoma of the larynx (except glottis St.I), pharynx or oral cavity (HNSCC) eligible for primary radiotherapy alone were randomized to receive accelerated hyperfractionated radiotherapy with 76 Gy in 56 fx with 10 fx per week or accelerated fractionation with 66−68 Gy in 33−34 fractions given with 6 fx per week.All patients were also treated with the hypoxic radiosensitizer Nimorazole. Patients were recruited from Danish Oncological Centers and from the Norwegian Radium Hospital in Oslo.
Results: The trial was planned for a total of 1,000 patients. It was, however, introduced at a time were radiotherapy resources was limited in Scandinavia, and thus, a hyperfractionated regime demanding more treatments was difficult to implement. Consequently was the trial stopped prematurely. In total, 77 patients patients were randomized between 2000–2004. The median follow-up time was 73 months (range 1–151). All patients were eligible for analysis (41 pts treated with hyperfractionation (hyperfx) and 36 pts with acceleration only (control). The patients were evenly distributed according to the stratification parameters (gender, T and N stage, tumor site).
The compliance to the treatment was good and only 2 pts did not complete treatment due to early death (one in each arm).
Overall, the results showed no significant difference in 5-year actuarial loco-regional control (71% vs. 69% (p = 0.74, HR: 0.86 [0.34–2.17])) for the hyperfx vs. control arm, respectively. This was also seen for the endpoint of disease-specific survival (83% vs. 71% for hyperfx vs. control, respectively, p = 0.20, HR: 0.52 [0.19–1.44]). Overall survival was indistinguishable HR: 1.05 [0.54–2.04]). Despite the difference in total dose, we did not observe significant differences in neither acute, nor late radiation related morbidity.
Conclusion: Hyperfractionated accelerated raditotherapy to HNSCC was a feasible treatment and suggested at better outcome than conventional accecerated radiotherapy. However, the study was closed prematurely due to lack of sufficient radiotherapy resources.
Supported by grants from the Danish Cancer Society.
No conflict of interest.

3197 POSTER

Volumetric stratification of cT4 stage head neck cancer

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Background: Advanced stage head neck cancer (HNC) is known for generally unfavorable outcome with only ~40−50% 3-year overall survival (OAS). Clinical T4 stage includes a wide range of tumor burden. The lack of further subgrouping of cT4 stage makes inter-center comparison of outcome results in irradiated cT4 cohorts difficult. In addition, in- or exclusion of very advanced cT4 anyNM0 into curatively aimed treatment regimens remains quite subjective.
Aim of this analysis was to further stratify cT4 stage HNC disease using volumetric staging. Included in the presented analysis were all cT4 stage HNC patients referred to our center for definitive radiation.
Material and Methods: Between 01/2002 and 05/2012, 202 cT4 stage HNC patients have curatively been irradiated. Radiation was performed using modulated radiation techniques +/− concomitant systemic therapy. All patients have retrospectively been stratified using a prospectively evaluated volumetric staging system which bases on 3 cut offs (15/70/130cc, see also former publications 2007//08/11/12) to stratify the total gross tumor volumes (tGTV: primary and nodal tumor volume), allowing a subdivision of cT4 into 4 prognostic subgroups (V1: 1−15cc (n = 17), V2: 16−70cc (n = 108), V3: 71–130cc (n = 61), V4: >130cc (n = 16)). OAS, disease free survival (DFS), loco-regional control (LRC) and distant metastasis free survival (DMFS) rates were calculated (Kaplan Meier curves).
Results: The mean follow up was 31 months (1–113). 3-year OAS, DFS, LRC and DMFS rates of the entire cohort were 73%, 54%, 61%, and 81%, respectively. Volumetric staging revealed its potential to prognostically statistically significantly divide the cT4 cohort into 4 volume subgroups (V1/V2/V3/V4), see the table.
Conclusion: Volumetric staging allowed a highly statistically significant stratification of cT4 HNC stages into prognostic subgroups, which offers the chance of better inter-center comparability of irradiated advanced stage HNC cohorts.
No conflict of interest.

cT4 (N = 202)	n (%)	3-year survival rate (%)			
		LRC	DMFS	DFS	OAS
V1 (1−15cc)	17 (7%)	92	93	83	90
V2 (16−70cc)	108 (64%)	70	85	52	72
V3 (71–130cc)	61 (21%)	61	68	42	60
V4 (>130cc)	16 (8%)	32	47	12	18
p-value	–	<0.0001	<0.0001	<0.0001	<0.0001

3198 POSTER

Changes in brain white matter diffusion tensor imaging indices following radiotherapy for head & neck cancer

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Background: Radical radiotherapy (RT) for head and neck cancer (HNC) by intensity modulated techniques typically results in radiation doses to adjacent brain tissues which may cause acute and chronic neurotoxicity. This study uses diffusion tensor imaging (DTI) to examine regional variation in brain white matter changes following RT for HNC.
Materials and Methods: Permission for the study was obtained from institutional review boards. Adult patients undergoing curative RT (with or without concomitant chemotherapy) for HNC, including primary radical and post-operative RT, were eligible. All patients gave written informed consent. Patients underwent DTI before, during (week 5) and after (2 and 6 months) RT. Changes in three DTI parameters over time were analysed: fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD). Voxelwise statistical data analysis was carried out using tract-based spatial statistics as implemented in the FSL software suite.
Results: DTI data from 17 patients have been processed: 10 men, and 7 women, of median age 55 (range 27 to 68) years. Primary cancer sites were: 9 nasopharyngeal, 3 nasal cavity, 3 unknown primary, 2 para-nasal sinus. All patients experienced RT-related fatigue, to maximum grade 2 severity, but no other neurological symptoms. Changes in DTI parameters occurred in brain areas receiving the highest RT doses but did not correlate with RT dose, and the data provide evidence that brain white matter structures vary in their response to RT. Changes in DTI parameters were greatest at 2 months post-RT and included decreased FA in the left cingulum bundle.
Conclusions: Radical RT for HNC causes detectable brain white matter changes in specific regions as measured by DTI. Changes in DTI parameters following RT for HNC may reflect RT-induced disruption to specific brain white matter structures, including the cingulum. Such disruption may partly explain the acute fatigue noted in patients receiving RT for HNC, and may also relate to longer term neurocognitive side-effects. It may be possible to lessen such side effects by specifically limiting RT dose to brain regions identified as showing greatest changes in DTI parameters.
No conflict of interest.

3199 POSTER

N09C6 (Alliance) − a phase III, randomized double-blind study of doxepin rinse versus placebo in the treatment of acute oral mucositis pain: secondary analysis of the continuation phase

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Background: Patients undergoing radiotherapy (RT) for head and neck (H&N) cancers often develop painful oral mucositis (OM), which may cause patient distress and lead to treatment interruptions.
Materials and Methods: N09C6 (Alliance), a Multi-Institutional Phase III randomized controlled trial with a cross-over phase and optional continuation phase compared a single dose of doxepin rinse (25 mg in 5 ml water) versus placebo rinse in patients with breakthrough OM pain rated $\geqslant$4 out of 10 (on a linear analog 0 to 10 scale) during H&N RT, with and without chemotherapy. Analysis of the primary endpoint demonstrated a modest benefit in the reduction of the AUC of patient reported OM pain over fours hour for doxepin (−9.1) over placebo (−4.7), p = 0.0003. Average pain reduction was 2.0 for Doxepin and 1.0 for placebo. This was confirmed in the single dose cross-over phase, AUC reduction for doxepin (−7.9) vs. placebo (−5.6), p = 0.009. (ASTRO Plenary 2012) Following completion of the cross-over, the study agents were unblinded and the patients were given the option of continuing doxepin rinse on as needed basis for pain, up to every four hours, during the remainder of RT until their OM pain resolved. A weekly questionnaire was administered to assess pain during the continuation phase.
Results: 155 patients were enrolled in the study between 12/17/2010 and 5/17/2012. 129 patients were evaluable for continuation of doxepin after the cross-over phase of the study. 81 patients (64%), p = 0.002, chose to receive doxepin in the continuation phase. 69 of 81 patients (86%) reported doxepin was helpful in alleviation of pain in the continuation phase. 14 of 81 (17%) patients discontinued doxepin before completion of RT − 2 because of pain improvement, 3 because of lack of pain relief, 8 because of side effects (drowsiness, stinging, or taste), and 7 because of other reasons.
Conclusions: The majority of patients completing the blinded portion of the study expressed a preference to continue the active study agent, with most patients reporting improvement in pain with use of doxepin. A minority of patients discontinued the drug due to side effects. Doxepin rinse provides superior pain relief in comparison to placebo rinse and should be considered as a breakthrough medication in addition to conventional analgesics.
No conflict of interest.

3200 POSTER

Effect of short course palliative radiotherapy (RT) for head and neck cancer: A prospective single institution quality of life (QoL) trial

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Background: Almost every second patient with head and neck cancer treated with curative intent recur, additionally a substantial group of patients can not be treated with curative intend due to age or co-morbidity. A treatment option for these patients is palliative radiotherapy. There exist only limited knowledge about optimal dosage and outcome.
Material and Methods: 30 patients with a median age of 67, with cancer of the, oral cavity (7), pharynx (13), larynx (6) and other sites (2) were included in a prospective study of QoL during and after palliative RT using 20 Gy in 4 fx. Patients filled in the EORTC QLQ-C30 and H&N35 quality of life questionnaire at inclusion, after 1 and 2 weeks, at 1, 2, 3, 5, 7, 9 and 11 months after treatment. Questions regarding odour, bleeding and perceived benefit of the radiotherapy was added using the usual scale. Nineteen patients were previously treated with RT and 9 have had surgery with curative intent. After treatment per protocol nine patients proceeded to systemic therapy after progression and 8 had further palliative radiotherapy in their remaining life span.
Results: Side effects (HN pain and HN swallowing) peaked at 2 weeks after RT and were resolved at 1 month. At 2 weeks there was a significant increase in pain compared with baseline score. Previously irradiated patients' had more symptoms, including pain in general except pain at 2 weeks after RT i.e. no indication of increased acute toxicity. Median survival was 6.1 months (range 0.5−26.4 months). At the time points after RT 14, 15, 46, 47, 22, 27, 22, 36 and 0 percent of the patients' stated that they have had 'some' or 'a lot' of benefit of the therapy. This perceived improvement was not reflected by a significant improvement of symptom scores in the quality of life questionnaire compared with baseline. Nevertheless, 8 patients had an improved HN pain score and 10 patients had an improved HN swallowing score at 2 months (n = 21) compared with baseline. This was related to perceived benefit of the RT, however not significant.
Conclusion: Short course radiotherapy had very limited side effects among the patients. Contrary to the overall positive evaluation from the patients a statistically significant improvements of specific symptoms could not be proven in this cohort with often rapid disease progression. There were no indication of difference in treatment response between patients previously irradiated with curative intent and never irradiated patients.
No conflict of interest.

3201 POSTER

Prospective longitudinal assessment of salivary function using quantitative pertechnate scintigraphy and estimation of dose-volume response relationship after parotid-sparing radiotherapy in head-neck cancers

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Background: Conformal radiotherapy can reduce acute and late xerostomia with potential positive impact on quality of life in head and neck squamous cell carcinoma (HNSCC). Limitations of salivary flow-rate estimation have encouraged the use of dynamic salivary gland scintigraphy for quantification of post-radiation deterioration of salivary function. The aim of this study was to assess functional changes in parotid glands using quantitative pertechnate scintigraphy and estimate their dose-volume response relationship in patients treated with definitive three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiation therapy (IMRT).
Methods: Quantitative salivary gland scintigraphy was performed at baseline prior to definitive (chemo)radiotherapy, 3-months after completion of therapy, and yearly thereafter using 15 mCi of 99mTc-pertechnetate. Salivary excretion fraction (SEF) was quantified by determination of the maximal excretion activity per gland as a fraction of the maximal uptake. SEF ratio (SEF at time point't'/baseline SEF x 100%) <45% was used for defining severe xerostomia based on previously published data. Dose-volume response curves were calculated using standardized methodology and modeled for normal tissue complication probability (NTCP) to calculate parotid tolerance doses (TD).
Results: Forty-one patients with non-metastatic HNSCC with a median age of 54 years (range 33−65 years) treated definitively on a prospective trial of 3D-CRT or IMRT constituted the study cohort. The mean (interquartile range) parotid doses were 50 Gy (36.2–59.7 Gy) and 35.4 Gy (28.0–53.5 Gy) for the ipsilateral and contralateral glands respectively. There was good correlation of SEF at all post-treatment time-points with mean parotid doses. Using SEF ratio <45% as the endpoint, TD50 (defined as 50% probability of complications) of the parotid gland was 32.8 Gy and 40.5 Gy at 3-months and 1-year respectively. The corresponding values increased to 55.9 Gy and 64.3 Gy at 2-year and 3-years respectively suggesting significant recovery of salivary function over time.
Conclusions: There is consistent and significant decline in salivary function even after parotid-sparing conformal radiotherapy. However, there is significant recovery of salivary function over time. Quantitative pertechnate scintigraphy is a simple, reproducible, and minimally invasive test of major salivary gland function that has the potential to replace direct salivary flow-rate measurements.
No conflict of interest.

3202 POSTER

Intensity-modulated radiation therapy for head and neck cancer: Systematic review and metanalysis

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Background: The potential overall benefit of Intensity-modulated radiation therapy (IMRT) over two-dimensional (2D-RT) or three-dimensional

conformal radiation therapy (3D-CRT) for head and neck cancers has not yet been clarified, except for reduction of side effects, especially xerostomia. This systematic review and metanalysis was undertaken to assess whether IMRT can improve clinical outcomes when compared to 2D-RT or 3D-CRT including xerostomia, local control, and overall survival.
Material and Methods: Only prospective phase III randomized trials were eligible and had to compare IMRT with 2D-RT or 3D-CRT in previously untreated patients, with non-metastatic head and neck cancers. Patients underwent radiotherapy either primarily or combined with surgery or chemotherapy. Medline, CENTRAL, EMBASE, and LILACS databases were searched with no language, publication year or publication status restrictions. Two authors independently selected and assessed the studies regarding eligibility criteria and risk of bias.
Results: Five studies fulfilled the eligibility criteria. A total of 871 patients were randomly assigned for 2D-RT or 3D-CRT (437), versus IMRT (434). Most patients presented with nasopharyngeal cancers (82%), and stages III/IV (62.1%). Three studies were classified as unclear risk and two as high risk of bias. A significant overall benefit in favor of IMRT was found ($p<0.0001$) for all studies (hazard ratio [HR], 0.76; 95% CI: 0.66–0.87) regarding xerostomia scores grade 2−4. At a mean follow-up of 4.23 years, the overall number needed to treat analysis of the prevention of 'xerostomia grade 2−4' was 19.3 (95% CI:13.5–36.2). There were non-significant increases in local control (HR 1.07; 95% CI:0.93–1.23; p=0.35) and overall survival (HR 1.12; 95% CI:0.97–1.29; p=0.11) in favor of IMRT.
Conclusions: Based on moderate to high risk of bias studies, IMRT significantly reduces the incidence of grade 2−4 xerostomia. No differences were observed in local control and overall survival in patients with head and neck cancers.
No conflict of interest.

3203 POSTER

Change of practice: Does an outpatient tube clinic affect patient weight and duration of tube feeding?

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Background: In our radiotherapy department 63% of patients with head and neck cancer (HNC) treated with chemoradiation receive a feeding tube during their treatment. Previously, the patients were admitted to hospital for training in tube use and care. After discharge, nurses assisted with adjustment of the nutrition plan. All HNC patients were seen by doctor two weeks after treatment, but there was no systematic follow-up on nutrition. In November 2010, we started an outpatient-based tube clinic with the purpose to train and support patients with a feeding tube, adjust nutrition plans and start up normal feeding after treatment.
The purpose of the study was to investigate if the outpatient clinic could be a substitute for hospitalisation and if systematic follow-up affects patient weight loss and duration of tube feeding.
Material and Methods: A retrospective descriptive study of HNC patients receiving a tube because of curative chemoradiation, min 60 Gy.
The first group (38 patients) consisted of all patients completing treatment from December 2006 to August 2009 before establishment of the clinic. These data originated from an earlier study.
The other group (24 patients) consisted of all patients completing treatment after establishment of the clinic between November 2010 and November 2011. Some of these patients did not start up at the clinic, because other needs required hospitalisation, but was followed by the clinic at discharge. Only 5 patients had no contact at all. They were all included to obtain comparable groups.
The two groups were comparable in terms of baseline data.
Weight loss was calculated at three time points: During treatment, the first two months after treatment and from application of the tube until two months after treatment. Duration of tube feeding was measured from termination of treatment to discontinuation of tube feeding.
Results: This study showed no significant difference. Both groups had the same proportion of patients who lost weight and weight loss was similar at all tree time points. There was no significant difference in duration of tube feeding, neither for nasal nor gastric tube.
Conclusions: Although the patient number is small, the study suggests that there was no significant difference between the groups before and after establishing the tube clinic.
Thus, start-up training on an outpatient basis and a systematic follow-up after treatment can replace admission; Duration of tube feeding time was not reduced.
No conflict of interest.

3204 POSTER

A randomised study comparing prophylactic gastrostomy to feeding tube as needed in head and neck carcinomas

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Background: Weight loss is a major problem during chemoradiotherapy and the best way to prevent it remains controversial. The main objective of the study was to compare weight loss percentage between prophylactic percutaneous gastrostomy (PG) and feeding tube as needed (FT) during chemoradiotherapy. Secondary objectives were to evaluate difference in quality of life (QOL), number of hospitalisation and, treatment interruption between for both groups.
Material and Method: This randomised study was stratified according to site (larynx/hypopharynx vs other sites). The study was design to include 96 patients. It aims to detect a clinically significant weight loss with a power of 20% but, the study was interrupted after the demission of our interventional radiologist. The study was performed at the Hotel-Dieu de Québec between October 2008 and July 2012. All patients were treated with radical IMRT and cisplatin based chemotherapy. Exclusion criteria were: need for initial hospitalisation, aspiration, malnutrition or initial surgery.
Results: A total of 37 patients were randomised (18 in the GP group and 19 in the FT group). At the end of treatment, 3/18 (16%) and 9/19 (47%) of patients lost more than 10% of their initial body mass in the GP and FT group, respectively, $p = 0.04$. Mean percentage of weight lost was 5.4 kg and 8.7 kg in the GP and FT group, respectively, $p = 0.04$. At the end of treatment, mean pre-albumin was 275 vs 233 mg/l in the GP and FT group, respectively, $p = 0.13$. The need for enteral nutrition treatment was 17/18 (94%) for GP and 9/19 (47%) for FT, $p = 0.001$. At 6 months, only one patient still needed enteral nutrition in the FT group. There was 2/18 and 2/19 treatment interruption in the GP and FT group, respectively. Only 3 patients need treatment re-simulation. There were 7/18 (38%) and 6/19 (31%) unexpected hospitalisation in the GP and FT group, respectively, $p = 0.65$. For the global QOL assessment (EQ-5D, How good is your health today), the mean decline in QOL was 27% in the FT and 17% in the GP group, $p = 0.2$. In the EORTC HN35 questionnaire, only q48 (bothered by appearance) was significant, $p = 0.02$. Minors complications were seen in 12/18 (66%) patients in the GP group and in one patient in the FT group. One patient had peritonitis (GP group).
Conclusions: Compare to FT, PG was useful to prevent weight loss of more than 10% of the initial body mass during chemoradiation in this selected group of head and neck carcinomas patients. This has to be weighed against the invasive nature of the PG procedure.
No conflict of interest.

3205 POSTER

Speckle tracking to measure arterial strain as a marker of radiation-induced atherosclerosis

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Background: The late effects of radiotherapy in patients with head and neck cancer include increased risk of carotid artery stenosis and subsequent stroke. Reduced carotid arterial stiffness is thought to be a precursor of atherosclerosis and occur prior to arterial thickening. Carotid artery strain (a surrogate for arterial stiffness) can be measured using a novel ultrasound technique. We sought to investigate the effect of radiotherapy on arterial stiffness in patients with head and neck cancer.
Methods: Patients with head and neck cancer treated with unilateral hemi-neck radiotherapy to a dose of at least 50 Gy at least 2 years previously were included. Bilateral carotid artery ultrasound scans were obtained using a 10MHz transducer. Carotid arterial strain using speckle tracking was measured in 6 segments at three different arterial levels (proximal, mid and distal) (total of 18 segments) in the irradiated common carotid artery. Global circumferential strain for each level was calculated from the mean segmental value. Total global circumferential strain for the entire artery was calculated from the mean of proximal, mid and distal global circumferential strains. The contralateral unirradiated carotid artery served as a control.
Results: 15 patients (total 540 segments, 36 per patient) with a median age of 61 yrs (interquartile range (IQR) 52−67 yrs) were studied. Median global circumferential strain was reduced in the irradiated carotid artery (2.4% (IQR 1.7−3.1)) compared to the unirradiated carotid artery (3.1% (IQR 2.1−3.9)), $p = 0.05$. There was no difference in median global circumferential strain between proximal (−2.6% (IQR 1.7−4.2)), mid (2.5% (IQR 1.6−3.3)) and distal (2.1% (IQR 1.7−2.9)) segments of the irradiated artery, $p = 0.43$. There was no difference in global circumferential strain

between proximal (3.7% (IQR 2.3−4.4)), mid (3.0% (IQR 2.1−3.7)) and distal (3.0% (IQR 1.8−3.9)) segments of the unirradiated artery, p = 0.29.
Conclusion: Carotid arterial stiffness, measured by speckle tracking, is reduced in irradiated compared to unirradiated carotid arteries. Corroboration of these findings in a larger cohort may allow detection of early radiation-induced damage to the carotid arteries.
No conflict of interest.

3206 POSTER

Common carotid artery stenosis as measured by computed tomography following radiotherapy for early glottic carcinoma

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Background: Carotid artery stenosis is a late toxic effect followingradiotherapy (RT) for head and neck malignancies. Patients with T1-T2 glotticcarcinoma are usually treated with small radiation field, which yields highrate of cure. We conducted a retrospective study to evaluate the incidence ofcarotid artery stenosis in these patients.
Materials and Methods: Contrast-enhanced computed tomography(CECT) of head and neck performed from Jan 2009 to Jan 2013 for patients withT1-T2 glottic carcinoma after radiotherapy were retrospectively reviewed. CTswith interval less than 4 years after treatment were excluded. Rate of stenosiswithin distal half of common carotid artery (CCA) were measured inreconstructed images, then classified into four groups: grade 0 (no stenosis),grade 1 (stenosis <15%), grade 2 (15−50%), grade 3 (<50%). For comparison,pre-treatment CECT of patients with T1-T2 glottic carcinoma diagnosed duringthe same period were also reviewed. The rate of CCA stenosis in each group wascompared by Fisher's exact test. Association of each clinical parameters withCCA stenosis was analyzed through multiple logistic regression.
Results: Overall, 52 CECTs were reviewed, including18 patients in RT group and 34 patients in the control group. Thus, a total of104 coronary arteries (right and left) were evaluated for analysis. Theinterval between treatment and CT in the RT group ranged from 4 to 9 years. Theincidence of CCA stenosis grade 2−3 in the RT group and the control group were33% and 6%, respectively (p < 0.01). In multivariate analysis, only previousRT significantly correlated with grade 2−3 CCA stenosis (p < 0.001, odds ratio14.9 {95% confidence interval 2.6–86.5}).
Conclusion: Patients with T1-T2 glottic carcinoma whohad been treated by RT had higher incidence of CCA stenosis than those who hadnever received RT.
No conflict of interest.

3207 POSTER

Comparison of two stereotactic body radiotherapy protocols for recurrent head and neck cancers

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Background: This study aimed to compare the local control rate, overall survival rate, and toxicity rate associated with two stereotactic body radiotherapy (SBRT) protocols for re-irradiation in patients with locally recurrent head and neck cancer.
Materials and Methods: The study included 75 patients with inoperable recurrent head and neck cancer that were treated with SBRT. Group I included 43 patients that were treated sequentially and group II included 32 patients that were treated every other day. Median age of all the patients was 53 years (range: 15−87 years). There wasn't any significant difference in demographic or clinical characteristics between the 2 groups. The most common site of re-irradiation was the nasopharynx (n = 34 patients), followed by the oral cavity and larynx. Multiplan (Accuray Inc., Sunnyvale, CA) software was used for inverse planning. The treatments were delivered via a CyberKnife® (Accuray Inc., Sunnyvale, CA). The circumference of the carotid artery entrapped by the tumour was calculated in each patient; median carotid artery wall entrapment by the tumour in all patients was 180º, versus 270º in the patients that had bleeding were considered.
Results: Median overall survival in group I and group II was 11 months and 23 months, respectively (P = 0.006). Ultimate local control was achieved in 77.4% of the patients. The local control rate in group I was 67.5%, versus 90.6% in group II (P = 0.029). Progression-free survival was 9 months in group I, and 18 months in group II (P = 0.004). Dysphagia was observed in 10 patients (23%) in group I, versus only 3 patients (6.3%) in group II (P = 0.047). The overall survival and local control rates were higher, and the number of patients with grade 3 or higher side effects was lower in group II. The median radiation dose received by the carotid artery in patients with carotid blow-out syndrome (CBOS) was 36.5 Gy (range: 34–42.8 Gy), versus 34.7 Gy (range: 0−44 Gy) in the patients that didn't have CBOS (P = 0.15). CBOS was not observed in patients with lesions entrapping <180º of the carotid artery.
Conclusions: CBOS did not occur in any of the patients with a maximum carotid artery radiation dose <34 Gy. Every other day SBRT protocol for re-irradiation of recurrent head and neck cancer is promising.
No conflict of interest.

3208 POSTER

Dosimetric evaluation of nasopharyngeal carcinomas irradiated with different IMRT techniques

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Background: To compare intensity modulated arc radiotherapy (IMAT), dynamic IMRT and step and shoot IMRT on nasopharyngeal carcinomas (NPC).
Material and Methods: IMRT plans of 48 NPC patients treated between May 2010 and December 2012, were evaluated. Median age was 43.5 (14−79) and 73% of the patients were male. The majority of patients showed advanced clinical stages (stage III/IV:72.9%) with undifferentiated histology (70.8%). PET-CT or MRI images were fusioned with planning CT for all patients. Target volumes and critical organs were delineated 2.5 mm sliced planning CT according to RTOG atlas. Forty patients were planned using the Eclipse (ver. 8.6) treatment planning system (22 IMAT, 18 dynamic IMRT) and treated with Varian Rapid-Arc linear accelerator. Eight cases were planned using the planning system of Prowess Panther V5.01. The plan was delivered on an Elekta Synergy Linac equipped with an 80-leaf 1 cm multileaf collimator with step-and-shoot intensity-modulated radiation therapy. IMRT was administered using sequential (9 patients) or simultaneous integrated boost (39 patients) approach. A median of 70 Gy (63−70 Gy) was given to primary tumour and involved lymph nodes and 50 Gy for electively irradiated neck nodes with sequential boost tecnique. The doses of the planning target volumes of primary tumor and involved lymph nodes, high risk, and uninvolved regional nodal areas were 70 Gy, 60 Gy, and 54 Gy respectively and delivered simultaneously over 33 fractions. Maximum doses to spinal cord and brain stem were limited to 45 Gy and 54 Gy respectively. Mean parotid dose was aimed to be less than to 26 Gy. Conformity index (CI), homogenity index (HI), monitor unit (MU) and normal tissue doses were calculated for each plan. CI, HI and MU were compared between the three IMRT modalities.
Result: Dmean, D98, D2, CI and HI were 102.2±2.04%, 97±2.27%, 105.1±2.23%, 1.18±0.23 and 1.08±0.02 for all patients, respectively. Maximum doses to brain stem and spinal cord were 54.2±2.2 and 44.7±1.9 respectively. The maximum MU was found in dynamic IMRT technique (1657.2±674.8 versus 548.1± 249.8 and 451.3± 41.2) CI; 1.10±0.12 for dynamic IMRT, 1.19± 0.251 for IMAT and 1.35±0.26 for step and shoot IMRT technique.
Conclusion: The improvement in tumour target coverage and significant sparing of adjacent critical structures allow the feasibility of IMRT for NPC. MU values were similar with IMAT and step and shoot IMRT techniques while two-thirds less monitor units than dynamic IMRT. IMAT and dynamic IMRT techniques gave superior results in terms of CI compared with step and shoot IMRT. This difference is thought to be due to the technical differences of linear accelerator devices like fiber size, variable fiber, dose rate and gantry.
No conflict of interest.

3209 POSTER

Role of adjuvant postoperative external beam radiotherapy for well differentiated thyroid cancer

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Background: To analyze the outcome of adjuvant postoperative external beam radiotherapy (EBRT) in well differentiated thyroid cancer (WDTC).
Material and Methods: We identified of 84 WDTC patients treated with EBRT for WDTC in Seoul National University Hospital from February, 1981 to December, 2010. Among them, we analyzed 40 patients who received EBRT after initial radical surgery. Twenty-five females and 15 males were included. Median age was 49 years (range, 16−72 years). There were 35 papillary thyroid carcinomas and 5 follicular thyroid carcinomas. Most

patients showed pathologic T3 or T4 stage (55%/25%). Eleven patients (27.5%) had gross residual tumors. Five (12.5%) patients were involved by tumor cells at margin. Median EBRT dose and fraction size was 62.6 Gy and 1.8−2.0 Gy, respectively.
Results: Median follow-up was 66 months (range, 22–377). Five-year overall survival (OS) and locoregional recurrence free survival (LRFS) was 97.5% and 86.1%, respectively. Locoregional failures occurred in 5 and all failure sites were neck node area. In univariate analysis, OS was significantly influenced by invasion of trachea ($p = 0.028$) or esophagus ($p = 0.005$). LRFS rates was significantly decreased by male ($p = 0.016$), gross residuum after resection ($p = 0.006$), close or positive tumor at surgical margin involvement ($p = 0.0015$), and tracheal invasion ($p = 0.046$). There was no significant prognostic factor in multivariate analysis. No patient experienced RTOG grade 3 or more toxicity.
Conclusions: Our locoregional control rate of 87.5% is comparable to historical controls with surgery alone, even though mainly with advanced stage. EBRT is effective and safe treatment option in patients with WDTC.
No conflict of interest.

3210 POSTER

Clinical effect by improvement of facilities in the radiotherapy of locally advanced head and neck squamous cell cancer patients

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Background: Improvement of facilities is expected to reflect the improvement of treatment outcome. Technical and methodological aspect which surrounds radiotherapy has rapidly progressed in these decades. We investigated how improvement of facilities had an impact on the treatment outcome in the radiotherapy of locally advanced head and neck squamous cell cancer (HNSCC) patients.
Material and Methods: Eligibility is locally advanced HNSCC patients whose curative radiotherapy was conducted between 2002 and 2012. (n = 92, male: 81, female: 11, 43−92 (68) years old). Clinical stage was III: 29, IVA: 50 and IVB: 13, The site of origin was oropharynx: 31, hypopharynx: 31, larynx: 16, nasal-paranasal sinus: 7, oral: 6 and nasopharynx: 1. Total irradiation dose was 65−86 (70.2) Gy and concurrent chemotherapy was performed in 67 patients. Patients were divided into 3 groups according to the presence or absence of PET operation before radiotherapy and type of treatment machine as group A: before introduction of PET, linear accelerator with the energy of 4 and 10 MV (2002–2006): n = 32, group B: presence of PET operation before radiotherapy, linear accelerator with the energy of 4 and 10 MV (2006–2009): n = 27 and group C presence of PET operation before radiotherapy, linear accelerator with the energy of 6 and 10MV equipped with on-board imaging function (2009–2012): n = 30. No large variety of age, disease type, clinical stage or total irradiation dose was observed among the groups. Cause specific survival (CSS) and progression free survival (PFS) were compared among the groups.
Results: CSS at 3 years was much improved in group B and C than A such as 54.2% in group A, 80.1% in group B and 81.0% in group C (p = 0.023). PFS at 3 years was 44.8% in group A, 53.8% in group B and 63.4% in group C. Although no significant change was observed in PFS, number of the patients who showed recurrence within 6 months after treatment tended to be smaller in group B and C than group A such as 8 in group A, 4 in group B and 4 in group C.
Conclusions: Improvement of facilities favorably reflected the improvement of treatment outcome in the radiotherapy of HNSCC patients. Especially, presence of PET operation before radiotherapy was suggested to reduce early recurrence after treatment, consequently contributed to improve treatment outcome in the radiotherapy of HNSCC patients.
No conflict of interest.

3211 POSTER

Role of fluconazole in the prevention of radiation induced mucositis in head and neck cancer patients

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Background: To evaluate the effect of fluconazole on prevention of oral candidiasis and also to determine whether fluconazole prophylaxis will reduce the severity of oral mucositis induced by radiotherapy.
Materials and Methods: The study was conducted on 48 patients with histopathologically proven Head and Neck cancer.Each patient underwent thorough dental prophylaxis before start of radiation. Patients were randomly divided into two groups A and B.Group A represents treatment arm and group B control arm. Oral swabs were collected from both groups. Maximum of three swabs were collected, one before the start of radiotherapy, second one three weeks after start of radiotherapy and last one after completion of radiotherapy. Oral swab were cultured on Sabouradad's dextrose agar for candidial growth. Patients in both groups received radiotherapy with or without chemotherapy which was decided by the radiation oncologist depending on the site and stage of tumor. Patients in group A received oral fluconazole 50 mg/day after food from the first day of radiotherapy till the completion of radiotherapy treatment. Patients in Group 'B' did not receive fluconazole as prophylactic therapy. Patients in both groups were examined weekly for oral mucositis and were graded according to CTC version 2.0.
Results: Oral swab taken from patients before start of radiotherapy for candidial growth showed that it was present in 22% of all patients. During the course of radiation treatment, oral candidal culture was positive in 44% of control patients and 37.5% of treatment patients. When the grade of mucositis was assessed in both the arms, it was found that there was statistically significant reduction in the severity of mucositis in the treatment arm (p = 0.021). In the control arm, there was no grade 0 mucositis noted, grade 1 was seen in 20%, grade 2 in 64%,grade 3 in 16% and no grade 4 mucositis. In the treatment arm there was grade 0 mucositis in 25%, grade 1 in 25%,grade 2 in 29.2%, grade 3 in 20.8% and no grade 4 mucositis. Patients in whom candidal culture was negative had less severe mucositis as compared to patients with positive candidal culture(p = 0.029).
Conclusion: Prophylactic use of oral fluconazole is effective in reducing the severity of oral mucositis. Presence of oral candidasis increases the severity of mucositis and the incidence of oral candidasis can be reduced by flucanzaole, there by reducing the severity of oral mucositis.
No conflict of interest.

3212 POSTER

Is FDG-PET-CT a valuable tool in prediction of persistent disease in head and neck cancer

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Objectives: To evaluate accuracy of FDG-PET CT in prediction of persistent disease in head and neck cancer and to determine prognostic value of metabolic tumor response.
Methods: Between 2009 and 2011 46 patients with squamous cell carcinoma of Head and Neck who had pre treatment PET- CT were treated with definitive Radiotherapy with or without chemotherapy. There were 29 Nasopharyngeal, 11 Hypopharyngeal, 3 Oropharyngeal, 3 Laryngeal cancer patients median age of patients was 50.5 years (range 16−84) there were 32 males and 14 females. All patients were evaluated with PET-CT median 3.5 months (2.4−9.4) after completion of radiotherapy.

Table 1. Patterns of outcome in patients with control FDG PET CT non-complete responders.

Patients	PET-CT result	Location site	Recurrence	Recurrence site	Follow up (months)
Patient 1	suspicious	Nasopharyngeal	absent	–	20.1
Patient 2	suspicious	hypopharyngeal	present	Local	19.3
Patient 3	suspicious	hypopharyngeal	absent	–	25.6
Patient 4	suspicious	oropharyngeal	Present	Regional	14.8
Patient 5	suspicious	laryngeal	present	Local	36.3
Patient 6	positive	Nasopharyngeal	Absent	–	13.5
Patient 7	Positive	Nasopharyngeal	Present	Locoregional	9.5
Patient 8	Positive	Nasopharyngeal	Absent	–	19.1
Patient 9	Positive	Nasopharyngeal	Absent	–	24.2
Patient 10	Positive	hypopharyngeal	Present	Local	13.1
Patient 11	Positive	hypopharyngeal	Absent	–	18
Patient 12	Positive	hypopharyngeal	Present	Local	14
Patient 13	Positive	hypopharyngeal	Present	Locoregional	11.3
Patient 14	Positive	hypopharyngeal	Present	Local	8.9
Patient 15	Positive	hypopharyngeal	Present	Local	15.4
Patient 16	Positive	oropharyngeal	Present	Locoregional	15
Patient 17	positive	hypopharyngeal	Present	regional	31.9

Results: After median 20 months of follow up complete metabolic response was observed in %63 of all patients. Suspicious residual up take was present in 10.86% and residual metabolic up take in 26% of patients. The overall sensitivity, specificity, positive predictive value and negative predictive value of FDG-PET-CT for detection of residual disease was 64% and 96%, 91% and 82% respectively. Two year LRC was 95 % in complete responders while it was 34% in non complete responders (Table 1).

Conclusion: FDG PET CT is a valuable tool for assessment of treatment response especially in high risk patients for local recurrence, is also good indicator for prognosis. Definitely more precise criteria is required for assessment of response, there is no clear cut up take value indicating residual disease, on the other hand repair process of normal tissue may consume glucose which appear as increased up take in control FDG PET CT.
No conflict of interest.

3213 POSTER

Long-term treatment outcomes of patients with mucoepidermoid carcinoma of the parotid gland treated with surgery plus postoperative radiotherapy

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Background: To investigate the long-term treatment outcomes and to evaluate the prognostic factors in patients with mucoepidermoid carcinoma (MEC) of parotid gland treated with surgery and postoperative radiotherapy.
Material and Methods: We retrospectively reviewed the clinical data of 31 patients with MEC of parotid gland who were treated with surgery followed by radiotherapy between 1991 and 2010. Radiotherapy was delivered with a median total dose of 60 Gy (range, 50−67 Gy). Elective nodal irradiation (ENI) was applied to T3−4 or node-positive tumors. The histopathologic features of all cases were prospectively reviewed by one head and neck pathologist. The median follow-up period was 102 months (range, 9–232 months).
Results: Overall outcomes at 5 and 10 years were overall survival (OS), 83%; locoregional recurrence-free survival (LRFS), 93% and 89%; distant recurrence-free survival (DRFS), 90%; disease-free survival (DFS), 87% and 83%, respectively. On univariate analysis, N stage (N0−1 vs. N2, $p < 0.01$), overall stage (I−II vs. III−IV, $p = 0.04$), and histologic grade (low vs. intermediate vs. high, $p < 0.01$) were statistically significant predictors of OS. A poorer survival was observed in patients with high grade tumors or more than N2 disease than in patients without any factor (5-year OS, 86% vs. 29%, $p < 0.01$; 5-year DRFS, 100% vs. 57%, $p < 0.01$).
Conclusions: Our results demonstrated that surgery plus postoperative radiotherapy resulted in excellent locoregional control. However, high grade tumors or node-positive disease more than N2 showed a poor distant control and overall survival. More aggressive treatment including adjuvant chemotherapy or targeted therapy should be investigated for patients with such high risk factors.
No conflict of interest.

3214 POSTER

Superselective intra-arterial chemoradiotheapy for locally advanced maxillary sinus carcinoma

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Background: For stage III or IVA maxillary sinus carcinoma (MSC), standard treatment is craniofacial surgery with postoperative radiation therapy. However, surgical approaches are often complicated accompanied with risk of serious functional deformity and lack of satisfactory surgical clearance. For stage IVB MSC, standard treatment is not established. Definitive radiation therapy (RT) including 3D-conformal radiation therapy (3DCRT) with super-selective intra-arterial chemoradiothearpy (SIACRT) is indicated in selected patients unfit for surgery. Here we retrospectively evaluated the treatment outcome of SIACRT in patients with locally advanced MSC.
Materials and Methods: We identified consecutive 34 patients with locally advanced MSC underwent SIACRT at our institution between January 2009 and March 2013. The treatment protocol consisted of 3DCRT (60 Gy/30 fractions) with super-selective arterial infusions of weekly docetaxel (10−36 mg) and cisplatin (100–350 mg) for 4−6 cycles.
Results: Patient characteristics were: median age, 68 years (range 43−86); male 29 (85%), female 5 (15%); squamous cell carcinoma 31 (91%), small cell carcinoma 1 (3%), others 2 (6%); stage III 4 (12%), stage IVA 20 (59%), stage IVB 10 (29%). With median follow-up period of 12 months, the 1-year overall survival, progression free survival, and local control rate were 68%, 45%, and 80%, respectively. Seven (21%) patients died of MSC. As to first site of progression, 7 (21%) local progression and four (12%) regional progression, all of which were successfully salvaged by surgery, and 5 (15%) distant metastases were seen. Grade 2 keratoconjunctivitis occurred in 11 (32%) patients. Grade 3 or 4 mucositis and dermatitis occurred in 18 (53%) and 5 (15%) patients, respectively. Grade 4 optic neuritis occurred in 3 (9%).
Conclusions: SIACRT showed good local control, but longer follow up is needed to confirm the efficacy and toxicity of SIACRT.
No conflict of interest.

3215 POSTER

Postoperative image-guided intensity modulated radiation therapy in sinonasal cancer: Dosimetry, clinical outcome and quality of life − an updated series

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Background: This study is aimed to assess the dosimetry, clinical outcome and quality of life in patients of locally advanced sinonasal cancer undergoing surgery followed by adjuvant image-guided intensity modulated radiation therapy (IGIMRT).
Materials and Methods: We enrolled 10 patients (pts) of sinonasal cancer (stage II−IV, age $\leqslant$70 years, KPS $\geqslant$70, R0/R1 resection) for IGIMRT in a project. Clinical target volume (CTV) comprised high risk (HR) CTV: surgical bed and low risk (LR) CTV: retropharyngeal, level IB and II lymphnodal site (only in T3/T4 squamous carcinoma). An isotropic 3 mm expansion was given around CTV to generate planning target volume (PTV). Prescribed dose was 60−64 Gy/30#/6 weeks to HRPTV (as per margin status) and 50 Gy/30#/5 weeks to LRPTV (simultaneous integrated boost). IMRT was planned by 7−9 coplanar equally spaced beams (step & shoot multileaf collimator with DMPO) with 6 MV photons (Pinnacle TPS v8.0m). Treatment verification was performed with kilo-voltage cone beam CT(KVCBCT, Elekta Synergy S) on first 3 days of treatment & subsequently twice a week. Positional correction was done when translational error was >3 mm. Quality of life was assessed pre-RT, immediate post-RT & 3 month post-RT using EORTC QLQ-C30 version3 & QLQ-H&N35module.
Results: The median age was 45 years with male: female ratio of 1:1. Primary site was maxilla-5 pts, nasal cavity-4 pts, and eithmoid-1 pt (stage T4:T3:T2 = 8:1:1 and N0M0 in all). Histology was adenoid cystic, squamous, & adenocarcinoma in 6, 3 &1 pt respectively. Median D95 PTV was 97.39% of prescribed dose. Median conformity & homogeneity (D2/D98) indices were respectively 1.14 & 1.16. Median value of dose maximum to organs at risk (OAR) were- brainstem: 51.93 Gy, spinal cord: 35.37 Gy, optic chiasma: 52.79 Gy, optic nerve: 53.95 Gy (left) & 51.6 Gy (right), eye: 49.99 Gy(left) & 49.3 Gy(right), temporal lobe: 61.6 Gy (left) & 62.23 Gy (right). Median value of mean dose to OAR were- parotid: 20.67 Gy(left) & 21.48 Gy (right) & oral cavity: 23.9 Gy. Median number of KVCBCT done per patient was 11. Median translational error (cm) in x, y & z axis was 0.11, 0.16 & 0.14 respectively. Acute radiation morbidity (RTOG criterion) included dermatitis: Gr1 (60%) & Gr2 (30%), mucositis: Gr2 (60%), Gr3 (10%) & Gr4 (20%), salivary gland toxicity: Gr1 (80%) & Gr2 (10%), conjunctivitis: Gr1 (50%) & Gr2 (10%), pharyngitis: Gr1 (50%), Gr2 (30%) and Gr3 10%). After a median follow-up of 2.23 years, local recurrence and death were observed in 40% and 10% of the patients respectively (1 year actuarial rate of overall and recurrence-free survival − 90% & 80%). Median overall and recurrence free survival were not reached. Median global health status (QoL) declined from 75(pre-RT) to 62.5(immediate post-RT) but recovered back to baseline value 3 months post RT. Symptom scores pertaining to pain, sense organ dysfunction, mouth opening worsened immediately post RT but gradually came back to baseline level (median-0) 3 months after RT.
Conclusion: Adjuvant IGIMRT in locally advanced sinonasal cancer permits precise delivery of radiation to the target with sparing of the adjacent OAR with excellent toxicity profile, quality of life & clinical outcome.
No conflict of interest.

3216 POSTER

Long-term outcomes of tongue hemiatrophy and patient satisfaction following low-dose-rate interstitial brachytherapy for mobile tongue cancer: An almost 20-year follow-up study

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Background: Tongue hemiatrophy is a relatively common disorder that typically progresses over a long period following low-dose-rate interstitial brachytherapy (LDR ISBT) for mobile tongue cancer. However, there are few reports regarding long-term follow-up of the grade of tongue hemiatrophy. In this study, we evaluated tongue hemiatrophy and patient satisfaction during a follow-up period of almost over 20 years.
Material and Methods: We selected 9 patients (5 males and 4 females) with mobile tongue cancer that were treated with LDR ISBT at Osaka University Hospital and followed-up for almost over 20 years. The median age at the time of LDR ISBT was 43 years (range: 21−57 years). The mean duration of follow-up was 297 months (range: 238–373 months). Using the UICC classification system, 4 patients were classified as T1, 3 as T2, 1 as T3N0M0, and 1 as T4N1M0. Prior to treatment, we obtained verbal and written informed consent from all patients. For primary lesions, LDR ISBT was performed using Ir-192 hairpins with or without a single pin. Four patients were treated with LDR ISBT alone with a total dose of 70–84.6 Gy (median: 74.12 Gy) and 5 were treated with 50−70 Gy of LDR ISBT (median: 61.2 Gy) combined with 20–54.6 Gy (median: 30 Gy) of external beam radiation (EBR). Using the grading system proposed by Yoshioka et al. (G0−G3), we evaluated the tongue hemiatrophy and analyzed association between the grade of hemiatrophy and receipt of EBR. We also investigated the relationship between the grade and patient characteristics (duration of follow-up, target volume, age at the time of LDR ISBT, tumor thickness) using Spearman's rank correlation coefficient. All patients were queried regarding their satisfaction with the extent of return of oral function to pretreatment levels using a visual analog scale.
Results: Concerning the grade of tongue hemiatrophy, 2 patients were classified as G0, 3 as G1, 1 as G2, and 3 as G3. All G0 patients were treated with LDR ISBT alone. Patient satisfaction rate was 50−90% (mean: 85%). There were no statistically significant correlations between the grade of tongue atrophy and patient characteristics.
Conclusions: LDR ISBT with or without EBR for mobile tongue cancer showed a high degree of patient satisfaction after a long-term follow-up for almost over 20 years, although tongue hemiatrophy occurred.
No conflict of interest.

3217 POSTER

Efficacy of reirradiation in head and neck cancer

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Background: Despite advances in treating head and neck cancer, 15−50% of patients will relapse. Survivors also face the risk of second primary tumors, their incidence is estimated at 8−22% and third place in the head and neck. In this retrospective research we assessed toxicities secondary to initial radiotherapy and reirradiation and analyzed the PFS (Progression-free survival) from the primary tumor and local recurrence or second primary on the previously irradiated field. The response to reirradiation was assessed.
Material and Methods: We evaluated 31 patients diagnosed with squamous cell carcinoma of head and neck who underwent reirradiation in our service from 1999–2011. Patients were classified into 2 groups according to local recurrence, 7 of these second primary tumors in the treated area and 24 local recurrences.
Results: We analyzed acute and late toxicities after initial treatment and reirradiation. In addition to the PFS between primary tumor recurrence or second primary tumor in the treated field. We realise that acute toxicities (RTOG) more frequent after initial treatment were mucositis G2 (28.8%), dermatitis G1 (22%) and G2 xerostomia (22.2%). Late toxicities were mainly G1 xerostomia (54.5%) and odynophagia G1 (13.6%). The most prevalent acute toxicities after reirradiation were: mucositis G1−2 (25.7%), dermatitis G1 (22.8%), xerostomia G1 (14.2%), dysphagia G1−2 (11.4%). Late toxicities secondary to reirradiation were xerostomia G2(35%), fibrosis G1−2 (20%) and dysgeusia G1 (15%). PFS to local recurrence mean was 37.3 months and to second primary tumors was 81.6 months. Currently, we have 17 patients in complete remission, 5 in partial response and 9 in progression.
Conclusion: Recurrence in head and neck on previously treated areas present a therapeutic challenge and therapeutic options are limited. Reirradiation with or without chemotherapy is an acceptable alternative when it's not suitable salvage surgery. However this treatment regimen is associated with considerable acute and late toxicity therefore must be assessed in highly selected cases.
No conflict of interest.

3218 POSTER

High dose re-irradiation using 3D-CRT and IMRT for recurrent and second primary head and neck cancers

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Background: Head & neck cancer is one of the most common cancers in India. Management of recurrent & second primary head and neck cancers in previously irradiated cases pose a significant therapeutic challenge. The role of external re-irradiation was rarely investigated and practiced mainly due to the fear of severe toxicity from cumulative high radiation doses exceeding the normal tissue tolerance. However, in the last decades re-irradiation has begun to gain conceptual acceptance as experimental and clinical studies have demonstrated that high dose re-irradiation can be administered successfully in a significant proportion of patients without unacceptable toxicities.
Material and Methods: Twenty four consecutive recurrent or second primary head and neck cancer patients treated with 3D-CRT (n = 2) or IMRT (n = 22) techniques with MV-CBCT image guidance from May 2009 to February 2013. All patients are biopsy proven squamous cell carcinomas with no evidence of distant metastasis investigated using a PET-CT or CT scan. Surgery prior to radiotherapy and concurrent chemotherapy with radiotherapy has been received by selected patients. Radiotherapy target volume delineation included the GTV with strict margin (5−7 mm) to create CTV and elective nodal irradiation was avoided.
Results: All patients have completed prescribed treatment with acceptable acute radiation toxicities managed conservatively. Fourteen patients are alive without disease; one of them underwent salvage surgery for relapse outside radiation field. Three patients are alive with disease; one of them remains locally controlled. Seven patients died of progressive cancer; again one of them was locally controlled. Overall sixteen patients achieved local control of the disease indicating efficacy of re-irradiation in controlling local recurrence.
Conclusion: Re-irradiation in recurrent and second primary head and neck cancers is feasible using newer radiotherapy techniques. In our study we have observed good patient compliance, encouraging local control of disease. However, with strict CTV delineation we have observed recurrences in the adjacent area suggesting use of larger CTV margin as and when necessary. Head and neck cancer is a heterogeneous disease and each patient needs proper evaluation and planning depending upon the clinical parameters.
No conflict of interest.

3219 POSTER

Surgical management of primary tracheal tumours − a herculean task

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Background: Surgical management of primary tracheal tumors is a complex task. Surgical expertise in this field is also very limited. The peculiar surgical anatomy of the trachea and lack of an ideal tracheal substitute,issues with anesthesia all make the surgical management more complicated. We, herein, share our experience in the surgical management of primary tracheal tumors.
Materials and Methods: Retrospective analysis of the patient's records was done to identify patients with primary tracheal tumors who underwent surgery, during the last 6 years at our tertiary care institute.
Results: A total of 11 cases of primary tracheal tumours having undergone surgical management were identified. On histo-pathological analysis there were 6 adenoid cystic carcinoma, 2 schwannoma, 1 carcinoid tumour, 1 squamous cell carcinoma, 1 mucoepidermoid carcinoma. On evaluation with contrast enhanced computerized tomography, 10/11

cases had disease confined to trachea. All cases with localized disease underwent definitive surgical management in the form of primary resection and anastomosis (9), carinal pneumonectomy with tracheobronchial anastomosis (1). One patient had presented in emergency with stridor, underwent emergency tracheostomy and debulking. On further evaluation, this patient was found to have locally advanced disease and so was referred to palliative treatment. The length of trachea resected ranged from 2.8−6 cms. Laryngeal release- (suprahyoid and in some cases subhyoid release) and hilar release were done to achieve adequate tracheal mobilisation for primary tension free anastomosis. All patients had margin free resection. Patients with adenoid cystic carcinoma were also given adjuvant radiotherapy. At follow up (range 8−45 months), all patients having received definitive surgical management are doing well with no symptoms/disease recurrence on imaging and bronchoscopy. There were no perioperative mortality.
Conclusion: Primary resection and anastomosis for tracheal tumours is a complex procedure. With experience and adequate planning, this can be achieved without significant mortality or morbidity.
No conflict of interest.

Patient	Histopathology	Length of trachea resected(cms)	Adjuvant therapy	Follow up (months)
1	Adenoid Cystic	3.1	RT	45
2	Adenoid Cystic	3.8	RT	44
3	Carcinoid	3.0	Nil	41
4	Adenoid Cystic	4.8	RT	39
5	Mucoepidermoid	3.6	Nil	36
6	Schwannoma	5.1	Nil	34
7	Adenoid Cystic	6.0	RT	20
8	Schwanoma	3.4	NIL	14
9	Adenoid Cystic	2.8	RT	8
10	Adenoid Cystic	5.2	RT	10
11	Squamous cell carcinoma	Debulking of tumour	Palliative treatment	11

3220 POSTER

Drugs affecting bone remodeling and postoperative hypercalcemia in patients with primary hyperparathyroidism

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Background: Primary hyperparathyroidism (PHPT) is a benign disease which, if left untreated, carries a near two-fold increase in development of several cancers and doubles the risk of cardiovascular diseases. Single adenoma is the source of an excess parathyroid hormone (PTH) in up to 90% of pts. Cure can be achieved with parathyroidectomy in up to 98% of cases which is reflected by normocalcemia on the first postoperative day. However, some patients (pts) remain hypercalcemic after the procedure. The usual cause is failure to recognize multigland disease but drugs affecting bone remodeling (bisphosphonates, calcitonin-salmon) may have the influence on early postoperative calcium levels as well.
Materials and Methods: Since January 2003 until December 2012, 577 pts with PHPT were operated at the Institute of Oncology Ljubljana. Pts with hypercalcemia on the first postoperative day were divided according to the PTH levels in two groups; normal/low PTH level or increased PTH level. The influence of preoperative application of drugs affecting bone remodeling on serum calcium level on the first postoperative day was compared between the groups with normal/low PTH level and increased PTH levels with Fisher's exact test.
Results: Out of 577 pts operated for PHPT, 495 (85.7%) were normocalcemic on the first postoperative day and 31 (5.4%) pts were hypocalcemic. Out of the remaining 51 pts (8.8%) with hypercalcemia, 16 pts had normal/low PTH level and 35 pts had increased level of PTH. Fifteen pts received drugs affecting bone remodeling preoperatively (8/16 with normal/low PTH, 7/35 with increased PTH). The influence of drugs on serum calcium level was compared between the groups with normal/low PTH level and increased PTH level. The difference was statistically significant with $p = 0.047$. Spontaneous resolution of the hypercalcemia in one week was observed in all pts with normal/low PTH level who received drugs affecting bone remodeling (8/16).
Conclusion: Drugs affecting bone remodeling may affect early postoperative serum calcium levels in pts with PHPT causing spontaneously resolving hypercalcemia with no need for repeat imaging and reoperation.
No conflict of interest.

3221 POSTER

Significance of depth of invasion in squamous cell carcinoma of buccal mucosa

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Background: (1) To study if the depth of invasion of primary site has an impact on neck node metastasis in squamous cell carcinoma (SCCA) of the buccal mucosa.
(2) A comparison of the impact of depth of invasion in buccal mucosa carcinoma versus tongue carcinoma on nodal metastasis.
Material and Methods: It is a retrospective study conducted in the Departments of Head and Neck oncology surgery and Department of Pathology at Medanta, The Medicity, Gurgaon, India.
66 consecutive patients of primary buccal mucosa and tongue squamous cell carcinoma who underwent surgery from January 2011 to December 2012 were included in the study. There were 39 buccal mucosa and 27 tongue carcinoma patients.
Patients were divided into two categories:
1. Tumors with depth of invasion of 4 mm or less
2. Tumors with depth of invasion of more than 4 mm

Results: Depth of invasion was a statistically significant criteria in predicting neck nodal metastasis (p value <0.01) in patients with buccal carcinoma.
When compared with tongue SCCA, the depth of invasion of the primary tumor in buccal mucosa SCCA correlated better with predicting presence or absence of neck metastasis.
Conclusion: Depth of invasion is significant criteria for predicting neck node metastasis in buccal mucosa cancer. There is only limited literature available on this aspect and needs further evaluation with prospectively collected data. Overall impact on prognosis of depth of invasion has not been studied in our data and would need further evaluation.
No conflict of interest.

3222 POSTER

Clinicopathologic study and outcome analysis of major glossectomy: Experience from a tertiary cancer center

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Background: Advanced cancers of the tongue is a therapeutic challenge due to associated high morbidity and poor survival. Despite advances in treatment options and improved rehabilitation methods it is still considered a bottleneck. Major glossectomy is considered a radical form of treatment with significant associated morbidity and more or less considered an palliative procedure because of poor survival in this group of patients.
Methods: With this background we retrospectively evaluated 194 patients operated at a tertiary cancer center during a period of 2007−11. The patients were evaluated for clinico-pathological details and various predictive factors associated with it.
Results: Of 194 patients who underwent major glossectomy mean age at presentation was 49 years with M:F ratio of 2.88:1. Total/Near total glossectomy was performed in 58.7%, anterior 2/3rd glossectomy in 20.1% and tongue composite resections in around 21.1%. Pull through approach was mainly used for access to the tumor (73.1%) with peroral access used only in 5 % of patients. Pedicled flaps were the mainstay of reconstruction with Pectoralis major flap ruling the roost in around 64% patients. All patients except 3 had histology in form of squamous cell carcinoma with moderately differentiated squamous cell carcinoma in around 54.6% patients.
Conclusion: Major glossectomy in present era of advanced chemoradiation protocols is still an valid option despite being associated with high morbidity and poor survival rates.
No conflict of interest.

3223 POSTER

Reconstruction of extensive composite oromandibular defects with FFOCF role of pre operative mapping of septocutaneous perforators

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Introduction: Oromandibular cancers are very common in India. Resection results in varying defects and are classified according to tissue loss. Even extensive defects can be reconstructed with single FFOCF. From 2005 to 2012, 850 oromandibular reconstructions with single FFOCF were done at Tata Memorial Hospital Mumbai, India. The outer paddle loss was observed mainly in extensive defects when skin paddle was de-epithelised and rotated out for skin cover. Study was done to identify and resolve the problem.

Table (abstract 3223).

Year	Fibula flaps	Single paddle	Skin excision	Primary closure	Faciocervical flap	De-Epithelise		Divided paddle	Regional Flap	2nd Free Flap	Super charge
							*				
2005	85	47	38	−	−	38	6	0	5	−	−
2006	81	54	27	−	−	27	4	0	4	−	−
2007	66	35	31	−	−	31	3	0	3	−	−
2008	77	43	34	−	−	34	5	0	3		
2009	109	68	41			41	4	0	3		
2010	119	58	61	1	4	51	8	03	1	0	1
2011	140	70	70	9	4	27	4	26	1	3	0
2012	143	57	86	3	2	27	5	39	1	14	0

*Partial necrosis.

Material and Method: See the table.
Septocutaneous perforator vessels for fibular skin paddle were studied extensively. Number of perforators, location of perforators in relation to bone segments to be used were analysed and a protocol is developed and followed since 2010.
Technique: Pre op Doppler mapping is done to locate number and location of perforators. Perforators are marked from distal to proximal on the leg. Osteotomy is planned from distal to proximal end. Location of perforators to bone segment to be used play significant role during osteotomy planning.
Results: Since this protocol is followed there is no loss in divided skin paddle used for outer cover.
Conclusion: Pre op perforator mapping is important and helpful in planning reconstruction of composite or extensive oromandibular defects where external skin cover is required.
Tentative plan for second flap is made at the time of perforator mapping depending on number and location of perforators and the defect size.
Ideally located perforators are, one on bony segment for mucosal lining and other one just beyond required bone segment. Based on second perforator skin is divided and rotated out.
No conflict of interest.

3224 POSTER

Suboccipital lymphadenectomy for patients with occipital squamous cell carcinoma of the scalp: Results in 14 patients

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Aim: To highlight the role and benefit of suboccipital lymph node dissection as an integral step in the surgical management of occipital scalp squamous cell carcinoma.
Methods: Between 2007 to 2011 fourteen patients with pathologically proven squamous cell carcinoma at the occipital region of the scalp underwent suboccipital and retro auricular lymph node dissection in continuity with the contents of the upper part of the posterior triangle of the neck.
Results: All patients underwent elective suboccipital lymphadenectomy; the number of dissected lymph nodes ranged from 3−9 LNs (mean 5.8 LNs). No serious complications were observed apart from mild wound infections in 2 patients. In 6 out of 14 patients lymph nodes were metastatic (42.8%). 4 patients lost follow-up. All the remaining 10 patients were followed up between 12−26 months. One patient developed local recurrence after 8 months and another one developed nodal recurrence at the spinal accessory group of lymph nodes after 14 months; both patients had +ve LN metastases at the suboccipital nodes at the initial dissection.
Conclusion: Suboccipital lymphadenectomy is a safe procedure with low morbidity and should be done in all patients with scalp squamous cell carcinoma at the occipital region of the scalp which could add to the locoregional control of the disease and serves as a prognostic indicator for future locoregional recurrences.
No conflict of interest.

3225 POSTER

Lymphatic drainage and regional metastases in papillary thyroid carcinoma of pyramidal lobe − a single institution experience

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Background: The pyramidal lobe (PL) represents the remnant of the distal part of thyroglossal tract. PL varies in position, size and shape. Papillary thyroid carcinoma (PTC) is the most common histological type of thyroid malignancy. It may be multicentric in up to 80% of cases and it frequently involves both lobes. The aim of our retrospective study was to find out the incidence of primary single focus PTC in PL and routes of lymphatic drainage and lymphonodal metastases from PL.
Material and Methods: A chart review of all patients who had thyroid surgery in our tertiary center by a single surgeon from year 2003 to 2012 was presented. Altogether 753 patients were treated surgically for PTC. The patients who had PTC located only in PL or in PL-isthmus junction were included in this study. Cases with primary PTC in lateral and pyramidal lobe (multifocal) were excluded from our study. In all cases, methylene blue dye was injected in isthmus of thyroid gland (periturmoraly) during surgical procedure in order to perform sentinel lymph node (SLN) biopsy in lateral neck compartments. In all cases of PTC a total thyroidectomy was done together with central neck dissection. Additionally, SLN biopsy was performed in both lateral compartments. Lateral neck dissection was not performed because frozen section analysis in all SLNs from lateral compartment was benign, which was confirmed also on standard histopathology.
Results: Only 3 of 753 patients (0.4%) had primary PTC in PL and that was the only PTC focus. All of them were females, aged 22, 36 and 41. Blue lymph nodes were present in 5, 14 and 5 nodes per patient. Primary tumor diameter in pathological report was 12, 15 and 20 mm. In all three patients blue SLNs were present bilaterally in central compartment and in lateral neck compartments. Altogether 9, 22 and 31 lymph nodes per patient were examined by a pathologist. The only metastatic lymph node was present in a midline prelaryngeal node (Delphian). One patient was postoperatively treated with 131-I, while all patients had suppression of TSH with L-thyroxin. Patients were followed for 5 to 108 months and there were no recurrences.
Conclusion: Incidence of primary PTC in PL was 0.4%. The only site of metastasis in our patients with primary T1 stage of PTC was a midline prelaryngeal node (Delphian). All other lymph nodes from central compartment, as well as SLNs from lateral compartments, were benign.
No conflict of interest.

3226 POSTER

Minimally invasive parathyroidectomy seems suitable for day surgery in patients with primary hyperparathyroidism

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Background: Minimally invasive parathyroidectomy (MIP) is performed in several high-volume foreign centers in day care. However, that is not the standard in the Netherlands. Our retrospective study was designed to evaluate if our population and surgical technique are suitable to perform minimally invasive parathyroidectomy in day care.
Methods: Eighty-two patients with primary hyperparathyroidism were included in the period December 2005 to October 2012. Patients with previous neck surgery including parathyroid surgery were excluded. Patients with secondary and tertiary hyperparathyroidism were also excluded. Sestamibi scan and ultrasound were performed for preoperative localisation. In addition, we measured the perioperative PTH (5, 10, 15 min) and performed intraoperative frozen section analysis of the adenoma. We have also searched for predictive factors for hypocalcemia. Group analysis was performed using non-parametric tests. Univariate analysis was performed with the Log-Rank or Chi2 test. Multivariate analysis was performed with Cox regression analysis.
Results: A solitary adenoma was found in 77 patients (93.9%). MIP was performed in 69 patients (84.1%) and bilateral in 13 patients due to insufficient preoperative localisation. Based on the frozen section results we have performed bilateral exploration in 2 patients (2.4%). The operation time was 80 minutes (including PTH measurement and frozen section analysis). Temporary hoarseness was noticed in 3 (3.6%) patients.

Postoperative asymptomatic hypocalcemia was diagnosed in 5 patients. Sestamibi scan was more sensitive than the ultrasound (58.5% vs. 24.7%). The weight of the resected adenoma was significantly correlated with the baseline value of PTH ($p < 0.001$). After univariate analysis operation time was the only significant predictive factor for the development of hypocalcemia ($p < 0.05$).
Conclusion: The weight of the adenoma is associated with the baseline PTH. For the localisation of the adenoma has ultrasound limited contribution. Given the limited effect on the course of the operation, the time consuming frozen section analysis should only be performed in selected cases. Operation time is the only risk factor for hypocalcemia after parathyroidectomy. Overall, minimally invasive parathyroidectomy seems a suitable method for day surgery in patients with primary hyperparathyroidism.
No conflict of interest.

3227 POSTER

Surgical resection post neoadjuvant chemotherapy in technically unresectable locally advanced oral cancers rendered resectable by neoadjuvant chemotherapy

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Background: Locally advanced oral cancers (T4) with extensive disease and skin infiltration are commonly considered as unresectable, as in such tumors the need of resection of vital organs is high or probability of achieving a negative margin is low. Can giving neoadjuvant chemotherapy (NACT) render these large tumors resectable with negative tumor margins is an open question.
Materials and Methods: We retrospectively analysed our data of locally advanced oral cancers that were technically unresectable upfront and were rendered resectable after NACT. The hypothesis of this analysis was to test whether NACT enabled us achieve a R0 resection in more than 90% of these patients, who were considered resectable at the end of 2 cycles of NACT. The figure of 90% was chosen as in T4 oral cancers that are upfront resectable, margin positive rates of upto 15−20% are described in literature. Predetermined (our previously published) landmarks of extensive skin involvement upto zygoma in buccal cancers, extensive soft tissue extension leading to involvement upto either the level of the hyoid bone in primary of tongue cancers or floor of mouth cancers, extensive involvement of base of tongue and vallecula from a primary in tongue and involvement of the infratemporal fossa in any oral cavity primary was used for definition of technically unresectable. The criteria used for deciding resectabiliy post neoadjuvant chemotherapy was disappearance of the disease or decrement in the disease leading to clearance of disease from these anatomical landmarks on radiology. Two hundred and thirty six patients out of 528 technically unresectable locally advanced oral cancers underwent surgery. The margin status & resection status were noted.
Results: Five hundred and twenty eight patients were given chemotherapy with the intention of making them resectable.The chemotherapy delivered was TPF in 35 (6.6%) and two drug combination of taxane & platinum in rest. Out of these, 245 patients (46.4%) were considered resectable in the multidisciplinary clinic and 236 (44.7%) underwent resection. The median time to surgery after last dose of chemotherapy was 4 weeks. R0 resection was achieved in all patients (100%). The incidence of close margin (<5 mm) was 2.96% (7 patients). There was no postoperative mortality noted in these patients.
Conclusion: Surgical resection post NACT in technically unresectable oral cancers is possible in nearly half of such advanced patients. In the patients undergoing surgical resection at our centre, all patients could be resected with a negative margin.
No conflict of interest.

3228 POSTER

Outcome of patients treated with palliative weekly paclitaxel plus cetuximab in recurrent head and neck cancer after failure of platinum-based therapy

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Background: Few therapeutic options are available for recurrent/metastatic head and neck cancer when progression occurs after initial chemotherapy with platinum-based regimens. We analyzed retrospectively the efficacy of weekly paclitaxel plus cetuximab as second line of palliative chemotherapy.
Material and Methods: Patients with squamous carcinoma of head and neck with documented progression after initial treatment were enrolled. Tumor response was evaluated through the RECIST 1.1 criteria. The retrospective analysis focused on overall survival (OS) and progression-free survival (PFS).
Results: Between 2008 and 2011, 33 consecutive patients were treated. An overall response rate (ORR) of 55% was observed, with median response duration of 5.0 months. The median PFS was 4.0 months and the median OS time was 10.0 months. Chronic anemia was the most common adverse event and it ocurred in 12 patients.
Conclusions: A weekly schedule of paclitaxel plus cetuximab is a promising regimen for patients with advanced head and neck cancer after failure of platinum-based therapy. Good tolerance allows treating more fragile patients.
No conflict of interest.

3229 POSTER

A phase II study of combination chemotherapy with S-1 and nedaplatin as neoadjuvant manner for oral squamous cell carcinoma patients

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Background: In oral cancer therapy, functional preservation is very important matter. Effective preoperative (neoadjuvant) chemotherapy is required. We investigated the feasibility of combination chemotherapy with S-1 (an oral fluoropyrimidine) and Nedaplatin (CDGP) as a neoadjuvant regimen for oral squamous cell carcinoma patients.
Materials and Methods: Twenty-three fresh cases with stage II−IV oral squamous cell carcinoma were enrolled in this study from April 2010 to March 2012. Patients were administered S-1 80 mg/m^2/day (day 1−14) and CDGP 80 mg/m^2/day (day 8) and followed by definitive surgery. Clinical response was examined by clinical findings and/or CT and histopathological effects were evaluated with surgical specimens.
Results: The rate of clinical response including complete response(CR) and partial response(PR) was 43.6%: CR 21.8%, PR 21.8%, NC 56.4%. The rate of histological response was same. The response rate by T category was 53.3% for T2, 33.3% for T3 and 20% for T4 tumor. Main toxicities were myelosuppression and gastrointestinal disturbances; leukocytopenia 39.1%(Grade II:6, III:2), neutropenia 34.8%(Grade II:5, III:2, IV:1), thrombocytopenia 47.8%(Grade I:2, II:4, III:5), hypohemoglobinemia 47.8%(Grade I:10, II:1), anorexia 21.7%(Grade I:5), nausea 47.8%(Grade I:9, II:2). The toxicities more than grade III were leukocytopenia (8.3%), neutropenia (13%), thrombocytopenia (21.7%), diarrhea(4.3%) and oral mucositis(4.3%). The most part of toxicities disappeared within 4 weeks after chemotherapy. No serious adverse effects were observed in all patients.
Conclusions: Combination chemothetapy with S-1 and CDGP represents an effective antitumor activity and mild to moderate toxicities. It is suggested that this regimen is suitable for neoadjuvant chemotherapy.
No conflict of interest.

3230 POSTER

Angiotensin-converting enzyme (ACE) inhibitors could prevent aspiration pneumonia in head and neck cancer patients treated with concurrent chemoradiotherapy (CCRT)

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Background: Concurrent chemoradiotherapy (CCRT) is a standard treatment for locally advanced head and neck cancer patients, but some patients complicate aspiration pneumonia, which might interrupt their therapy. For preventing aspiration pneumonia, angiotension-converting enzyme (ACE) inhibitors have been known to be effective in high risk patients such as post -stroke. We retrospectively evaluated the effectiveness of ACE inhibitors on the risk reduction of aspiration pneumonia in head and neck cancer patients treated with CCRT.
Methods: We retrospectively analyzed non-metastatic head and neck cancer patients treated with CCRT from November 2005 to December 2012 in our hospital. Chemotherapy consisted of cisplatin (CDDP) (80 mg/m^2 per

3 weeks), but carboplatin (AUC 1.5 weekly) or docetaxel (10 mg/m^2 weekly) was administered in case patients were consider to be intolerable to CDDP. Radiation therapy was performed as three-dimensional radiotherapy (3D-RT) or intensity-modified radiotherapy (IMRT).
Results: A total of 224 patients (192 male, 32 female; median age 59.6 years) received CCRT, of which 128 (57.1%) were Stage4. Median follow-up time was 19.3 months (range 0.99–71.4 months). Patients were divided into three groups based on their antihypertensive medication; 17 patients (7.6%) received ACE inhibitors,56 patients (25.0%) received antihypertensive drugs other than ACE inhibitors, and 151 patients (67.4%) received no antihypertensive drugs. Twenty-nine (12.9%) patients were complicated by aspiration pneumonia, but no patient with ACE inhibitors had aspiration pneumonia. On the other hand, 17.8% (10 patients) of patients with other antihypertensive drugs, and 12.5% (19 patients) of patients without antihypertensive drugs were complicated by aspiration pneumonia. Statistical analysis could not be performed because of lack of aspiration pneumonia events in patients with ACE inhibitors.
Conclusion: In head and neck cancer patients treated with CCRT, ACE inhibitors could be effective for preventing aspiration pneumonia.
No conflict of interest.

3231 POSTER

Development of hyponatremia on neoadjuvant chemotherapy in locally advanced head & neck cancers

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Background: Hyponatremia is a potential life threatening complication. The incidence of this toxicity is minimal to absent in recently reported studies of neoadjuvant chemotherapy (NACT) in head & neck cancers.
Material and Methods: This is a retrospective analysis of 528 patients of locally advanced oral cancers who received NACT at our centre. The aim of this study was to report the incidence of hyponatremia & to study the factors leading to its development. The database maintained in our department, electronic medical record system & case charts of these patients were reviewed to note the incidence of hyponatremia. The hyponatremia was graded in accordance to CTCAE version 4.02. In addition factors like age, sex, body mass index, drug regimen, types of drugs, co morbidities & concurrent medications which can lead to hyponatremia were noted. SPSS version 16 was used for analysis.
Results: The median age of this cohort was 45 years (22−78 years). It was a male predominant population (83.72%). Co morbidities in the form diabetes mellitus was present in 118 patients (22.3%), hypertension in 100 patients (18.9%) & ischemic heart disease in 70 patients (13.3%). The concurrent use of thiazide diuretics was present in 60 patients (11.36%) & sulfonylurea hypoglycaemic in 82 patients (15.15%). Baseline hyponatremia prior to start of chemotherapy was present in 43 patients (8.14%) & median baseline sodium levels in these 43 patients were 132 meq/L(129–134 meq/L). The chemotherapy delivered was TPF in 35 (6.6%) and combination of taxane with platinum in rest all. Taxane used in the 2 drug combination was Docetaxel in 249 patients (47.3%) & Paclitaxel in 244 patients (46.3%). The platinum administered in 2 drug combination was cisplatin in 419 patients (79.6%). The incidence of any grade hyponatremia was 34.5% in the first cycle of chemotherapy & 19.1% in the second cycle of chemotherapy. The nadir value of hyponatremia was seen mainly on day 8 (5−14 days) in both first & second cycle The cumulative incidence of hyponatremia was 44.5%. The cumulative incidence of grade 3−4 hyponatremia was 35%. Among the variables tested on univariate analysis use of a 3 drug regimen of TPF ($p = 0.0001$) & in 2 drug regimen use of docetaxel ($p = 0.0034$) was significantly associated with hyponatremia. Use of Cisplatin containing regimen was not associated with hyponatremia.
Conclusion: Around one-third of our patients develop grade 3−4 hyponatremia post neoadjuvant chemotherapy. Regular monitoring & vigilance about development of this complication is recommended.
No conflict of interest.

3232 POSTER

Neoadjuvant chemotherapy (CT) with docetaxel, cisplatin and 5-fluorouracil (TPF) before concomitant chemoradiation for locoregionally advanced (LA) squamous cell carcinomas of the head and neck (SCCHN): single-center experience and results of an intensive nurse-led support program (INLSP)

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Background: SCCHN is the sixth most common cancer worldwide, 2/3 of the patients (pts) presenting in advanced stages (III and IV). Since 2007, in some centres, the standard of care for LA SCCHN is neoadjuvant CT with TPF, followed by concomitant chemoradiation. This approach has led to improved progression-free and overall survival. In 2012 we started at our institution an INLSP for these pts. We present our toxicity and survival results.
Material and Methods: Patients were treated with Docetaxel 75 mg/m^2 (day 1), Cisplatin 75 mg/m^2 (day 1) and 5-Fluorouracil 750 mg/m^2/day (days 1−5) for three cycles, followed by concomitant chemoradiation.
The clinical records of all pts were retrospectively reviewed. We retrieved demographical, epidemiological and clinical information. We evaluated efficacy using clinical criteria. Toxicity was evaluated using Common Terminology Criteria for Adverse Events 4.0. Statistical analysis was performed using STATA (R) and Microsoft Excel 14.2.3 (R). Survival was estimated using Kaplan–Meier method.
Results: Between July 2008 and February 2013 117 pts were treated at our institution (87% male). Mean age at diagnosis was 53 years-old. 92% of the pts had ECOG PS 0 or 1. The most common primary tumor locations were Oropharynx (47%), oral cavity (23%) and hypopharynx (22.2%). The majority had stage IVA (47%) or IVB (51.3%) disease. Tobacco (95.7%) and Alcohol use (92.3%) were the most common comorbidities. 29.92% of the pts were enrolled on our INLSP. Pts received a mean number of 2.73 cycles of TPF. Overall Clinical Response rate with TPF was 87.2%, with a Complete Clinical Response Rate of 14.5%. The most common adverse events were anemia (50.4%) and diarrhea (28.2%). 26.5% of the pts experienced grade 3−4 toxicity (mainly neutropenia and diarrhea). Six pts died as a result of the treatment (5.1%). With a median follow-up of 7.17 months, median PFS is 14.97 months. With a median follow-up of 14.48 months, 1- and 3-year OS are 82% and 38%, respectively, with a median OS of 20.5 months. Pts enrolled in the INLSP experienced less toxicity and fewer grade 3−4 events, but diferences were not statistically significant.
Conclusions: Neoadjuvant CT with TPF followed by concomitant chemoradiation is an effective treatment for pts with LA SCCHN. Toxicity is important. These pts should be treated at high-volume, experienced institutions. Our INLSP is improving toxicity and treatment-associated death rates, but differences are still nonsignificant.
No conflict of interest.

3233 POSTER

Bone marrow toxicity from large cumulative activity of radioiodine therapy in advanced differentiated thyroid cancer patients

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Radioiodine therapy (RAIT) is usually repetitively given to patients with advanced differentiated thyroid cancers (DTC) provided the tumors remain iodine-avid. However, bone marrow depression with permanent leukopenia might happen with large cumulative dose used. We intend to investigate the possible factors influencing its occurrence.
Material and Methods: We retrospectively reviewed 728 consecutive DTC patients receiving RAIT during 2006 Feb to 2012 Aug at our institute (the most important academic tertiary referral center for RAIT in Taiwan). All the patients were treated based on empirically selected dosage regimen (100–200 mCi for each time) and had WBC tested on a pre-RAIT routine and/or at least 6 months apart from prior RAIT. Totally 43 patients with cumulative RAIT dose to $\geqslant$500 mCi were studied. 8 cases with initially low leukocyte count (WBC) or experiences of external beam radiotherapy were excluded and 35 patients were used to analyze their WBC decrease in related to various factors, including age, gender, histopathology, metastases, and cumulative dose.
Result: Eight out of 35 cases revealed WBC <4000/uL after repetitive RAIT. The counts varied from 2080 to 3900/uL and none of the patients experienced severe infection. The change of WBC (i.e. percentage difference between post RAIT and original ones) ranged from +34% to −70% (Average: +0.5% $\pm$ 41.3%). The reduction in WBC was significantly related to the presence of bony metastases and non-papillary cancer type, while age at RAIT, gender, cumulated dose did not affect the WBC change. After the adjustment for age and gender, we found that metastases and histopathology were strong predictors to indicate decreased WBC after large cumulative dose.
Conclusion: The permanent bone marrow toxicity is regarded as a serious RAIT-related side effect but its occurrence seems not high. From our data, bone metastasis is a reliable predictor for DTC patients more sensitive to large cumulative RAIT dose. However, whether the reduced WBC is due to bony metastases *per se* or via more absorbed dose from RAIT requires further clarification.
No conflict of interest.

3234 POSTER

Induction chemotherapy followed by either chemoradiotherapy or bioradiotherapy in locoregionally advanced head and neck cancer

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Background: To compare the efficacy and safety of induction chemotherapy (ICT) followed by chemoradiotherapy (CRT) or bioradiotherapy (BRT) in locoregionally advanced head and neck cancer.
Methods: Previously untreated patients with stage III to IV larynx/hypopharynx squamous cell carcinoma received three cycles of ICT−docetaxel and cisplatin 75 mg/m^2 each on day 1. Poor responders (<50% response) underwent salvage surgery. Responders (>50% response) were randomly assigned to conventional radiotherapy (RT;70 Gy) with concurrent cisplatin 40 mg/m^2 per week of RT (arm A) or concurrent cetuximab 400 mg/m^2 loading dose and 250 mg/m^2 per week during RT (arm B). Primary end point was Larynx Preservation (LP). Secondary end points were larynx function preservation(LFP) and overall survival (OS) at 24 months.
Results: Of the 77 enrolled patients, 52 patients enrolled in Arm A, 25 patients enrolled in Arm B. Toxicity of both CRT and BRT was substantial following ICT. However, treatment compliance was higher in the BRT arm. In an intent-to-treat analysis, there was no significant difference in LP at 3 months between arms A and B (92% and 93%, respectively), LFP (87% and 82%, respectively), and OS at 24 months (75% and 72.2%, respectively). There were fewer local treatment failures in arm A than in arm B; salvage surgery was feasible in arm B only.
Conclusions: Induction DP chemotherapy followed by Chemoradiotherapy or Bioradiotherapy is feasible treatment strategy for patients with locoregionally advanced head and neck cancer. However,There is no evidence that one treatment was superior to the other or could improve the outcome reported with ICT followed by RT alone.
No conflict of interest.

3235 POSTER

Cetuximab plus platinum-based chemotherapy in head and neck cancer: A retrospective study in a single European Institution

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Background: Cetuximab in association with platinum plus 5-fluorouracil was previous demonstrated to be effective in metastatic squamous tumor of head and neck. We investigated in a retrospective cohort the efficacy and outcome of this protocol as first line treatment for patients with recurrent or metastatic disease, with the primary end point of overall-survival (OS); and secondary end-point, progression-free-survival (PFS) and toxicities profile.
Material and Methods: We enrolled 121 out of 280 eligible patients (between January 2010 and December 2012) with untreated recurrent or metastatic squamous-cell carcinoma of the head and neck to receive cisplatin (at a dose of 100 mg per square meter of body-surface area on day 1) or carboplatin (at an area under the curve of 5 mg per milliliter per minute, as a 1-hour intravenous infusion on day 1) plus fluorouracil (at a dose of 1000 mg per square meter per day for 4 days) every 3 weeks for a maximum of 6 cycles plus cetuximab (at a dose of 400 mg per square meter initially, as a 2-hour intravenous infusion, then 250 mg per square meter, as a 1-hour intravenous infusion per week) for a maximum of 6 cycles. Patients with stable disease who received chemotherapy plus cetuximab continued to receive cetuximab until disease progression or unacceptable toxic effects, whichever occurred first.
Results: The median age was 53.5 (37−78) years old. Male gender was predominant: 86.3%. Primary tumor site was: oropharynx (21%), hypopharynx (20.3%), larynx (25.3%), oral cavity (30.4), others (2.5%). Extent of disease was only localrecurrent (51.3%) and metastatic with or without locoregional recurrence (48.7%). The addition of cetuximab to platinum plus 5-fluorouracil in recurrent or metastatic setting provided an OS of 11 (Confidential Interval, CI, 95%, 9.065–12.935) months and PFS of 9 (95% CI, 6.425–11.575) months. The most common grade 3 or 4 adverse events in the chemotherapy-alone and cetuximab groups were febrile neutropenia (6.3%), skin rash (5.1%), mucosistis (5.1%) and anemia (3.8%). Of total patients receiving cetuximab, 6.3% had grade 3 skin reactions and 7.7% had grade 3 or 4 infusion-related reactions. There were no cetuximab-related deaths.
Conclusions: Our group suggests that cetuximab plus platinum–fluorouracil chemotherapy is indeed a very good option for systemic treatment in advanced head and neck squamous tumors notwithstanding well-tolerated toxicity profile and management.
No conflict of interest.

3236 POSTER

Indications for neoadjuvant chemotherapy (NACT) in head & neck cancers − do we differ from the West?

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Background: Use of any treatment modality in cancer depends not only on the effectiveness of the modality but also on other factors like local expertise, tolerance of the modality, cost & prevalence of the disease. Oropharyngeal & laryngeal cancer are the major subsites in which majority of NACT literature in head & neck cancers is available. However oral cancers form a major subsite in Eastern Asia.
Method: This is an analysis of a prospectively maintained data on NACT in head & neck cancers from 2008–2012. All these patients were referred for NACT for various indications from a multidisciplinary clinic. Descriptive analysis of indications for NACT in this data base is presented.
Results: 862 patients received NACT within the stipulated time period. The sites were oral cavity 721 patients (83.6%), maxilla 41 patients (4.8%), larynx 33 patients (3.8%), laryngo-pharynx 8 patients (0.9%) & Hypopharynx 59 patients (8.2%). Out of oral cancers, the major indication for NACT was to make the cancer resectable in 703 patients (97.5%of oral cancers) while preservation of mandible was an indication in 19 patients (2.5% of oral cancers). The indication in carcinoma of maxilla was to make the disease resectable in 29 patients (70.7% of maxillary cancers) & in 12 patients it was given as an attempt to preserve the eyeball (29.3% of maxillary cancers). The indication for NACT in laryngeal cancers was organ preservation in 14 patients (42.4% of laryngeal cancer) & to achieve resectability in 19 patients (57.6%of laryngeal cancer). The group with laryngo-pharynx is a cohort of 8 patients in whom NACT was given to prevent tracheostomy, these patients had presented with early stridor (CTCAE grade 3). The reason for NACT in hypopharyngeal cancers was for organ preservation in 24 patients (40.7% of hypopharyngeal cancer) & for acheivement of resectability in 35 patients (59.3% of hypopharyngeal cancer).
Conclusion: The major indication for NACT is to make disease resectable at our centre while cases for organ preservation are few.
No conflict of interest.

3237 POSTER

Is gemcitabine & nimotuzumab (Nim-Gem) an option post cetuximab based chemotherapy failure in head & neck cancers?

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Background: There is no standard recommended treatment post Cetuximab failure in squamous cell carcinoma of head & neck region. In our institute some patients received Nim-Gem on compassionate basis.
Material and Methods: This is a retrospective analysis of patients who received Gemcitabine & Nimotuzumab post progression on Cetuximab based therapy in squamous cell carcinoma of head & neck cancer. This data was obtained from a prospectively maintained database of patients treated with Cetuximab in our department. The above mentioned regimen was administered weekly. The dose of Nimotuzumab was 200 mg weekly (fixed dose) & Gemcitabine 1000 mg/m^2 given on D1 & D8 of a 21 day cycle. This regimen was delivered till progression or unacceptable toxicity. The response was measured clinically at each week & radiologically at 2 months interval. The toxicity was charted in accordance with CTCAE version 4.02. SPSS version 16 was for used analysis. Progression free survival & overall survival were estimated by Kaplan Meier survival analysis.
Results: Ten patients received Nim-Gem regimen. The median age was 51.5 years (43−66 years). The site distribution was oral cancers in 7 patients, pharyngeal cancers in two & laryngeal cancers in one. All patients except one patient were treated initially with radical intent. In these 9 patients all had received platinum based chemotherapy either as concurrent Cisplatin during radiation or as neoadjuvant chemotherapy. Post failure all nine patients & one patient per prima received weekly Paclitaxel & Cetuximab chemotherapy. On progression all 10 patients received Nim-Gem. It was third line chemotherapy in 9 patients & second line in one patient. The best response achieved at 2 months was stable disease in 3 patients & progression in 6 patients. One patient didn't undergo response evaluation at 2 months. The median PFS was 56 days (14−97 days). The median OS was 112 days (29–228 days). The grade 2 or above toxicity

noted were mucositis grade 2 in 5 patients, grade 2 vomiting in 3 patients, myalgia grade 2 in 3 patients, myalgia grade 3 in 1 patient. There was no discontinuation because of toxicity.
Conclusion: Nim-Gem regimen appears to be a promising regimen in patients post cetuximab failure. We plan to evaluate it further in a phase 2 study.
No conflict of interest.

3238 POSTER

Induction chemotherapy of docetaxel and cisplatin combination with or without doxorubicin in locally advanced nasopharyngeal carcinoma

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Introduction: Compare the tumor control, progression-free and overall survival of patients with nasopharyngeal carcinoma (NPC) underwent two alternative regimen of induction chemotherapy (CT).
Materials and Methods: Previously untreated patients with locally advanced NPC. From 2004 to 2010, 50 pat. were included in group A, age 20−71 years (mediana 42 years), 33 men and 17 women. Nasopharyngeal carcinoma was diagnosed in 29 pat., squamous cell carcinoma G2−3 in 21. Initial staging at diagnosis: T2−3N2M0 in 4 pat., T4N0−2M0−36 and T2−4N3M0−10 pat., respectively. Treatment regimen: docetaxel 75 mg/m^2 − 1 day, cisplatin 75 mg/m^2 − 1 day, doxorubicin 45 mg/m^2 − 1 day. In August 2011 began the set in group B. Now in this group 15 people were included − 5 women and 10 men, from 19 to 73 years (mediana 48.8 years). Squamous-cell carcinoma G2−3 was diagnosed in 8 pat., undifferentiated nasopharyngeal in 7. Tumor characteristics: T3N1−2M0 and T1−3N3M0 on 3 pat., T4N0−2M0−6 and T4N3M0−3 pat. Treatment regimen: docetaxel 75 mg/m^2 − 1 day, cisplatin 75 mg/m^2 − 1 day. Cycles were repeated every 21 days in both groups. Efficiency was estimated after 3 courses of CT. If the tumor regress was 50% and more, treatment continued to 6−8 courses from the subsequent radiotherapy (RT) and if positive lymph nodes were found out in the neck, they were subjected to lymphadenectomy.
Results: Overall response rate in group A (WHO) was 88% − 44 pat. (CR − 48% − 24 pat., including T4N2M0 and PR in 40% − 20 pat.). Stabilization of disease is noted in 3 (6%) and the progression of disease in 3 (6%) pat. The median time to progression of disease was 32 months and the median of overall survival 37.5 months. In group B OR after end of induction chemotherapy was 87% − 13 people (CR in 3 cases − 20%, PR in 10 patients − 66%). Disease progression was in 2 pat. Supervision periods in second group made from 3 to 18 months.
Conclusion: Induction CT on a basis docetaxel and cisplatin combination is a highly active regimen in locally advanced NPC and allows to carry out further RT at this category of patients that significantly improves results of treatment. But question of choice the optimum treatment modes still open.
No conflict of interest.

3239 POSTER

Clinical outcomes of induction chemotherapy in locally advanced head and neck cancer

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Background: The aim of this study was to evaluate the efficacy and survival analysis of induction chemotherapy in locally advanced head and neck cancer.
Material and Methods: Fifty patients who received induction chemotherapy for squamous cell carcinoma of the head and neck in Seoul St. Mary's Hospital between January 2000 and December 2012 were evaluated. Clinical records and pathology reports were reviewed retrospectively.
Results: Twenty patients received docetaxel plus cisplatin (DP); 12 patients received 5-fluorouracil plus cisplatin (FP); 18 patients received docetaxel, cisplatin, and 5-fluorouracil (TPF). There was no significant difference in clinical characteristics between the three groups except for smoking and performance status. The overall response rate (ORR) for DP, FP, and TPF was 80.0%, 83.3%, and 88.9%, respectively (p = 0.755). Two patients for DP and a patient for FP experienced disease progression after induction chemotherapy. Among 25 patients who underwent surgery, pathologic complete response (pCR) was observed in 3 (33.3%) for DP, 1 (25.0%) for FP, and 6 (50.0%) for TPF, respectively (p = 0.044). Complete metabolic response measured at post-chemotherapy F-18 fluorodeoxyglucose positron emission tomography/ computed tomography was observed in 1 (9.1%) for DP, 1 (25.0%) for FP, and 9 (69.2%) for TPF, respectively (p = 0.009). Patients with human papillomavirus (HPV)-positive cancer showed higher pCR rates than patients with HPV-negative cancer, regardless of the type of chemotherapy (p = 0.012). Disease relapse or progression occurred in 16 (32.0%) patients. The relapse/progression rate did not differ between the three regimens (p = 0.197). There were no significant differences in hematologic and non-hematologic toxicities between the three regimens. The relative dose intensities of DP, FP and TPF were approximately 85%, with no significant difference. In univariate analysis using Kaplan–Meier method, the prognostic factor significantly affecting progression-free survival (PFS) was a pCR (p = 0.027).
Conclusions: The TPF induction chemotherapy had a better ORR and higher pCR rate in locally advanced head and neck cancer, but did not improve survival outcomes. The achievement of pCR was a good prognostic factor for PFS.
No conflict of interest.

3240 POSTER

Concurrent chemoradiation with low dose weekly cisplatin in stage IV head and neck squamous cell carcinoma

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Background: Concurrent chemoradation(CCRT) with 3-weekly cisplatin in loco-regionally advanced head and neck squamous cell carcinoma(HNSCC) is standard treatment. But 3-weekly cisplatin is often associated with several adverse events because of high dose cisplatin. In this retrospective analysis, we conducted to determine the efficacy and tolerability of CCRT with low dose weekly cisplatin in stage IV HNSCC patients.
Material and Methods: Review of medical records of patients who diagnosed stage IV HNSCC and received definitive CCRT were analyzed. All patients treated with weekly cisplatin 10−30 mg/m^2 until radiotherapy completed.
Results: Total 35 patients were reviewed, all were stage IV and 15 patients had an oropharyngeal primary. Median follow up was 10.7 months (range 1.7–90.5 months). Median radiation dose were 7040 cGy, and median dose of actually received cisplatin were 157 mg/m^2. Two(5.7%) patients were reduced dose of radiation, and 16(45.7%) patients received modified dose or schedule of chemotherapy. Twenty-five(71.4%) patients achieved complete response(CR), 8(22.9%) had partial response(PR), but 6(24%) recurred after CR.
Grade 3−4 adverse events were stomatitis(82.9%), dermatitis(22.9%), infection(11.4%), dysphagia(8.6%), and neutropenia (5.7%). One patient died due to pneumonia during CCRT. Long term grade 3 adverse events after treatment were only 2 cases of xerostomia.
Median overall survival was 42.7 months, 3 year survival rate was 51.2%. Disease free survival was not reached to median, and 3 year disease free survival rate was 72.8%. Overall survival was improved in patients who achieved CR than others (59.7 vs. 13.4 months, $p = 0.008$).
Conclusions: In this retrospective study, low dose weekly cisplatin showed acceptable response compare to 3-weekly cisplatin, and seemed to reduce severe adverse events, especially long term toxicities. CCRT with low dose, weekly cisplatin will be effective and tolerable even in patients with stage IV head and neck cancer.
No conflict of interest.

3241 POSTER

Next generation sequencing: A powerful tool providing new insights into the genomic landscape of oral verrucous carcinomas

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Background: Oral verrucous carcinoma (OVC) is a low grade, non-metastasising, slow growing variant of oral squamous cell carcinoma (OSCC), with an estimated incidence range between 2%-10% of all OSCC cases. In general, OVC histopathological diagnosis is ambiguous and difficult. Distinguishing OVC from classical OSCC is a common problem for pathologists due to the poorly defined diagnostic criteria and sampling difficulties. Early OVC usually presents as a pre-malignant lesion such as proliferative verrucous leukoplakia (PVL) or oral verrucous hyperplasia (OVH). OVH lesions may transform into either an OVC or an OSCC. The genomic alterations underlying OVH, and OVC lesions is still not clear and requires further investigations. The rarity of these lesions also makes

them difficult to investigate, so most previous studies have been made on small numbers of cases. The aim of this study is to use next generation sequencing (NGS) copy number analysis to identify oral verrucous lesions (including OVC, and OVH cases) genomic characteristic features, and to investigate the differences in the genomic damage pattern between OVC and OSCC lesions.
Methods: We identified a total of 62 oral verrucous cases: 49 OVCs, and 13 OVHs in this study. FFPE blocks were retrieved for all samples and DNA was extracted from the macro-dissected tumour tissues. DNA libraries were prepared and assessed for quality and concentration followed by sequencing at coverage between 2.5% and 13%. Copy number (CN) gain and loss pattern along the whole genome was compared between OVH, and OVC karyograms, besides OSCC karyograms from another study conducted by our group.
Results: Genomic copy number karyograms were produced for all samples, and visual inspection of the 62 patient genomic copy number karyograms demonstrated regions of gain and loss along the whole genome in OVC cases. In general, OVC karyograms showed different types of copy number patterns, in terms of both the complexity of the damage and the proportion of the genomes involved. This pattern ranged from whole chromosome gain to amplified or lost chromosome arms and regions. On the other hand, gain and loss features were minimally found in OVH cases. The analysis of CN aberrations across the entire OVCs data set revealed lower chromosomal instability features in OVC samples when compared to OSCC samples.
Conclusion: This study shows that NGS analysis can be used for a more specific assessment and evaluation of OVCs heterogeneity based on the analysis of the whole genome CN karyograms. The results of our study show a lower degree of tumor heterogeneity and chromosomal instability in OVCs when compared to OSCCs. Such a result confirms the well-known definition of OVC and that they appear as a low grade, slow growing variant of OSCC.
No conflict of interest.

3242 POSTER

Systemic inflammation is an independent predictive marker of clinical outcomes in mucosal squamous cell carcinoma of the head and neck

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Background: Inflammation is a key driver of the tumour progression and response to treatment. Elevations in markers of systemic inflammation are prognostic in many different cancer types. This study aimed to investigate whether a marker of systemic inflammation, the neutrophil-to-lymphocyte ratio (NLR), was predictive of clinical outcomes in patients with mucosal oropharyngeal cancers.
Material and Methods: We performed a retrospective analysis of the association of NLR and clinical outcomes (recurrence and overall survival) in patients with mucosal oropharyngeal cancer. The NLR was determined prior to start of radiotherapy (RT) from routine full blood counts using the absolute neutrophil count/absolute lymphocyte count (cut-off >5). NLR and clinicopathological features were correlated with clinical outcomes using Chi squared and log-rank tests and Cox-regression analysis.
Results: A total of 152 patients with AJCC Stage I−IV mucosal oropharyngeal cancer were included in analysis. All patients had RT as part of the treatment regimen (11% RT alone, 24% surgery + RT, 56% chemotherapy + RT and 9% surgery + CRT). Elevated NLR >5 was observed in 21% patients and was only associated with higher tumour stage ($p < 0.001$). Current/previous smoking, and not NLR, was associated with older age, tumour site (oropharynx) and poorer ECOG performance status. Smoking status was the only independent predictor of locoregional recurrence ($p < 0.001$). While, elevated NLR and tumour site were predictive of metastatic recurrence ($p < 0.03$). On multivariate analysis, elevated NLR, poor performance status and smoking status were independent predictors of overall survival (Cox Regression model $p = 0.001$, hazard ratios = 4.4 [95% CI: 2.0−9.3], 2.9 [95% CI: 1.8−4.8], 2.9 [95% CI: 1.6−5.3], respectively).
Conclusions: The results of this study show that the presence of tumour-related systemic inflammation, as measured by NLR, is a better predictor of metastatic recurrence and overall survival than tumour grade/stage/site. NLR is a routinely available, cheap biomarker that can aid in the prognostication of patients with oropharygeal cancer. Understanding whether tumour biology, such as p16 status, impacts NLR is unclear and is currently being investigated.
No conflict of interest.

3243 POSTER

p16 expression in HNSCC: Identification of the cut-off and prognostic value in oropharynx tumours (OT) vs non OT

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Background: We analysed tumour samples from patients with locally advanced HNSCC, to establish a predictive cut-off of p16 expression and to compare its role in OT vs non OT.
Materials and Methods: We analysed 206 samples from patients treated with CRT from 1997 to 2011. Pts characteristics were: M/F 175/31; median age 59.6 (range 20–85.6); primary site OT/non OT 66/140. Smoking information is available in 186 pts. Among them, 93% were heavy smokers (>10 pack/year).
P16 was calculated by IHC.
Positivity (pos) was defined as $\geqslant$1% pos cells. On the basis of the clinical literature, we considered two cut-off in pos cells (10% and 70%). Therefore, we initially compared four groups: negative (0 pos cells), low pos (1−9%), median pos (10−69%), and high pos (70–100%). Based on early results, we later considered only one cut off (50% pos cells) and 3 groups: negative, low pos (1−50%) and high pos (51–100%).
Results: P16 pos was 68% in OT and 50% in non OT ($p < 0.007$). Taken together, the pos status confers a survival (OS) advantage (36.8 months vs 19.5 months, $p = 0.06$). Considering the 3 pos levels (low, median and high), only high pos tumours show a better OS in the OT group (median 22.5, 15 and 97.9 months respectively, $p = 0.098$) while no difference emerges in the non OT. If we include also the p16 negative tumours, the latter behaves as the low pos and the median pos group in OT, and as all the three pos groups in non OT.
The cumulative analysis showed that the pos values place around two focus points at a median value of 2% (lower focus, the median value of all the pos values between 0 and 50%, range 1−45) and 96% (higher focus, the median value of all pos values between 51 and 100%, range 55−99). On these findings, we than divided p16 pos tumours in two groups < or >50% pos.
OT showed a larger number of cases in the >50% group (31%) compared to non OT (17%) ($p = 0.08$).
P16 high pos (>50%) confers a survival advantage in patients with OT, while in the non OT the same pos values correlate with a non significant negative prognostic effect (tab 1).
Conclusions:
1. The cut-off of p16 expression of clinical relevance can be considered 50% of positive cells.
2. Effect of high p16 pos expression is evident only in OT while it disappears in non OT. A possible negative prognostic impact in non OT should be investigated.
3. Smoking cannot be considered a confounding factor in the present series since most of our patients were heavy smokers (>10 pack/year). For the same reason, the prognostic role of p16 expression may result attenuated.

No conflict of interest.

Table 1.

	Med OS (months)		P value
	<50% pos cells	>50% pos cells	
OT	15.8	97.9	0.16
Non OT	38.3	15.3	0.46
P value	0.31	0.27	

3244 POSTER

Targeting Rac1 as a novel treatment for chemo-radioresistant head and neck squamous cell carcinomas (HNSCC)

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Purpose: In order to improve therapy for HNSCC patients, novel methods to predict and combat local and/or distant tumor relapses are urgently needed. This study has been dedicated to identify proteins involved in HNSCC cell insensitivity to chemo-radiotherapy resulting in recurrence development.

Material and Methods: Radiation resistant IRR cells were derived from parental HNSCC cells after repeated exposure to ionizing radiation at a total dose of 100 Gy. All cells were investigated for their sensitivity to ionizing radiation and cisplatin. Protein profiling in parental and IRR cells was carried out using two-dimensional differential gel electrophoresis (2D-DIGE) followed by MALDI-TOF/TOF mass spectrometry. Cell viability, cell migration assays, G-LISA and Western blot analysis were used to confirm results obtained using the proteome approach. Additionally, tumor tissues obtained from 60 HNSCC patients showing different therapy response were evaluated for intratumoral Rac1 expression.
Results: Forty-five proteins that were similarly modulated in IRR cells compared to parental HNSCC cells were selected to analyze their common targets. It was found that these either up- or down-regulated proteins are closely related to the enhancement of cell migration which is regulated by Rac1 protein. Radiation and cisplatin resistances of IRR cells were accompanied by increased expression, activity and trend towards nuclear translocation of Rac1 protein. Chemical inhibition of Rac1 expression and activity resulted in significant improvement of HNSCC sensitivity to ionizing radiation and cisplatin and inhibition of migratory activities of IRR cells. Pre-clinical results were confirmed in clinical samples. While Rac1 was poorly presented in normal mucosa, tumor tissues revealed increased Rac1 expression. The most pronounced Rac1 presence was observed in HNSCC patients with poor early or late responses to chemo-radiotherapy. Tissues taken at recurrence were characterized not only by enhanced Rac1 expression, but also increased nuclear Rac1 content.
Conclusion: Increased expression, activity and subcellular localization of Rac1 could help to predict early response rates and higher risk of tumor recurrences in HNSCC patients and warrants further validation in larger independent studies. Inhibition of Rac1 activity can be useful in overcoming treatment resistance and could be proposed for HNSCC patients with primary or secondary chemo-radioresistance.
No conflict of interest.

3245 POSTER

2D, 3D and in vivo models of head and neck cancer identify novel correlates of resistance to epidermal growth factor receptor tyrosine kinase inhibitors

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Background: Clinical responses to single agent epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have been disappointing, especially in head and neck cancers (HNSCCs), most of which overexpress EGFR. Reported predictive response markers do not reliably translate between different cancer types. There is a need to identify patients likely to fail therapy and to understand the underlying molecular mechanisms. We aimed to discover markers of EGFR TKI resistance in HNSCC, focussing on parameters translatable to the clinic via minimally invasive techniques and with potential mechanistic relevance.
Materials and Methods: Chronic exposure of human HNSCC cells (CAL 27 and PE/CA-PJ34) to gefitinib *in vitro* yielded sublines resistant to EGFR TKIs, including erlotinib and afatinib. Biological behaviour was analysed in standard 2D monolayers and 3D tumour spheroids. Culture supernatants and patient sera were analysed using immunoassays for potential secreted biomarkers. Xenografts were investigated using intrinsic susceptibility magnetic resonance imaging (IS-MRI) and immunohistochemistry. Metabolic profiles were obtained using ^{1}H and ^{31}P magnetic resonance spectroscopy (MRS).
Results: EGFR TKI-resistant and -sensitive HNSCC cell lines grew at similar rates in 2D cultures. *In vivo,* however, resistant cells generated rapidly-growing, invasive tumours, a phenotype that was replicated in 3D tumour spheroid cultures. MRS revealed that acquired drug resistance was associated with changes in glycolytic, bioenergetic and choline phospholipid metabolism, both *in vitro* and *in vivo*. Resistant xenograft tumours also exhibited an attenuated haemodynamic response, decreased vessel perfusion and increased hypoxia as determined by IS-MRI and *ex vivo* microscopy. Molecular analyses of resistant cells identified overexpressed hypoxia-regulated proteins with functions linked to tumour angiogenesis and invasion. Subsequently, we were able to define a 'resistance-associated protein signature' detectable in the sera of a small cohort of HNSCC patients and associated with reduced survival.
Conclusions: We developed and characterised models of EGFR TKI-resistance using a wide range of biological and physical techniques. This led to the identification of 1) a metabolite profile, 2) a serum protein signature and 3) magnetic resonance imaging parameters, linked to a more aggressive phenotype, which warrant further investigation as potential markers of EGFR TKI-resistance.
No conflict of interest.

3246 POSTER

Reduced methylation and increased protein expression of CSPG4 negatively influences survival of HNSCC patients

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Background: Several family members of the proteoglycans have shown their importance in many cancer types as well as in head and neck squamous cell carcinoma (HNSCC). In this study we analyzed in-depth the role of chondroitin sulfate proteoglycan 4 (CSPG4) (also known as NG2/ MCSP/ HW-MAA) in HNSCC tumor progression.
Material and Methods: Tissues of HNSCC and non-tumorous mucosa were analyzed for CSPG4 expression by immunohistochemistry (IHC) and quantitative-real-time PCR (qPCR) as well as for CSPG4 promoter methylation by MassARRAY. Functional validation was performed by 5-AZA treatment in HNSCC cell lines exhibiting CSPG4 promoter methylation. Results were compared with survival estimates by log-rank test.
Results: Examination of protein expression in HNSCC patients (n = 72) compared to normal controls (n = 14) by IHC staining revealed an over-expression in a subgroup of HNSCC tumors. Furthermore, survival analysis using a log-rank test showed a significant correlation of high CSPG4 protein levels and shortened HNSCC patient survival, whereas patients with low or no expression had better survival times. In addition, the CSPG4 over-expression was confirmed by qPCR on mRNA levels (n = 42) as well as in three public available microarray data sets. As a potential cause for differential CSPG4 expression in HNSCC the DNA methylation in a CpG-island in the promoter region was analyzed by MassARRAY. No difference of the mean methylation in HNSCC (n = 100) and normal controls (n = 25) was observed. Nevertheless, in HNSCC tissue samples mean methylation correlated significantly with CSPG4 mRNA and protein expression. The functional relation of CSPG4 DNA methylation and expression were confirmed by demethylating treatment of two highly methylated HNSCC cell lines and subsequent mRNA and protein re-xpression. In addition, survival analysis of HNSCC patients grouped in high and low methylation revealed like shown before for protein levels an inverse correlation of methylation and patient survival.
Conclusions: We identified DNA methylation as a regulatory factor of CSPG4 protein and mRNA expression. Furthermore CSPG4 protein levels and DNA methylation might be useful as prognostic markers for HNSCC patient survival.
No conflict of interest.

3247 POSTER

Evaluation of hTERC (3q26) gain by fluorescence in situ hybridization (FISH) to predict the behavior of oral epithelial precursor lesions

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Background: Oral Squamous Cell Carcinoma (OSCC) is the most common tumor of the oral cavity with 500.000 new cases/year worldwide. Infection of oral mucosa by oncogenic HPV is strongly associated with OSCC among subjects with the established risk factor of tobacco and alcohol abuse. The development of OSCC is a multistep process where genetic and epigenetic events accumulate leading to cell cycle deregulation and chromosomal abnormalities. Based on the evidence that genomic integration of oncogenic HPV and gain of human telomerase RNA gene (hTERC), which is located on chromosome 3q26, appear to be an important genetic events in the progression of cervical intraepithelial neoplasia to invasive cancer, we evaluated the gain of hTERC in oral epithelial precursor lesion and if this genetic alteration could predict the progression to OSSC.
Material and Methods: Preliminary retrospective analysis was performed on 9 out of 40 oral samples with long-term follow up (ranging from 5 to 10 years) with histological diagnosis of: squamous cell hyperplasia (2 cases), mild dysplasia (2 cases) and moderate dysplasia (5 cases). Formalin fixed paraffin embedded (FFPE) tissue from each case was cut into 3 μm sections and were assayed by dual-color interphase FISH for

LSI 3q26 (gold), to investigate the gain of hTERC, and for CEP 7 (aqua) as a control probe. The slides were analyzed with the aid of automated fluorescence microscope Ikoniskope® for counting the gold and aqua signals. Scoring was performed only in the single non overlapping nuclei with clear intact nuclear membranes and signals of both probes present. The cell is considered abnormal if more than two hTERC signals were observed.
Results: 4 out of 9 cases (2 cases of hyperkeratosis and two of moderate dysplasia) showed tissue foci with an increase in the number of 3q26 signals. Interestingly, looking to the follow-up, these tissues belong to patients that developed an OSSC. The 5 cases without hTERC gain never progress to OSSC.
Conclusions: Our preliminary results seem very promising since only those cases with the gain of hTERC developed OSCC. Since we've analyzed only a limited number of cases i.e 9/40, the result should be taken very cautiously. If the result in the rest of the case reflect the clinical outcome, the evaluation of hTERC gain by FISH could precisely predict the behavior of oral epithelial precursor lesion and help the clinician in the early diagnosis of OSSC to address further clinical treatment.
No conflict of interest.

3248 POSTER

Relationship of p16INK4A cellular localization and overall survival in head and neck cancer (HNC)

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Background: Overexpression of nuclear and/or cytoplasmic p16 is regarded as a surrogate of Human papillomavirus (HPV)-positive oropharyngeal carcinoma (OPC) and associated with good outcomes. Conversely, loss of nuclear p16 expression has been associated with poor outcome in many cancers. While $p16^{INK4A}$ protein acts as a cell cycle inhibitor in the nucleus, cytoplasmic p16 expression has also been reported, particularly in association with poor outcomes, suggesting differing roles of cytoplasmic and nuclear p16. We evaluated the relationship of nuclear and cytoplasmic p16 expression with overall survival (OS) in OPC and hypopharyngeal squamous cell carcinoma (HPC).
Patients and Methods: p16 immunohistochemical analysis was performed in 176 (101 OPC, 75 HPC) patients (pts) who were treated with curative intent. p16 nuclear and cytoplasmic expression status was dichotomized according to the mean product of staining intensity and percentage of tumor cells. Clinicopathological characteristics were assessed using a Cox regression model and overall survival (OS) evaluated by Kaplan–Meier method.
Results: Among 176 pts, median age was 63 years and comprised 79.8% males, of which 72% had a positive smoking history and 91.6% had locally advanced HNC. 41 pts (23.2%; 34 with OPC) had high nuclear and high cytoplasmic p16 staining (HN). 6 pts (3.4%, 3 OPC) had low nuclear and high cytoplasmic staining (HC) and 128 (72.7%, 64 OPC) had low nuclear and cytoplasm (LC) staining. Compared to pts with HN, pts with low nuclear p16 (HC and LC) had poor overall survival outcome regardless of cytoplasmic p16 status (HC: Hazard ratio (HR) 3.78, $p = 0.003$, LC: HR 3.71, $p < 0.001$; median OS not reached (HN) vs 24.9 months (HC) vs 24.6 months (LC)). On multi-variable analysis, higher Charlson co-morbidity index (HR 1.31, $p = 0.001$), low nuclear and low cytoplasmic p16 (LC: HR 2.79, $p = 0.047$) and positive smoking status (HR2.47, $p = 0.011$) were associated with poor overall survival, independent of tumor site and HPV status.
Conclusion: High nuclear p16 expression is associated with superior OS, independent of tumor site and HPV. Conversely, high cytoplasmic p16 expression, in presence of loss of nuclear p16, had poor survival. Thus, in HNC, nuclear and cytoplasmic localization of p16 may reflect differential p16 function and affect outcomes differently.
No conflict of interest.

3249 POSTER

Low incidence of PI3KCA, BRAF, and KRAS mutations in refractory squamous cell carcinoma of the head and neck (SCCHN) treated with temsirolimus in the phase II TEMHEAD study

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Background: Temsirolimus has been shown to exert clinical activity in previously treated SCCHN in a phase II study. We now evaluated KRAS, BRAF, PI3KCA as predictive molecular markers for temsirolimus activity.
Material and Methods: Patients with progressive SCCHN and failure of platinum-based and cetuximab therapy were eligible for the trial. Tumor assessment was assessed according to RECIST 1.0 and the primary endpoint was the progression free survival rate (PFR) at 12 weeks >20%. PFS, PFR, and OS estimates were calculated by Kaplan–Meier-Curves. 25 mg temsirolimus was given i.v. weekly until progression or toxicity prevail. KRAS, BRAF, and PIK3CA mutations were assessed in formalin-fixed, paraffin-embedded archived tumor tissue by DNA sequence. Tumors have been collected prior to study entry from previous procedures.
DNA was extracted from manually microdissected tumor sections. An H&E stained serial section served as guidance. Tumor cell content of selected areas was in all cases well above 70%. K-RAS Codon 12 and 13 and B-RAF Codon 600 were analyzed by pyrosequencing. PIK3CA exon 9 and 20 were analyzed by Sanger sequencing.
Results: 42 patients entered the trial of whom 40 were eligible. 25 patients had accessible archived tumor tissue for sequencing. KRAS and BRAF have been analysed in 25 patients each, and 23 patients for PI3KCA. None of the patients showed mutations of KRAS or BRAF. H1048Y and G1050S PIK3CA missense mutations have been found in 1 patient each and were associated with a PFS of 46d and 27d, respectively. OS were 26d, and 55d (censored), respectively. The unselected patient population achieved a PFS and OS of 56 d (95% CI 36–113d), and 152d (95% CI 76–256d), respectively.
Conclusions: The incidence of activating mutations were lower than anticipated. No mutations were found for BRAF and KRAS. PIK3CA missense mutations were detected in 2 out of 25 patients only (8%), which was not associated with an improved PFS. However, the small sample size limits mutational sequencing and supports a larger study set in order to assess the predictive nature of PI3KCA mutations for temsirolimus treatment in SCCHN.
Conflict of interest: *Advisory board: Sanofi and Merck Serono SA. Other substantive relationships: Sanofi and Merck Serono SA*

3250 POSTER

Prognostic impact of the enhancer of zeste homolog 2 overexpression in node-positive laryngeal cancer

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Background: Epithelial mesenchymal transition (EMT) has an important role in invasion and metastasis of tumor cells. Elevated Enhancer of Zeste Homologue 2 (EZH2) is a polycomb group family protein and its overexpression is involved in many human malignancies through epigenetically silencing related genes. EZH2 overexpression is also commonly associated with poor prognosis in a variety of tumor types. However, the exact role of EZH2 and its clinical significance in laryngeal cancer are not yet known. The purpose of this study is to evaluate the roles of EZH2 and other EMT associated proteins on progression and metastasis in locally advanced node-positive laryngeal cancer.
Materials and Methods: We analyzed the significance of these EMT associated protein expression in curatively resected (R0) laryngeal cancer patient as a prognostic marker. Total twenty nine consecutive patients were included in our study. We used protein immunohistochemistry to evaluate EZH2, vimentin, E-cadherin and ki-67 expression on tissue microarray in duplicate. Also we retrospectively reviewed all medical records and tried to analyze the relationship between the expression of EMT markers and

prognosis. The relationship between these protein expressions and survival was plotted on a Kaplan–Meier curve.
Results: EZH2 was expressed in 11 patients (37.9%). Recurrence rate was significantly higher in patients with positive EZH2 expression than that of patients with no expression (Recurrence rate 72.7% vs 33.3%, p = 0.039). Patients with a positive EZH2 expression showed a tendency of shorter their disease progression free survival (median PFS; 11.8 months) than did the patients without expression (median PFS; 23.9 months). However there was no statistical significance (p = 0.0892). The presence of EZH2 expression was not associated with patients' age, pattern of recurrence, T-stage, smoking status, alcohol consumption and histology.
Conclusions: Our immunohistochemical stainings confirm that EZH2 overexpression showed a close correlation in recurrence rate and relapse free survival. Our findings suggest an important role of EZH2 in progression of laryngeal cancer.
No conflict of interest.

Proffered Papers Session (Mon, 30 Sep)
Central Nervous System

3300 ORAL

Bevacizumab, irinotecan and radiotherapy versus standard temozolomide and radiotherapy in newly diagnosed, MGMT-non-methylated glioblastoma patients: Updated results from the randomized multicenter GLARIUS trial

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Background: Alkylating chemotherapy with temozolomide (TMZ) is only marginally effective in patients with MGMT-non-methylated glioblastoma (GBM). Thus, more effective therapies are urgently needed in this large subgroup of GBM. Based on encouraging results of phase II trials with the antiangiogenic agent bevacizumab (BEV) +/− irinotecan (IRI) in recurrent GBM, the GLARIUS trial investigated the efficacy of BEV/IRI therapy as compared to standard TMZ in the first-line therapy of MGMT-non-methylated GBM.
Material and Methods: In the randomized, multicenter, open-label GLARIUS trial (NCT00967330, sponsored by Roche Pharma), adult patients with newly diagnosed, histologically confirmed and MGMT-non-methylated GBM received local radiotherapy (RT, 30 x 2 Gy) and were randomized (2:1) for experimental therapy with BEV (10 mg/kg q2w) during RT followed by maintenance BEV (10 mg/kg q2w) + IRI (125 mg/m^2 q2w (without enzyme-inducing antiepileptic drugs (EIAEDs)) or 340 mg/m^2 (with EIAEDs)) or standard therapy with daily TMZ (75 mg/m^2) during RT followed by 6 courses of TMZ (150–200 mg/m^2/day for 5 days q4w). The primary endpoint was progression-free survival rate after 6 months (PFS-6). Determination of PFS-6 als included a central neuroradiological review of MRI scans.
Results: The intent-to-treat population included 170 patients with a median age of 56 years (range 25−78 years). 67.1% of patients were male. 48.8% had a complete resection rate, and 78.8% of patients had a KPS of 90% or higher. 116 patients received BEV/IRI, 54 patients had TMZ. The frequencies of adverse events in both arms of the trial were within the expected range. The PFS-6 rate was significantly higher in the BEV/IRI arm (71.1%, 95% CI 58.1–80.8%) than in the TMZ arm (26.2%, 95% CI 13.1–41.4%, p < 0.0001 logrank test). Updated PFS and overall survival data will be also presented.
Conclusion: The increase in the primary endpoint PFS-6 upon BEV/IRI chemotherapy is significant and clinically meaningful. This suggests that BEV/IRI is more effective than standard TMZ therapy in newly diagnosed MGMT-non-methylated GBM patients.
Conflict of interest: *Advisory board: Roche. Corporate-sponsored research: Medac, Merck KG & Co. Other substantive relationships: Medac, Roche*

3301 ORAL

Do we know the optimal bevacizumab (BV) dose in recurrent malignant glioma? Final results of a prospective multicenter GEINO protocol using BV 5 mg/kg/2w

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Background: Bevacizumab (BV) received FDA approval as a single-agent therapy for patients with progressive glioblastoma (GBM) based on the results of 2 phase II trials using 10 mg/kg/2w. Although Stark-Vance's initial experience showed a high response rate (RR) using 5 mg/kg and a metha-analysis not showed differences between 5 and 10 mg/kg.
Aim: To evaluate efficacy of BV 5 mg/kg in a prospective series of patients with recurrent malignant glioma (MG) and to compare with a GEINO previous cohort treated with BV 10 mg/kg plus irinotecan (CPT11) with the same inclusion criteria.
Methods: Data from 6 Spanish hospitals was prospectively collected following a clinical protocol. Inclusion criteria were age ⩾18; histology of MG; progression after radiation (RT) and temozolomide; IK ⩾60 and informed consent. Treatment schedule: BV 5 mg/kg/2w. BV was scaled to 10 mg/kg and CPT11 125 mg/m^2/2w was added if progression. RR was determined by MRI using RANO criteria every 8−12 w. Kaplan Meier and Cox model were performed to calculate PFS and OS.
Results: 71 patients were included between Feb2011-Jan2013. Histology: GBM 55 and grade 3 MG 16. Median age: 52 (18−75). Median IK: 70 (50–100). BV was used after first relapse in 42 and after second relapse in 29 patients. Time between end of RT and beginning BV was over 3 months in 93% of patients, median time 8.2 months (1.9–113.5). 51 patients received dexamethasone (DX) at inclusion: median 5.5 mg/day (1−18).
Toxicity: At 5 mg/kg dose the incidence of BV selected adverse events (AE) and G3 AE was consistent with the reported in the 2 pivotal trials. Grade 3−4 were asthenia 9 pts; thromboembolic events 6; diarrhea 4; neutropenia 4; cognitive deterioration 4 and hemorrhage 3 (2 died).
Efficacy: Mean follow-up: 6.1 months (0.5–18.67). BV at 5 mg/kg leads to an IK and neurological improve in 28.2% and reduced/withdraw of DX in 40.8%.
After progression to BV 5 mg 43.6% (24/55) patients received BV10 mg/kg plus CPT11.
Only 1 of 14 evaluable patients showed MRI response.
Conclusion: BV 5 mg/kg in recurrent MG offers similar OS than BV 10 mg/kg although seems to be lower inferior in RR and PFS.
Conflict of interest: *Advisory board: Roche: M. Gil-Gil and C. Balana*

	All	[95% CI]	GBM	[95% CI]
N	71		55	
ORR (%)	26.8	16.9–38.6	27.3	16.1−41
Median PFS (months)	2.7	2.3−3.2	2.6	2.2−3
6 month PFS rate (%)	28.9	18.1–39.7	25.7	13.9–37.5
Median OS (months)	8.4	6–10.9	7.7	5.1–10.3
6 month OS rate (%)	63.6	52–75.2	60.8	47.4–74.2

3301A ORAL

Efficacy and safety of bevacizumab (Bv) plus standard combination temozolomide (T) and radiotherapy (RT) in newly diagnosed glioblastoma: final results from AVAglio

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Background: Glioblastoma has a high disease burden and poor prognosis, despite the widespread use of combination therapy with RT and T. AVAglio is the first randomised, double-blind, placebo (P)-controlled phase III study to evaluate the efficacy and safety of the addition of bevacizumab (Bv) to standard T/RT for newly diagnosed glioblastoma.
Methods: In AVAglio, patients (pts) ⩾18 yrs with newly diagnosed glioblastoma were randomised to receive P or Bv (10 mg/kg, q2w) with

6 wks of T (75 mg/m^2/d) + RT (2 Gy, 5d/wk) followed by 28 treatment-free days, then 6 cycles of T (150–200 mg/m^2/d, 5d q4w) with P or Bv (10 mg/kg, q2w), and then single-agent P or Bv (15 mg/kg, q3w) until disease progression (PD)/unacceptable toxicity. Co-primary endpoints were investigator-assessed progression-free survival (PFS) and overall survival (OS). Secondary endpoints included HRQoL (EORTC QLQ-C30 and BN20) and safety, and exploratory endpoints included Karnofsky performance score (KPS) and corticosteroid (CS) use.

Results: Baseline characteristics were well balanced. The study met the co-primary endpoint for PFS (HR 0.64, 95% CI 0.55–0.74, $p < 0.0001$; median 10.6 vs 6.2 mo) and this result was supported by measurements of clinical benefit, including delayed deterioration in HRQoL with Bv compared with P ($p < 0.0001$, predefined analysis in 5 preselected domains) and reduced reliance on CS; among pts on CS ($\geqslant$2 mg) at baseline, CS discontinuation ($\geqslant$5 consecutive days) was more frequent with Bv than P (66% vs 47%), and in those off CS at baseline (<2 mg), time to CS initiation was significantly longer with Bv than P (HR 0.71, 95% CI 0.57–0.88; median 12.3 vs 3.7 mo). Functional independence (KPS $\geqslant$70%) was maintained during PFS in both arms (median Bv vs P: 9 vs 6 mo). Interim OS did not cross the threshold for significance with Bv+T/RT (HR 0.89, 95% CI 0.75–1.07, $p = 0.2135$) and one-year OS rates were 72% and 66% with Bv+T/RT and P+T/RT, respectively ($p = 0.052$). Safety was consistent with known bevacizumab side effects. Final OS data, 2-year OS rates, OS subgroup analyses and updated safety will be presented.

Conclusions: Addition of Bv to T/RT achieved clinically meaningful benefits, including a statistically significant and clinically meaningful PFS improvement associated with stable/improved HRQoL and KPS, and reduced CS requirement. Interim OS did not cross the threshold for significance; final OS will be presented.

Conflict of interest: *Other substantive relationships: Oliver L Chinot has received honoraria from F. Hoffman*La Roche, Astra-Zeneca and MSD, acted as a consultant for F. Hoffman*La Roche, received research support from F. Hoffman*La Roche and Schering*Plough, and received compensation for serving on the steering committee for this trial from F. Hoffman*La Roche. Timothy Cloughesy has acted as a consultant (compensated) for F. Hoffman*La Roche, Genentech, Merck, Merck Serono, Celgene, Tocagen, Apogenics and Newgen and has received compensation for serving on the steering committee for this trial from F. Hoffman*La Roche. Roger Henriksson has received compensation for serving on the steering committee for this trial from F. Hoffman*La Roche. Received honoraria from F. Hoffmann-La Roche. Frank Saran has acted as a consultant for F. Hoffman*La Roche and has received compensation for serving on the steering committee for this trial from F. Hoffman*La Roche. Warren Mason has acted as a consultant for F. Hoffman*La Roche and received compensation for serving on the steering committee for this trial from F. Hoffman*La Roche. Ryo Nishikawa has acted as a consultant for F. Hoffman*La Roche and has received compensation for serving on the steering committee for this trial from F. Hoffman*La Roche. Magalie Hilton is an employee of F. Hoffman*La Roche. Lauren Abrey is an employee of F. Hoffman*La Roche. Lauren Abrey is an employee of F. Hoffman*La Roche. Lauren Abrey is an employee of F. Hoffman*La Roche and holds stock in F. Hoffman*La Roche. Wolfgang Wick has acted as a consultant for F. Hoffman*La Roche and Eli Lilly, received research support from Boehringer Ingelheim, Alogenix and MSD, and received compensation for serving on the steering committee for this trial from F. Hoffman*La Roche. Received honoraria from F. HOffmann-La Roche and MSD.*

3302 ORAL

Standard chemoradiotherapy ± cilengitide in newly diagnosed glioblastoma (GBM): Updated results and subgroup analyses of the international randomized phase III CENTRIC trial (EORTC trial #26071-22072/Canadian Brain Tumor Consortium)

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Background: Cilengitide is a selective $\alpha v\beta 3$ and $\alpha v\beta 5$ integrin inhibitor interfering with cell attachment and migration. In preclinical models, synergy with other treatments including chemotherapy and irradiation was shown. Randomized dose finding phase II studies in both recurrent and newly diagnosed glioblastoma indicated a dose-related trend towards prolonged survival with a high dose of cilengitide (2000 mg twice weekly i.v.) compared to a lower dose (500 mg tiw).

Materials and Methods: This randomized phase III study investigated the addition of cilengitide (2000 mg tiw) to standard chemoradiotherapy (RT 30x2 Gy with concomitant and adjuvant temozolomide, TMZ/RT->TMZ for up to 6 cycles). A methylated *MGMT* gene promoter was required aiming at exploiting the synergy with alkylating agent chemotherapy. Cilengitide was to be continued for 18 months or until progression. The primary endpoint was overall survival; secondary objectives comprised progression-free survival (PFS) per independent read, Quality of Life, and safety.

Results: After screening over 3000 patients for *MGMT* gene promoter methylation, a total of 545 were randomized. 34% of patients tested for *MGMT* status were methylated. Baseline characteristics were well balanced. Median age was 58 years, and 23% $\geqslant$ over age 65 years. ECOG performance status was 0 in 56% and 1 in 44% of patients; prior tumor resection was reported as complete in 49% of patients, partial in 48%, and 3% had a biopsy only. Median OS was 26.3 months in both groups (Hazard Ratio [HR] = 1.02 [95% CI: 0.81–1.29], $p = 0.86$) while median PFS per independent read was 10.6 months in cilengitide treated patients and 7.9 months in the control group (HR = 0.92 [95% CI: 0.75–1.12], $p = 0.41$). The Quality of Life analysis did not reveal significant differences. Cilengitide treatment was generally well tolerated and its known safety profile was confirmed. 56% of patients received subsequent second-line therapy after disease progression including repeat surgery 10%, re-irradiation 12%, cytotoxic chemotherapy 40%, and bevacizumab 19% of all patients.

Conclusions: Cilengitide failed to improve survival in patients with newly diagnosed GBM despite promising preclinical and early clinical results; the absence of benefit is observed in all predefined clinical subgroups. Feasibility of upfront molecular testing and *MGMT* determination was demonstrated.

Trial was sponsored by Merck KGaA.

Conflict of interest: *Ownership: -. Advisory board: RS: consultant or advisory role for Merck Serono, MSD-Merck & Co, Roche/Genentech. MH: consultant or advisory role for MSD, MDxHealth. DR: consultant or advisory role for Roche/Genentech, Merck/Schering, EMD Serono, Abgenix, Novartis. WW: consultant or advisory role for MSD, Roche, magforce. MW: consultant or advisory role for Antisense Pharma, Merck Serono, Roche. Board of directors: -. Corporate-sponsored research: MH: research funding received from MDxHealth. WW: research funding received from Boehringer Ingelheim, MSD, Roche, Eli Lilly. MW: research funding received from Merck Serono, Roche, MSD, Antisense Pharma. Other substantive relationships: RS: honoraria received from Merck Serono, MSD-Merck & Co, Roche/Genentech. MH: honoraria received from MSD, MDxHealth. JP: honoraria received from Merck. DR: honoraria received from EMD Serono, Merck/Schering, Roche/Genentech. AM: Merck KGaA employee. WW: honoraria received from MSD, Roche. MW: honoraria received from Merck Serono, Roche, MSD.*

3303 ORAL

Progression-free survival as a surrogate endpoint for hazard ratio and median overall survival in glioblastoma: A literature-based meta-analysis from 91 trials

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Background: Glioblastoma, a highly malignant tumour, has a poor prognosis despite the introduction of combination temozolomide (TMZ)/radiotherapy. The gold standard for new anti-cancer therapy evaluation is a randomised, phase III trial with an overall survival (OS) endpoint, but use of OS is limited by long trial times and confounding post-protocol events. Proposed surrogates for OS include objective response rate (ORR) and progression-free survival (PFS), but responses are rare in glioblastoma and little is known about the PFS-OS relationship. This study aimed to determine correlations between ORR and PFS with OS in glioblastoma, in order to evaluate their potential as surrogates for OS.

Materials and Methods: Published glioblastoma trials reporting OS and ORR and/or PFS were identified; those reporting sufficient detail were included in the analyses. The correlations between: hazard ratio (HR) in PFS and OS, median PFS and OS, and between OS and ORR were evaluated using Pearson's R^2 coefficient. An ANCOVA was conducted to test for any differences in the PFS/OS correlations due to treatment and histology. The predictive power of 6-month PFS was evaluated by correlation with 1-year and median OS.

Results: Of 306 published glioblastoma trials, 91 were included in the analysis. No relevant correlation was observed between ORR and OS (R^2=0.22). HRs of PFS and OS were strongly correlated (R^2=0.92 95% CI, 0.71–0.99). Linear regression determined that a 10% risk reduction for PFS would yield a 8.1%±0.8% risk reduction for OS. The R^2 between median PFS and OS was 0.70 (95% CI, 0.59–0.79), with a higher value observed in trials using RANO (R^2=0.96, n = 8) compared with Macdonald criteria (R^2=0.70, n = 83). There were no significant differences in the correlations between TMZ- and bevacizumab-containing regimens (p = 0.10), between trials using RANO and Macdonald criteria (p = 0.49), or between trials conducted at different time periods (from 1991 to present). However, the slope of the regression line between median PFS and OS was significantly higher in newly diagnosed compared with recurrent disease (0.58 vs 0.35, p = 0.04). R^2 values for 6-month PFS and 1-year OS with median OS were 0.60 (95% CI, 0.37–0.77) and 0.64 (95% CI, 0.42–0.77), respectively.
Conclusions: In glioblastoma trials, PFS and OS are strongly correlated, indicating that PFS may be an appropriate surrogate for OS. Compared with OS, PFS offers earlier assessment of efficacy and higher statistical power.
Conflict of interest: *Ownership: D. Reardon owns stock in Paradigm Oncology. Advisory board: W. Wick has acted as a consultant for F. Hoffman-La Roche and Eli Lilly. D. Reardon has participated on an advisory board for Apogenix, EMD Serono, Genentech/Roche, Merck, Novartis and Paradigm Oncology. Corporate-sponsored research: W. Wick has received research support from Boehringer-Ingelheim, Alogenix and MSD. D. Reardon has received research funding from Abbott, Amgen, Astra Zeneca, Boehringher-Ingelheim, ESAI, Exelixis, Genentech/Roche, Geron, Medimmune, Merck, Novartis, Sanofi-Aventis and vascular biogenics. Other substantive relationships: K. Han, M. Ren, J. Jin and A. Das are all employees of Genentech. W. Wick has received compensation for serving on the steering committee for this trial from F. Hoffman-La Roche and has received honoraria from F. Hoffmann-La Roche and MSD.*

3304 ORAL

A phase II, randomized, open-label, multi-center study of weekly APG101 + reirradiation versus reirradiation in the treatment of patients with recurrent glioblastoma

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Background: Preclinical data indicate antiinvasive activity of APG101, an intravenous CD95 ligand-binding fusion protein, as well as synergistic activity together with radiotherapy (RT) in glioblastoma. Doses up to 20 mg/kg body weight were considered safe in a phase I trial in healthy volunteers. After application of 400 mg in two glioma patients steady state for AGP101 seemed to be reached.
Materials and Methods: Patients with recurrent glioblastoma after prior standard radiochemotherapy with temozolomide (± 1 second-line chemotherapy) were considered for re-irradiation provided a tumor diameter 1−4 cm and time since the end RT ⩾8 months. Patients were randomized 1:2 between RT (36 Gy; 5 times 2 Gy per week) or RT plus APG101 at 400 mg weekly flat dose to be continued until progression. RT plans were centrally evaluated. Primary endpoint was 6-months progression free survival (PFS-6). MRIs were performed every 6-weeks and centrally read.
Results: Between 12/09 and 09/11, a total of 84 pts in 25 centers were randomized. Median age was 57 years, median KPS 90%. Patients were stratified according to a maximal tumor diameter of ⩽2.5 cm and >2.5 cm. No SUSARs had to be reported. One patient achieved PFS-6 in the RT arm (4%) and twelve patients in the APG101 arm (21%). Median overall survival (OS) was 11.5 months in the RT and 11.8 months in the APG101 arm with 7% patients alive at 24 months in the RT and 22% in the APG101 arm. Subgroup analysis for CD95L expression by immunohistochemistry on the FFPE tissue of the initial diagnosis revealed an OS in the CD95L expressing patients of 8.2 months in the RT group and 11.5 months in the APG101 group and in patients with CD95L-negative tumors median OS was 15 months in the RT- and 13.5 months in the APG101-treated patients.
Conclusions: APG101_CD_002 is the first trial evaluating CD95-mediated pathway inhibition as a therapeutic strategy. This trial is also the first prospective trial on reirradiation in glioblastoma. The experimental arm met the primary endpoint; the activity of reirradiation alone was unexpectedly low. Subgroup analysis suggest CD95L as a negative prognostic biomarker, which may help to delineate patients with glioblastoma deriving benefit from APG101, that are patients with CD95L-expressing tumors. The approach to block the CD95 system is breaking a paradigm and CD95L would be one of the first predictive markers in neurooncology.
Conflict of interest: *Ownership: Apogenix GmbH for Claudia Kunz and Harald Fricke*

3305 ORAL

The human sub-ependymal zone harbors glioblastoma precursors and represents a distinct therapeutic target

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Background: We previously demonstrated that it is possible to objectively interrogate human glioblastoma (GB) by using 5-aminolevulinic acid (5-ALA), an endogenous intermediate of the porphyrin biosynthesis pathway. Tumour tissue resection is performed on a fluorescence-guided basis allowing direct visualization of tumour tissue. This approach gave us the possibility to identify and characterize tumour compartments in GB.
Material and Methods: The tissue was collected in GB debulking operations in accordance with local ethical guidelines. Sixty-five patients were administered with 5-ALA 5 hours before surgery as oral dose of 20 mg/kg. Primary culture, culture propagation and immunofluorescence were performed according to the Cambridge protocol. Intracerebral transplantation of $3X10^5$ cells into the right striatum of Nod/Scid mice was carried out according to the Home Office guidelines. Gene expression profiling was determined using standard array Illumina platform (HumanWG6_V3). Quality of RNA was evaluated by running tests. SNP analysis was performed using the Affymetrix SNP6 arrays. Molecular clock analysis was performed using the Roche 454 Junior system and Neighbor Joining was used to reconstruct phylogeny for each patient. Drug-response analysis was carried out using different concentration of Temozolomide (Sigma) and the in vitro BrdU cell proliferation assay.
Results: Our results demonstrate that:
1. cells residing in the tumour margin are not self-renewing *in vitro* but are tumorigenic *in vivo*,
2. fluorescence material is present in the sub-ependymal zone (SEZ) of 65% of our GB (n = 65 patients),
3. SNP analysis of SEZ tissues reveals distinct genetic aberrations,
4. molecular clock analysis shows that the SEZ contains precursor cells of the corresponding tumour mass,
5. drug-resistant tumour cells persist in the SEZ.

Conclusions: Fluorescence-guided tumour sampling allows identification of a new compartment in human GB, i.e. the SEZ. Tumour precursors residing in this compartment are resistant to conventional chemotherapies.
No conflict of interest.

Poster Session (Mon, 30 Sep)
Central Nervous System

3306 POSTER

Clinical research of simultaneous integrated boost intensity-modulated radiotherapy combined with temozolomide in treatment of postoperative residual glioblastoma

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Objective: To research clinical efficacy of simultaneous integrated boost intensity-modulated radiotherapy (SIB-IMRT) combined with temozolomide in treatment of patients with postoperative residual glioblastoma.
Methods: Fifty six patients with postoperative residual glioblastoma of brain received SIB-IMRT.The postoperative residual lesion was defined as gross tumor volume(GTV). The margin of GTV expanded 5 mm was defined as CTV. The margin of CTV expanded 5 mm was defined as PTV. The postoperative resectional cavity was defined as CTV1. The margins of CTV1 were enlarged 15 mm and 30 mm defined as PTV1 and PTV2 respectively. The prescribe doses of PTV, PTV1 and PTV2 were 2.5 Gy/f,2.3 Gy/f and 2.0 Gy/f respectively. All patients received

irradiation 5 weeks with 5 times per week. All patients were given temozolomide 75 mg/m^2 oral daily during radiotherapy. Four weeks after radiotherapy,there were 30 patients (defined as group 2) received 6 cycles of temozolomide,each cycle lasted 5 days with 28 days interval between two cycles. The other 26 patients (defined as group 1) did not continue to take temozolomide.
Result: In the 56 patients,CR was 7 cases (12.5%), PR was 38 cases (67.8%),SD was 8 cases (14.3%), PD was 3 cases (5.4%). The responed rate was 45 cases (80.3%). The median survival time in all patients, group 1 and group 2 was 30 months,23 months and 36 months respectively. The mean survival time was 29.82±9.11 months in all patients.The overall survival rates of one-, two- and three-year were 96.4%,73.2%, and 33.9% respectively. The mean survival time and survival curve in group 1 were significantly lower than that in group 2($P<0.05$). There were no severe radiochemotherapy-related toxicities.
Conclusion: Concurrent SIB-IMRT with temozolomide and followed by 6 cycles of temozolomide chemotherapy for postoperative residual glioblastoma have a better clinical outcome, good tolerance and no severe radiochemotherapy-related toxicities.
No conflict of interest.

3307 POSTER

Local delivery of the soluble form of the tumor suppressor and stem cell regulator LRIG1 potently inhibits in vivo growth of glioblastomas with either wildtype or mutant EGFR expression

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Background: Deregulated growth factor signaling is a major driving force in the initiation and progression of glioblastoma. The tumor suppressor and stem cell marker Lrig1 is a negative regulator of the epidermal growth factor receptor (EGFR) family. Here we addressed the therapeutic potential of the soluble form of Lrig1 (sLrig1) in glioblastoma treatment and the mechanism of sLrig1-induced growth inhibition.
Methods: Using encapsulated cells, recombinant sLrig1 was locally delivered in orthotopic glioblastoma xenografts generated from freshly isolated patient tumors. Tumor growth and mouse survival was evaluated. The efficacy of sLrig1 and the affected downstream signalling was studied *in vitro* and *in vivo* in glioma cells displaying variable expression of wildtype and/or constitutively active mutant EGFR (EGFRvIII).
Results: Continuous interstitial delivery of sLrig1 in genetically diverse patient-derived glioma xenografts led to strong tumor growth inhibition. Glioma cell proliferation *in vitro* and tumor growth *in vivo* were potently inhibited by sLrig1 irrespective of EGFR expression levels. Importantly tumor growth was also suppressed in EGFRvIII driven gliomas. sLrig1 induced cell cycle arrest without changing total receptor level or phosphorylation. Affected downstream effectors included MAP kinase but not AKT signaling. Importantly local delivery of sLrig1 into established tumors led to a dramatic survival advantage in treated mice.
Conclusions: This is the first report demonstrating that sLrig1 is a potent inhibitor of glioblastoma growth in clinically relevant experimental glioma models, and that this effect is largely independent of EGFR status. The potent anti-tumor effect of sLrig1, in combination with cell encapsulation technology for *in situ* delivery holds promise for future treatment of glioblastoma.
No conflict of interest.

3308 POSTER

Sensitivity of glioblastoma cell lines to GDC-0973/RG7420

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Background: Although therapeutic advances have accomplished, glioblastoma remains a devastating primary brain tumor in adults. Therefore new therapeutic strategies are urgently needed. Molecular targeted therapies have demonstrated their efficacy in multiples cancer subtypes including brain tumors. MAPK pathway is activated in human glioblastoma through various mechanisms including tyrosine kinase receptors, Ras or Raf activation contributing to several hallmarks of cancer cells, including uncontrolled proliferation, invasion, and evasion of apoptosis. In this setting, GDC-0973 compound, a novel small-molecule inhibiting MEK appears promising.
Material and Methods: We have investigated the effects of GDC-0973 on viability/proliferation in four preclinical models of glioblastomas including one cell line growing adherently (U87-MG) and three glioblastoma stem cell lines, established recently from human tumors, growing in serum-free media (4627, 6240, 7060).
Results: Using WST-1 assay and impedancemetry measurement, we have shown that GDC-0973 inhibits viability and proliferation of the four cells lines. Cell lines 6240 and 7060 exhibiting higher level of phospho-MEK determined by western-blot seem more sensitive, with an IC50 twice as low. This suggests that the sensitivity to GDC-0973 seems associated of the level of expression of phospho-MEK, but this correlation is currently being investigated. FACS analysis revealed that apoptosis is one of the mechanisms of glioblastoma cell death induced by GDC-0973.
Conclusion: To our knowledge, our study is the first showing in vitro efficacy of GDC-0973 in glioblastoma models. These encouraging results support the conduction of *in vivo* studies aimed at evaluating GDC-0973 therapeutic activity in orthotopic glioblastoma-bearing mice.
No conflict of interest.

3309 POSTER

Regulation of glioblastoma stem-like cell self-renewal and tumorigenicity

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Background: Glioblastoma (GBM) is the most common and malignant primary brain cancer. GBM prognosis remains dismal despite available treatments, mostly because of tumor recurrence. According to the 'glioma stem-like cell' (GSC) hypothesis, GBM tumorigenesis is mediated by a fraction of cancer cells resembling normal neural stem/progenitor cells (NSPCs). In potential agreement with this possibility, it is possible to establish primary cultures of human GBM-derived cells exhibiting the predicted properties of GSCs, namely unlimited self-renewal and multipotency *in vitro* and, most importantly, tumorigenic ability when transplanted intracranially into host mice *in vivo*. We hypothesize that the tumorigenic potential of GSCs may result from the deregulation of the normal balance between self-renewal and differentiation along the glial lineage. In this regard, the transcription factor FOXG1, a member of the forkhead family, is a key regulator of self-renewal, proliferation and differentiation in embryonic and adult NSPCs. In this study, we sought to characterize the expression and function of FOXG1 and its functional transcriptional partners belonging to the Groucho/TLE family (TLE) in high-grade glioma and cultured GSCs.
Material and Methods: FOXG1 and Gro/TLE expression was characterized at mRNA or protein level in human GBM surgical specimens and GSCs. Knock-down and dominant-negative approaches were utilized to interfere with the functions of FOXG1 and Gro/TLE in cultured GSCs in order to characterize their contribution to the self-renewal, proliferation, differentiation and *in vivo* tumorigenic ability of these cells.
Results: We show that human *FOXG1* mRNA level is inversely correlated with GBM patient survival and that FOXG1 is highly expressed in both GBM and cultured GSCs. FOXG1 knockdown in GSCs causes decreased self-renewal and downregulation of NSPC markers, reduced proliferation, upregulation of glial differentiation genes, and decreased tumorigenic potential upon intracranial transplantation. These effects are phenocopied by knockdown or dominant-inhibition of Gro/TLE using the Gro/TLE family member, GRG6.
Conclusions: These results show that FOXG1 is important for GBM progression and suggest that FOXG1 and Gro/TLE act in GSCs to promote a stem-like state and inhibit differentiation.
No conflict of interest.

3310 POSTER

The growth hormone receptor as an alternative oncogenic pathway in glioblastoma

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Background: Primary glioblastomas (GBM) are the most frequent and the most aggressive primary brain tumors in adults. Despite intensive treatments, the prognosis of GBM patients remains poor with a median overall survival comprised between 12 and 24 months. Improvement of the prognosis of GBM patients is highly dependent on a better understanding of molecular oncogenesis, which can ultimately lead to the development of new personalized targeted treatments.
We have conducted a large molecular screen with the objective of identifying signaling pathways that are activated in GBM that do not exhibit activation of classic oncogenic pathways (i.e. Receptor Tyrosine Kinase and PTEN/PI3K). Interestingly, we identified the Growth Hormone Receptor (GHR) pathway as a promising candidate for alternative oncogenic signaling pathways. This project aims at characterizing the role of GH signaling pathway in GBM oncogenesis.
Material and Methods: GBM cell lines exhibiting activated GHR pathway (type B) and cell lines which do not exhibit activated GHR pathway (type A) were selected from our primary cell line bank. The effects of stimulation with GHR substrate Growth Hormone (GH) were assessed *in vitro* by immunofluorescence staining and western blots analysis. Moreover, levels of Growth Hormone were measured by ELISA in the plasma of GBM patients and *in vitro* in the supernatant of GBM cells.
Results: It was found that stimulation of type B cell lines with the GH induces a translocation of GHR at the cytoplasm and nucleus membranes, and activates JAK2/STAT5 and ERK/Src pathways. These effects were not observed in type A cell lines. Levels of GH in the plasma of GBM patients were found to correlate with GHR expression in the tumor. Significant levels of GH were also detected in the supernatant of GBM cell lines *in vitro* but did not correlate with GHR expression in these cells.
Conclusion: Increased levels of plasmatic GH in type B GBM patients, secretion of GH by type B GBM cells *in vitro* and signaling changes induced by GH in type B GBM cells suggest a significant role of GHR pathway in type B GBM oncogenicity compared to type A GBM. Effects of GHR gain (transduction of *GHR* gene in non-GHR expressing GBM cells and immortalized astrocytes) and loss of function (pharmacological inhibitor Pegvisomant, shRNA and transduction of a *GHR* dominant negative gene in group B cells) are being characterized.
No conflict of interest.

3311 POSTER

Claudin-5 participates in the regulation of tight junction in brain vascular endothelial cells

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Background: A key step in brain metastasis (BM) is the interaction and penetration of the Blood–brain barrier (BBB) by cancer cells. Tight junction (TJ) of brain vascular endothelium, part of the BBB, is critical barrier which the cancer cells have to overcome in order to penetrate and initiate brain metastasis. The transmembrane protein claudin-5 is a key TJ protein in endothelial cells. However, its the molecular mechanisms in regulation BBB in the formation of brain metastases are poorly understood. In the present study, we aimed to investigate the pattern of expression of this molecule in regulation the tight junction of brain vascular endothelial cell and try to identify the role of claudin-5 in the regulation of BBB permeability during the brain metastatic process.
Materials and Methods: The Claudin-5 gene was highly expressed in human brain vascular endothelial cell, hCMEC/D3 cell line and was virtually negative in the non-brain vascular endothelial cells, HECV. Claudin-5 was either knocked down using ribozyme technology in hCMEC/D3 or over-expressed in HECV cells. Lung cancer cell line A549 was added to observe the interaction between the cancer cell and brain vascular endothelial cell. Changes in function were assessed using *in vitro* assays for growth, adhesion, wounding, endothelial cell barrier invasion, and transendothelial electrical resistance (TEER)/electric cell-substrate impedance sensing (ECIS). Results data was analyzed using a Students two sample t-test and by Two-way Anova test when the data was found to be normalized and have equal variances. In all cases 95% confidence intervals were used.
Results: Claudin-5 was successfully knocked down from the hCMEC/D3 cells. The knockdown resulted in a phenotype that had significantly increased cell motility ($p < 0.005$). Knockdown of Claudin-5 gene in hCMEC/D3 cells resulted in significant lower transendothelial electrical resistance (TEER) values were observed. Similarly, reduced levels of Claudin-5 in the hCMEC/D3 cells resulted in a decrease in adhesion to matrix ($p < 0.001$). Endothelial cell barrier invasion assay showed that lung cancer cells were more readily to penetrate the monolayer of hCMEC/D3 cells after knocking down claudin-5 from the endothelial cells. HECV cells were forced to over-express claudin-5. The overexpression markedly increased the barrier function of the cell layer and reduced the permeability.
Conclusions: The present study portrays an interesting role for Claudin-5 in keeping the the barrier functions of the brain vascular endothelial cells and blocking cancer cells from trespassing. Claudin-5 through the integrity of blood–brain barrier, reduces tumor cell penetration, which play an important role in controlling brain metastases.
No conflict of interest.

3312 POSTER

The role of MDGI in glioma progression

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Background: Gliomas, a class of highly malignant brain tumors, are the most common primary brain tumors in adults. Despite of advances in cancer therapies, the prognosis of high-grade glioma patients is poor due to the invasive growth of the tumor cells. Therefore, in order to develop novel therapeutic strategies, it is essential to clarify the molecular mechanisms underlying the behavior of these tumors. Using *in vivo* phage display technology we have identified a peptide, CooP, which, after systemic delivery, specifically homes to malignant brain tumor islets harboring co-opted blood vessels. Mammary-derived growth inhibitor (MDGI) was validated as an interacting partner for our peptide. This protein is involved in fatty acid metabolism but its role in glioma is currently unknown.
Materials and Methods: To facilitate functional studies of MDGI, stable human glioma cell line (U87MG) overexpressing MDGI was used in 2D and 3D cell culture systems as well as in orthotopical murine tumor models. Changes in the gene expression patterns in response to MDGI expression were studied using gene arrays. In addition, MDGI's effect on glioma cell metabolism was studied with a metabolic analyzer.
Results: Our preliminary results show MDGI to be expressed in a grade-dependent manner in clinical human astrocytoma samples. MDGI expression was also detected in several primary human glioma cell lines. Based on our first *in vitro* experiments MDGI overexpression increased cell invasion in matrigel matrix. The overexpressing cells had also a higher tendency to form colonies in soft agar. In addition, our metabolic analyses revealed altered metabolia-associated characteristics, such as reduction in the oxygen uptake, in the cells overexpressing MDGI.
Immunohistological analyses of the glioma xenografts overexpressing MDGI revealed more abundant vasculature *in vivo*. Interestingly, gene expression analysis from the xenografts revealed also several metabolia-associated genes that were potentially upregulated in the MDGI overexpressing xenografts.
Conclusion: Our results using CooP homing peptide suggest MDGI to be a novel biomarker for malignant gliomas. Since increased invasiveness is a well-known characteristic of gliomas, our *in vitro* results demonstrate a functional role for MDGI in glioma progression. Furthermore, since metabolic abnormalities are common among gliomas, both our gene array results and metabolic analyses suggest an interesting role for MDGI in glioma cell bioenergetics.
No conflict of interest.

3313 POSTER

Vascular endothelial growth inhibitor, VEGI, is an independent indicator for suprasellar invasion and sella destruction in human pituitary adenomas

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Background: Pituitary ademonas are benign tumours from the pituitary gland and mostly non-cancerous but may have invasive and destructive growth pattern. It is a relative common type of the primary intracranial tumours. An interesting feature of the tumours is that some of the tumours are functional, namely endocrine active from the pituitary tumours cells. There is little understanding of the growth and progression control of pituitary tumours. In the present study, we investigated the expression of vascular endothelial growth inhibitor (VEGI) which is also known as tumour necrosis factor superfamily member 15 or TNFSF15 and is a vascular endothelial growth and apoptosis regulator in clinical pituitary tumours.
Materials and Methods: Pituitary tumours from 101 patients were included in the study. Fresh pituitary tumours were obtained immediately after surgery and processed for histological, immunohistological and molecular based analyses. Histolopathological and clinical information including tumour type and size, tumour sphenoidal invasion and sella destruction and endocrine status were analysed against the gene transcript expression of VEGI and VEGF. VEGI and VEGF family and VEGF receptors were quantitatively determined for their gene transcript expression.
Results: The expression levels of VEGI was significantly lower in pituitary tumours which invaded cranial floor and sphanoid bone, and with suprasellar extension than the non-invasive tumours ($p = 0.0073$). Low levels of VEGI transcripts were associated with the intrapituitary haemorrhage ($p = 0.05$). VEGI levels were also seen to be correlated with tumour stage ($p < 0.0001$), in that high levels of VEGI was associated with low tumour grade. Of all the pituitary tumours, 59 were non-functional. Multivariat analysis has indicated that VEGI is an independent factor for the invasion ($p = 0.05$). It was further demonstrated the relationship between VEGI and pituitary tumour grade and invasion were independent of the expression of VEGF and its receptors. Of the functional tumours, it was found that FSH and gonadotrophic tumours tend to have markedly low levels of VEGI transcript, compared with non-functional tumours ($p = 0.0026$ and $p = 0.003$, respectively). The opposite was seen with thyroid-stimulating hormone secreting tumours.
Conclusions: Vascular endothelial growth inhibitor, VEGI, is a negative regulator of the aggressive nature of pituitary tumours and that the expression level is closely linked to the invasion and destruction of the suprasellar and sella region. It also has implications on the endocrine nature of the tumours. VEGI thus has an important predictive and prognostic value in patients with pituitary adenomas.
No conflict of interest.

3314 POSTER

Expression level of HOX genes is higher in human medulloblastoma tumorigenic cell line than in non-tumorigenic cell lines

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HOX genes are a family of homeodomain-containing transcription factors defined as master genes of development, altered in cancer cells and thus having implications for tumorigenesis. Developmental genes have been recognized as one of the keys to understanding the tumor development in some type of cancers. This study aimed to correlate gene expression profile of some HOX genes with the tumorigenic potential of medulloblastoma cell lines (MCL). We used three human MCL, UW473, UW472 and DAOY and two human cerebellum primary cultures (CPC). The MCL and CPC were characterized morphologically by light microscopy and immunophenotypically by flow cytometry. MCL were assessed by tumorigenic potential infusing $3x10^6$ cells subcutaneously in NUDE mice. MCL and CPC were evaluated for gene expression profile of HOXA3, HOXA10, HOXB3, HOXB4 and HOXB6 genes by quantitative real time PCR. MCL are morphologically heterogeneous (polygonal and fibroblastoid morphology) and CPC present fibroblastoid morphology. Immunophenotypically, MCL and CPC were similar for some CD markers and showed a high percentage (70−99%) for CD44, CD73, CD105, CD166 and CD29 and low or absence (0−5.3%) for CD144, CD31, CD34, CD45 and CD133. Some differences were observed for CD140b ($0.28\pm0.11\%$; $6.2\pm8.3\%$; $0.78\pm1.1\%$; 0.44%), CD24 ($52.5\pm1.7\%$; $64.6\pm6.4\%$; $20.5\pm6.4\%$; 1.9%), CD146 ($60.4\pm8.8\%$; $90.6\pm3.8\%$; $34.6\pm12\%$; 98.4%), CD73 ($77.2\pm6.9\%$; $81.4\pm8.98\%$; $52.97\pm12.4\%$; 99.1%), CD271 ($3.3\pm3.7\%$; $26.9\pm16.22\%$; $0.6\pm0.8\%$; 0.26%) and CD90 ($3.7\pm1\%$; $99.3\pm0.8\%$; $88.5\pm3.3\%$; 77%) in UW472, UW473 and DAOY MCL, and CPC respectively. Regarding to tumorigenic potential, among the UW402, UW473 and DAOY MCL, only DAOY cell line gave rise to tumor nodules that presented histology features similar to medulloblastoma. About gene expression, HOXA3 gene was $4{,}028\pm431$, $2{,}959\pm316$ and 14 ± 1.5 times higher expressed in DAOY when compared to CPC, UW402 and UW473 MCL respectively (**$p > 0.0001$**, $p = 0.004$, $p = 0.0066$), HOXA10 gene was $22{,}463\pm27$, $18{,}997\pm22.8$ and $25{,}103\pm30.1$ times (**$p > 0.0001$**, **$p < 0.0001$**, **$p < 0.0001$**), HOXB3 gene was $2{,}867\pm1{,}319$, 42.27 ± 19.4 and 24.73 ± 11.37 times ($p = 0.0074$, both non-significant), HOXB4 gene was $5{,}648\pm567$, 93.25 ± 9.37 and 105.38 ± 10.59 times (**$p > 0.0001$**, $p = 0.0003$, $p = 0.0051$) and HOXB6 gene was $2{,}422\pm580$, $1{,}650\pm394.8$ and 3.35 ± 0.8 times (**$p > 0.0001$**, $p = 0.0275$, non-significant). Taken together, our results demonstrates that MCL are morphologically heterogeneous and CPC present fibroblastoid morphology. MCL and CPC showed an immunophenotype somewhat different for some markers and DAOY cell line was the only one that gave rise to tumor nodules in NUDE mice. Correlating the tumorigenic potential with the expression level of HOX genes, all HOX genes (HOXA3, HOXA10, HOXB3, HOXB4 and HOXB6) were more expressed in DAOY tumorigenic cell line when compared to UW402 and UW473 non-tumorigenic cell lines. In detail, HOXA10 was the most expressed among HOX genes that were analyzed and the only one with a similar low expression in both UW402 and UW473 non-tumorigenic cell lines as well as in CPC. This implicates that HOXA10 gene might be related to tumor development in medulloblastoma.
No conflict of interest.

3315 POSTER

A novel fluorinated stilbene exerts antitumor activity in glioblastoma cells

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Background: Glioblastoma is the most common and aggressive form of malignant glioma and is very difficult to treat. Controlling glioblastoma cell invasion and angiogenesis is essential to improve the prognosis of glioblastoma patients. It has been reported that anti-inflammatory agents, such as NF-κB inhibitors, have antitmor effects to malignant tumors. A novel fluorinated stilbene, 2-fluoro-4' -methoxystilbene (NF-κB acitivity inhibitor 4; NF-κBAI4), which is known as a potent inhibitor of the NF-κB signalling pathway in vitro. Our study aimed to evaluate the antitumor effects of NF-κBAI4 on two human glioblastoma cell lines (U87MG, T98G) and the molecular mechanisms underlying these effects.
Material and Methods: The anti-invasive effect of NF-κBAI4 was analysed by an in vitro invasion assay. An in vitro angiogenesis assay was also performed. In vitro growth inhibition of glioblastoma cells by NF-κBAI4 was determined by the MTT assay. The effect of NF-κBAI4 on an orthotropic implantation model using athymic mice was also evaluated.
Results: NF-κBAI4 suppressed the proliferation of glioblastoma cells. NF-κBAI4 also suppressed both the invasion of glioblastoma cells and tumor-induced angiogenesis. Molecular-based studies demonstrated that NF-κBAI4 suppressed gene and protein expression of angiogenic factors. An *in vivo* intracerebral human glioblastoma xenograft mouse model demonstrated that NF-κBAI4 suppressed neovascularity and tumor growth.
Conclusions: The results of the present study suggest that NF-κBAI4 may be a new therapeutic agent for glioblastomas.
No conflict of interest.

3316 POSTER

Health-related quality of life (HRQoL) in AVAglio, a randomized, placebo (P)-controlled phase III study of bevacizumab (B), temozolomide (T) and radiotherapy (RT) in patients (pts) with newly diagnosed glioblastoma (GBM)

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Background: GBM is associated with poor HRQoL. AVAglio investigated P or B plus RT/T in GBM and results showed longer PFS with B+RT/T. To understand the added value of B, HRQoL was an important secondary endpoint.
Methods: Pts received B or P + standard of care (RT+T) until disease progression (PD)/unacceptable toxicity. HRQoL (EORTC QLQ-C30/BN20) time to definitive deterioration (TDD) was assessed − a 10-point change from baseline (BL) was considered clinically meaningful. Primary HRQoL analysis: five preselected scales. Exploratory analyses: TDD excluding PD as an event, duration of stable/improved HRQoL from BL, TDD for other non-preselected scales (no adjustment for multiple testing).
Results: P+RT/T, n = 463; B+RT/T, n = 458. There was high compliance: 78−91% of evaluable pts (no PD) completed each assessment (all scales) in the first year. BL scores were comparable between arms. B+RT/T achieved a clinically meaningful significant delay in TDD (all preselected scales, table). Post-hoc sensitivity analyses (excl. PD as an event) were supportive for 3 of these and B+RT/T benefit was seen in 8/21 non-preselected scales: cognitive (HR 0.74, p = 0.0018), role (HR 0.82, p = 0.0435) and emotional (HR 0.78, p = 0.0246) functioning; bladder control difficulty (HR 0.71, p = 0.0082); leg weakness (HR 0.81, p = 0.0396); visual disorder (HR 0.80, p = 0.0433); fatigue (HR 0.74, p = 0.0013); hair loss (HR 0.81, p = 0.0337). Treatment arms were not significantly different for appetite loss, headache, nausea/vomiting, constipation, pain, dyspnoea, insomnia, diarrhoea, future uncertainty, seizures, drowsiness, itchy skin, financial difficulty (TDD; p⩾0.05). Median duration of stable/improved HRQoL during PFS was longer with B+RT/T (7−8 mo) versus P+RT/T (4−5 mo) and as a proportion of PFS time it was similar between arms.
Conclusions: B+RT/T-treated pts experienced a longer time to HRQoL TDD compared with P+RT/T.

	TDD HR (95% CI), p [% pts with event, P+RT/T;B+RT/T]	
	Primary, incl. PD	Exploratory, excl. PD*
Global health status	0.64 (0.56–0.74), <0.0001 [86.6;82.5]	0.76 (0.63–0.92), 0.0041 [47.9;49.6]
Physical functioning	0.70 (0.61–0.81), <0.0001 [87.9;84.1]	0.90 (0.75–1.08), 0.2394 [47.7;54.4]
Social functioning	0.63 (0.55–0.73), <0.0001 [86.6;82.8]	0.78 (0.64–0.95), 0.0113 [45.8;48.7]
Motor dysfunction	0.67 (0.58–0.78), <0.0001 [82.7;79.7]	0.87 (0.68–1.11), 0.2747 [27.2;31.0]
Communication deficit	0.67 (0.58–0.77), <0.0001 [87.5;84.7]	0.80 (0.66–0.98), 0.0295 [42.5;46.9]

*Post-hoc.

Conflict of interest: *Ownership: A. Ravelo owns shares in Genentech. Advisory board: R. Henriksson has received compensation for serving on the steering committee for this trial from F. Hoffman*La Roche. Received honoraria from F. Hoffmann-La Roche. M.J.B. Taphoorn has served on an advisory board for F. Hoffmann-La Roche. T. Cloughesy has acted as a consultant (compensated) for F. Hoffman*La Roche, Genentech, Merck, Merck Serono, Celgene, Tocagen, Apogenics and Newgen and has received compensation for serving on the steering committee for this trial from F. Hoffman*La Roche. W. Wick has acted as a consultant for F. Hoffman*La Roche and Eli Lilly, received research support from Boehringer Ingelheim, Alogenix and MSD, and received compensation for serving on the steering committee for this trial from F. Hoffman*La Roche. W. Mason has acted as a consultant for F. Hoffman*La Roche and received compensation for serving on the steering committee for this trial from F. Hoffman*La Roche. F. Saran has acted as a consultant for F. Hoffman*La Roche and has received compensation for serving on the steering committee for this trial from F. Hoffman*La Roche. R. Nishikawa has acted as a consultant for F. Hoffman*La Roche and has received compensation for serving on the steering committee for this trial from F. Hoffman*La Roche. O.L. Chinot has acted as a consultant for F. Hoffman*La Roche, and received compensation for serving on the steering committee for this trial from F. Hoffman*La Roche. Corporate-sponsored research: A. Bottomley has received funding from F. Hoffmann-La Roche. O.L. Chinot has received research support from F. Hoffman*La Roche and Schering*Plough. Other substantive relationships: W. Wick has received honoraria from F. HOffmann-La Roche and MSD. A. Ravelo is an employee of Genentech. O.L. Chinot has received honoraria from F. Hoffman*La Roche, Astra-Zeneca and MSD.*

3317 POSTER

Final results from a large prospective Italian population study on glioblastoma and correlations with MGMT status: The Project of Emilia-Romagna Region in Neuro-oncology (PERNO)

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Background: The impact on the general population of temozolomide concurrent with and adjuvant to radiotherapy (RT/TMZ) was assessed in the context of the Registry of the Project of the Emilia-Romagna Region in Neuro-Oncology (PERNO), the first Italian prospective observational population-based study in the field of neuro-oncology.
Methods: Patients (pts) meeting the following inclusion criteria were evaluated: age ⩾18 years; PS 0−3; histologically confirmed GBM, no previous or concomitant non-glial tumoral disease, residence in the Emilia Romagna region. The data were collected prospectively.
Results: Study accrual, started on January 1 2009, was closed, as planned, on December 31 2010. Two hundred sixty-eight pts (F=111, M=157; median age, 63.5 [range 29−34] years) were studied. mOS was 10.7 months (95% CI: 9.2–12.3). MGMT status, assessed in 186 (89%) of 210 pts who had at least radiotherapy was evaluable in 174 pts (83%), being methylated in 76 (43.7%), and unmethylated in 98 (56.3%) pts. mOS for pts with MGMT methylated status was 18.5 months (95% CI: 14.4–22.6), and 12.4 months for those with MGMT unmethylated status (95% CI: 10.5–14.3, p < 0.0001). 140 pts <70 years were treated with RT/TMZ; mOS in this group was 16.4 months (95% CI: 14.5–18.4). mOS was 20 months in the 59 pts (42%) harboring MGMT methylation (95% CI: 12.8–27.2), and 13.5 months in the 73 pts (52%) without MGMT methylation (95% CI: 10.8–16.2, p < 0.0001). At multivariate analysis, a significant prognostic role was found for performance status (p = 0.001), extent of surgery (p = 0.009), age (p = 0.004), postsurgical treatment (p = 0.03), and MGMT status (methylated vs unmethylated, p = 0.01).
Conclusions: The data from the present large prospective population study are in line with those reported in the EORTC/NCIC randomized trial, confirming that this successful approach has been widely incorporated in daily practice.
No conflict of interest.

3318 POSTER

Factors impacting survival following second surgery in patients with glioblastoma (GBM) in the temozolomide (TMZ) treatment era, incorporating neutrophil/lymphocyte ratio (NLR) and time to first progression

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Background: Patients (pts) with progressive GBM have a poor prognosis. NLR, an inflammatory marker, is prognostic in several cancers. The

prognostic impact of either NLR or time to 1st progression (TTP), in GBM pts undergoing 2nd surgery, has not been assessed.
Material and Methods: We reviewed outcomes and prognostic factors in GBM pts having 2nd surgery in the TMZ treatment era, who were treated at Princess Margaret Cancer Centre, Toronto. Baseline demographics, NLR, treatment received, dexamethasone therapy, TTP, and overall survival (OS) were analyzed. Multivariable analysis (MVA) of OS from 2nd surgery was performed using Weibull model (accelerated failure time model).
Results: 107 (18%) of 584 adult pts who underwent primary surgery for GBM were followed from 01/04−12/11. Median (med) time between primary and 2nd surgery was 11.5 mo (range 1.2–85.8). Indication for 2nd surgery was both clinical and radiological in 74 (69%). Med age at 2nd surgery was 52 yrs (20−76), 76 (71%) were male, with performance status 0−1 in 80 (75%), partial resection in 104 (97%) and unifocality in 104 (97%). 88 pts (82%) had prior radiotherapy with concurrent and adjuvant TMZ. 72 pts (67%) had dexamethasone prior to 2nd surgery. Patients who underwent 2nd surgery had longer OS vs those having primary surgery alone; 20.9 mo vs 9.9 mo (P<0.001) and med OS from date of 2nd surgery was 7.1 mo (range 5.9−8.2). Med OS from 2nd surgery in pts with NLR⩽4 vs NLR>4 was 9.7 mo vs 5.9 mo (Logrank test P<0.05). NLR retained its prognostic significance for survival on MVA (Table) as did no chemotherapy post 2nd surgery (Time Ratio [TR] 0.23, 95% CI 0.16–0.33, P<0.001). In pts undergoing 2nd surgery, when TTP was ⩽12 mo, 12 to24 mo, or >24 mo, med OS from 1st progression was 9.5, 11.2 and 22.2 mo, respectively (P<0.05).
Conclusion: NLR>4 prior to 2nd surgery is a poor prognostic factor in GBM. In addition, later progression is associated with longer survival after 2nd surgery, and may be informative for those who have survived for some time after diagnosis.
No conflict of interest.

Variable	OS from 2nd surgery, TR (95% CI, P-value)	
	UVA	MVA
NLR ⩽4 vs NLR >4	1.86 (1.18–2.93, <0.01)	1.65 (1.15–2.35, <0.01)

3319 POSTER

A large prospective Italian population study (Project of Emilia-Romagna Region in Neuro-Oncology; PERNO) in newly diagnosed GBM patients (pts): Outcome analysis and correlations with MGMT methylation status in the elderly population

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Background: The role of temozolomide concurrent with and adjuvant to radiotherapy (RT/TMZ) in elderly pts with GBM remains unclear. We therefore evaluated the efficacy of this approach in pts >70 years in the context of the Project of Emilia-Romagna Region in Neuro-Oncology (PERNO), the first Italian prospective observational population-based study in neuro-oncology.
Methods: The criteria for selecting pts enrolled in the PERNO study were: age >70 years; PS 0−3; histologically confirmed GBM; postoperative radiotherapy after surgery; residence in the Emilia Romagna region. Data were collected prospectively.
Results: Pts accrual, started on January 1 2009, was closed, as planned, on December 31 2010. In the pts enrolled (n = 53), median overall survival (mOS) was 11.1 months (95% CI: 8.8–13.5); survival rates at 1-, 2- and 3-years were 41.5% (95% CI: 28.2–54.8%), 15.2% (95% CI: 4.8–25.6%) and 6.1% (95% CI: 0–15.9%), respectively. Twenty-eight pts received RT/TMZ, and 25 pts RT alone. mOS was 11.6 months (95% CI: 8.6–14.6) following RT/TMZ and 9.3 months (95% CI: 8.1–10.6) following RT alone. mOS for pts with MGMT methylated status (n = 17) was 13.5 months (95% CI: 7.7–19.2), being 17.2 months (95% CI: 11.5–22.9) in those treated with RT/TMZ (n = 6) and 8.8 months (95% CI: 2–15.6) in those treated with RT alone (n = 11, p = 0.09). Elderly pts with MGMT unmethylated status (n = 25) had a mOS of 8.5 months (95% CI: 6−11, p = 0.014), being 8.5 months (95% CI: 2.3–14.7) in pts treated with RT/TMZ (n = 10), and 8 months (95% CI: 3–12.9) in those treated with RT (n = 15, p = 0.55).
Conclusions: RT/TMZ appears to be more effective in prolonging the mOS of elderly pts in those with MGMT methylation status (17.2 vs 8.5 months), and seem to perform better than TMZ alone, for which mOS was 9.7 months in the Nordic phase III trial. These findings underline the value of the ongoing randomized EORTC 26062–22061/NCIC CE.6 phase III comparing RT/TMZ with short course RT alone.
No conflict of interest.

3320 POSTER

Early magnetic resonance image (MRI) assessment of diffusion and perfusion in patients (pts) with glioblastoma multiforme (GBM) following chemoradiotherapy (CRT). Is it prognostic?

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Background: Early MRI assessment of GBM pts following CRT with temozolomide can be misleading. Functional analysis using parameters such as apparent difusion coeficient (ADC) and relative cerebral blood volume (rCBV) can provide valuable information on cellularity, vascularity, metabolism and tissue micro-structure, and seem to correlate with patients outcomes in previous studies. Our objective is to correlate ADC and rCBV parameters obtained during the first MRI after completion of CRT with survival.
Methods: We retrospectively analyzed the first MRI done within 12 weeks post CRT in all consecutive GBM pts that included MR perfusion and diffusion sequences, at two brazilian institutions in a 3-year period. Maximum, minimum values of ADC and rCBV were calculated by a single observer. Overall survival was estimated by Kaplan–Meier and Cox regression analysis was used to evaluate the association between ADC and rCBV with survival. In addition, we also evaluated a possible association between ADC, as categoric variable and survival applying long-rank test (categorization cutoff of 1.0×10^{-3} mm^2/s).
Results: From February 2009 to July 2012, 41 pts were included. Median time for early MRI after CRT was 12 (2−65) days. Median pts age was 54 years (22−84), 56% were male and 82% had an ECOG ⩽1. Median survival was 24.04 months.Isolated ADC and rCBV values post CRT did not correlate with overall survival: maximum ADC value (OR 1.184 [95% CI 0.224–6.273] p = 0.842), minimum ADC value (OR 0.792 (95% CI 0.138–4.541) p = 0.794) and rCBV (OR 1.001 (95% CI 0.997–1.004) p = 0.707). ADCmin value was below 1.0×10^{-3} mm^2/s in 34 pts. Overall survival was 21.25 and 19.64 months in the low and high ADCmin value groups, respectively (p = 0.820). Thirty patients had a pre CRT MRI. Pre and post CRT rCBV variation was not prognostic for survival (OR 1.000 (95% CI 0.991–1.009) p = 0.941).
Conclusion: In this study, early MRI assessment of ADC and rCBV upon completion of CRT in pts with GBM was not prognostic for survival.
No conflict of interest.

3321 POSTER

Outcome evaluation in glioblastoma patients older than 65 years: A retrospective single center study

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Introduction: The NCT00820963 trial, the Nordic Glioma Study (NGS) started in 2003 to investigate an experimental radiotherapy scheme with 10x3.4 Gy vs. chemotherapy with Temozolomide (TMZ) 200 mg/m^2, days 1−5 for 6 cycles vs. radiotherapy with 60 Gy in 30 fractions for elderly patients with newly diagnosed glioblastoma (GBM).
Methods: In this retrospective study, we evaluated the outcome of patients with primary GBM, aged ⩾65 years, treated in our institution during the period of recruitment for the NGS study (2003–2009), to which our site contributed 35 patients (NGS group). The primary endpoint was overall survival.
The study population of 70 patients, 32 women and 38 men, aged 65 to 83, median 71 years, was divided into two groups: the NGS group consisted of 35 patients with13 patients in the standard radiation therapy arm with 60 Gy, 12 patients in the hypofractioned radiation therapy arm with 34 Gy and 10 patients in the TMZ arm. The other group of 35 patients consisted in 23 fit patients in the RCT arm who were treated with standard radiochemotherapy (RCT) like younger GBM patients and 12 frail patients who mostly started radiotherapy with 60 Gy but did not receive chemotherapy (nonRCT arm).

Results: 31 of the 70 patients underwent gross total resection (44%), 21 patients had subtotal resection (30%) whereas 18 patients underwent biopsy (26%).
The median overall survival in the three study arms of the NGS group in particular was 6.0 months in the 60 Gy arm, 7.0 months in the hypofractioned 34 Gy arm and 10.0 months in the TMZ arm (p = 0.012). The median overall survival in the RCT group was 21.0 months vs. 3.0 months in the nonRCT arm (p = 0.0001).
Karnofsky scores were evaluated in three months interval. The median time to the loss of functional independence (KI 60%) was >6 months in RCT patients, 6 months in the NGS group and less than three months in the nonRCT arm.
No grade 3 or 4 toxicities were documented in the 60 Gy and 34 Gy arm of the NGS group. In the TMZ arm 2 of 10 patients (20%) suffered from grade 3/4 thrombocytopenia.
In the RCT group grade 3 haematologic toxicity (thrombocytopenia and leucopenia) occurred in 2 of 23 patients (8.7%) and in one patient of the nonRCT arm (8.3%), probably due to dexamethasone.
Conclusion: This retrospective single center experience shows the wide variety of outcomes in elderly patients with GBM and underlines the need for individualized, geriatric assessment based therapy planning, performance and follow up.
No conflict of interest.

3322 POSTER

Pilot study defining patterns of relapse in high grade glioma receiving anti-VEGF treatment either in neoadjuvant setting or after first relapse

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Purpose: To determine at first progression, which kind of pattern of relapse is showed in patients who has received anti-VEGF treatment.
Methods: We analyse twenty-six patients from our centre, twenty of them included in two ongoing prospective trials. All GD-enhanced T1 and FLAIR MRI sequences were reviewed and co-registered with treatment planning done just before radiotherapy. Patterns of relapse after radiotherapy were defined as follows: *A*. all relapses were within the 95% of isodose; *B*. all relapses were between 95% and 50% of isodose; *C*. all relapses were outside 50% of isodose. Two groups of patients were include: those treated with neoadjuvant temozolomide (TMZ) and Bevacizumab (BV) before EORTC schedule and those who received BV at first relapse after concomitant treatment.
Results: Seventeen had progressed after BV and were available for evaluation (9 in neoadjuvant BV group and 8 in BV after first relapse group). GD-enhanced T1 did not show differences in patterns of relapse between both groups, being the pattern *A* the most common (88.8% in neoadjuvant BV group vs 87.5% in BV after first relapse). However, FLAIR sequence showed more *B* and *C* patterns than *A* pattern in both groups. *A, B* and *C* patterns were observed in 33.3% in neoadjuvant BV group for every pattern; and 50%, 25% and 25% after first relapse group, respectively.
Conclusions: These results show that FLAIR sequence is essential in defining the patterns of relapse in patients receiving anti-VEGF treatment. Sample will be updated at presentation. Defining patterns of relapse with new drugs could be definitive for radiotherapy volumes and doses.
No conflict of interest.

3323 POSTER

Brainstem glioma treated with radiation with or without temozolomide

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Background: Brainstem glioma (BSG) is an aggressive and rare tumour of childhood and adults. Treatment outcomes are dismal and role of concurrent chemoradiotherapy (CTRT) is not established in these patients. We intended to study the clinical characteristics along with outcome of BSG patients treated with CTRT at our institution.
Methods: We retrospectively evaluated 71 patients of all age groups with BSG treated at our department in the period January to December 2011. Demographic and disease characteristics in this patient cohort were recorded, and their progression free survival (PFS) was analysed with respect to age (</>18 years), gender, grade, use of CTRT and adjuvant chemotherapy.
Results: Median age at presentation was 15 years (range 3−66 years), with a male:female ratio of 1.5. 31 patients presented with gait ataxia and 29 presented with cranial nerve palsies. 34 patients were diagnosed radiologically as high grade, 32 as low grade and grade was equivocal in 5 patients. None of the patient underwent surgery. Radiotherapy dose was 56−60 Gray over 5.5 −6 weeks at 1.8−2 gray/fraction. All patients completed their radiotherapy except 7 patients.28 patients received concurrent temozolomide (75 mg/m^2), 17 patients received adjuvant temozolomide (150–200 mg/m^2 D1−5 every 4 weeks for 3−6 cycles) and 9 patient received both concurrent and adjuvant temozolomide. Median follow up duration was 8.2 months (range 1–65.3 months). At last follow up, 21 patients had progressive disease. Median PFS for the entire group was 16.7 months and PFS at 24 months and 36 months was 75% and 65% respectively. On univariate analysis, patients less than 18 years had poorer outcome as compared to older (Median PFS 9.5 vs. 41.32 months; p 0.004) and PFS was significantly poorer in the patients who received concurrent temozolomide than those who did not (Median PFS 9.8 vs. 21.5 months; p 0.05). Gender, grade and adjuvant chemotherapy did not statistically alter treatment outcomes. Age less than 18 years and CTRT with temozolomide continued to be statistically significant on multivariate analysis (p 0.01).
Conclusions: Younger age appears to be a bad prognostic factor for BSG patients. Temozolomide has a questionable role to play in the treatment of these patients.
No conflict of interest.

3324 POSTER

Reirradiation for recurrent glial tumors − experience from a regional cancer centre in North India

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Background: This study is aimed to assess the safety and efficacy of reirradiation in patients with recurrent glial tumor.
Materials and Methods: We identified 29 patients of recurrent glial tumor receiving reirradiation as a part of salvage treatment by retrospective chart review from 1993–2012. Event free survival (EFS) after recurrence was defined as the duration of time from date of recurrence to the date of death, disease progression or development of radiation necrosis. Survival analysis was done by Kaplan–Meier method.
Results: The median age at presentation was 32 years (range 11−57 years) with male: female ratio of 23:6. The initial site of disease was frontal (37.93%), parietal (10.34%), temporal (6.9%), occipital (3.45%), multilobed (31.03%), brainstem (3.45%) and optic nerve (3.45%). Initial surgical resection was gross total in 44.83% and subtotal in 48.28% patients. Histopathology was confirmative of diffuse astrocytoma (17.24%), gemistocyticastrocytoma (3.45%), ganglioglioma (3.45%), oligodendroglioma (24.14%), oligoastrocytoma (3.45%), anaplastic oligodendroglioma (10.34%), anaplastic oligoastrocytoma (6.9%), anaplstic astrocytoma (6.9%) and glioblastoma (10.34%). Initial radiotherapy dose varied from 56−60 Gy/ 28−30fractions/ 5.5−6 weeks as per the grade of the tumor(low grade-44.83%; high grade-55.17%). 37.93% and 51.72% of the patients received concurrent and adjuvant chemotherapy. The median recurrence free survival was noted to be 4.85 years. At recurrence, 44.83% of the patients underwent surgical resection (gross total-17.24%, subtotal-20.69%, details unavailable-6.9%). Median reirradiation dose was 45 Gy/ 25fractions/ 5 weeks (range 40−55 Gy at 1.8 Gy/ fraction/day). Majority (96.55%) underwent 3D-CRT and only 1 patient underwent SRT (mMLC based). Reirradiation was well tolerated and only 2 patients defaulted during the last week of treatment due to neurological deterioration. Concurrent and adjuvant temozolomide (EORTC-NCIC regimen) were used in 62.07% and 58.62% of the patients respectively. In the evaluable patients (N = 26), after a median follow-up of 10.38 months from the date of recurrence (range 1.77–88.52 months), complete response, stable and progressive disease were noted in 26.92%, 50% and 23.08% respectively. Radiation necrosis was discerned in 2 patients with 1 having debilitating neurological symptoms.The median EFS was noted to be 2.82 years. On univariate analysis, age (<40 vs. >40 years), sex, tumor grade, temporal pattern of recurrence (<2 years vs. >2 years), resurgery, use of concurrent or adjuvant chemotherapy along with reirradiation, had no significant impact on EFS.
Conclusion: Conformalreirradiation is a safe, feasible and useful treatment option in recurrent glial tumor.Radiation free interval (<2 versus >2 years) and cumulative brain dose (<100 Gy versus >100 Gy) should be taken into account before using this option.
No conflict of interest.

3325 POSTER

Treatment patterns and survival in patients with metastatic brain tumors

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Background: The rising incidence of metastatic brain tumors (MBT) due to better control of systemic disease represents a growing societal burden. The objective of this study was to characterize treatment patterns and outcomes of patients with MBTs using electronic health records of a major US cancer center in the Intermountain West.
Material and Methods: A cohort of patients diagnosed with MBTs during 1995–2010, was identified by linking the Utah Population Database and the University of Utah Enterprise Data Warehouse with the Huntsman Cancer Institute Tumor Registry. Patients were included if they were $\geqslant$18 years at MBT diagnosis (defined as $\geqslant$2 MBT diagnoses; ICD9-CM code 198.3), a primary cancer diagnosis, and $\geqslant$2 healthcare encounters during the study period. Patient demographics, survival, and treatment patterns (from 2002–2010) were assessed by the four most prevalent primary cancer sites.
Results: A total of 1900 cancer patients also diagnosed with MBT were identified from 1995–2010 (median age 60 years, 55% male). The most prevalent primary cancer sites were lung (30.5%), breast (16.2%), melanoma (15.5%), and kidney (8.3%). The median time from diagnosis of the primary cancer to the diagnosis of MBT was 51, 308, 761, and 1168 days for lung, kidney, melanoma and breast cancer, respectively. A subset of patients (n = 964), whose MBT was diagnosed during 2002–2010, were followed for survival and treatments received after MBT diagnosis. The first treatment used after MBT diagnosis was radiation (41%), followed by chemotherapy (19%), stereotactic radiotherapy (17%), and neurosurgery (12%); 117 (12%) patients received no treatment other than supportive care. Approximately 87% of patients received dexamethasone as a supportive therapy. Median survival after MBT diagnosis ranged from 114 days (lung primary) to 268 days (breast primary), which translates in mortality rates of 144.8 deaths per 100 person-years (lung) and 70.3 deaths per 100 person-years (breast). Compared to the median survival of 129 days for patients diagnosed with MBT during the period 1997–2000, the median survival for patients diagnosed during 2001–2004 and 2005–2008 were 160 days (p = 0.21) and 186 days (p = 0.02) respectively.
Conclusion: Survival of patients after the diagnosis of MBT has improved over time and differs by primary cancer site, but remains poor for most patients and reflects the high unmet need in this patient population.
No conflict of interest.

3327 POSTER

Clinical outcome of patients with primary gliosarcoma treated with concomitant and adjuvant temozolomide: A single institutional analysis of 27 cases

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Background: Primary gliosarcoma (PGS) is an aggressive and rare tumour and survival remain dismal with current treatment modalities. We intended to study the outcome of PGS patients treated with concurrent and adjuvant temozolomide (TMZ).
Materials and Methods: We retrospectively evaluated 27 patients of PGS treated with radiotherapy (RT) and TMZ at our institute during 2007–2012. Demographic and disease characteristics in this patient cohort were recorded. Overall survival (OS) was estimated by the use of Kaplan Meier method and univariate analysis (log rank test) was done to assess the impact of prognostic variables on OS. Multivariate analysis was done by Cox-proportional hazard model and SPSS (version 12.0) was used for all statistical analysis. Toxicities were evaluated using CTCAE version 2.0.
Results: Median age at presentation was 45 years (range 7−75 years) with a male: female ratio of 20:7. Median Karnofsky performance status (KPS) was 90 (range 70−90). Tumour was present in the temporal, parietal and frontal lobe in respectively 31%, 26% and 15% of the cases and involved more than 1 lobe in 28% of cases. 12 (44%) patients each underwent a gross total excision and sub-total excision and 3 (12%) had a decompression and biopsy of the tumour only. All patients received adjuvant RT to a total dose of 60 gray at 2 gray per fraction except 3 patients [one received 8 gray and two patients received 46 gray] median interval between surgery and RT was 38 days (range, 17−83 days). All patients except 1 received concurrent TMZ. All patients except 5 received adjuvant TMZ to a median number of 6 cycles (range 2−6 cycles). 2 patients had grade 2 (one neutropenia and one thrombocytopenia) and 1 patient had grade 3 (both neutropenia and thrombocytopenia) during concurrent RT. During adjuvant chemotherapy 3 patients (13.6%) had grade 3 thrombocytopenia and 2 patients had grade 3 neutropenia (9.5%). Median follow up duration for the entire cohort was 13 months (range, 2−48 months). At the time of last follow up 13 patients had expired, 4 had progressive disease and 10 patients were free of disease. Median OS of the entire cohort was 16.7 months. 1 year and 2 year actuarial OS was 70.8% and 32.6% respectively. On univariate analysis, use of adjuvant chemotherapy with TMZ was associated with a significantly better survival (median survival 21.21 months versus 11.93 months; p = 0.0046) and continued to be an independent prognostic factor for survival on multivariate analysis ((HR 1.82, 95% CI 1.503–25.58); p = 0.012). Other prognostic variables viz age, sex, extent of surgical resection, KPS and tumour site did not impact survival significantly.
Conclusion: The results of our study, largest series of patients with PGS treated with concurrent and adjuvant TMZ shows an impressive survival with acceptable toxicity. We suggest TMZ be included in the 'standard of care' for this tumour.
No conflict of interest.

3328 POSTER

Pineal parenchymal tumor − clinical experience from a regional cancer centre in north India

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Introduction: Pineal parenchymal tumor constitutes less than 1% of primitive tumors of the CNS and is classified by WHO into pineocytoma (PC)-grade I, pineal parenchymal tumor of intermediate differentiation (PPTID)-grade II/III and pinealoblastoma (PB)-grade IV.
Materials and Methods: We intended to assess the clinical features and treatment outcome in patients of pineal parenchymal tumor attending our hospital from 2003−13. Overall survival (OS) and recurrence free survival (RFS) were analyzed by Kaplan–Meier method.
Results: 23 patients met the study criterion (median age=22 years and male: female=14:9). Presenting complaints included headache (73.91%), visual symptoms (43.48%), vomiting (30.43%) and ataxia (26.09%). Preoperative contrast enhanced MRI and CT scan of brain were performed in 78.26% and 17.3% of patients respectively. Spinal drop metastasis and CSF cytology positivity were noted in 3 and 2 patients respectively. Surgery included gross total resection in 21.74%, near total resection in 13.04%, subtotal resection in 17.39% and tumor biopsy in 43.48% of the patients. 12 (52.17%) patients required the placement of VP shunt. Histopathology was confirmative of PB in 14 (60.87%) patients, PPTID in 6 (26.09%) patients and PC in 3 (13.04%) patients. MIB-1 labeling index varied from 2−80% with median value of 30% and 4.5% in PB and PPTID respectively. 22 (95.65%) patients underwent radiation therapy- craniospinal irradiation (CSI) in 14(60.87%) patients, whole brain radiation in 1 patient, whole ventricular radiation in 1 patient and local radiation in 6 (26.09%) patients. Majority (85.7%) of patients of PB underwent CSI- 36 Gy/ 20 fractions/ 4 weeks to whole brain followed by boost of 20 Gy/10 fractions/ 2 weeks to pineal region and 30−36 Gy/ 20 fractions/ 4 weeks to spinal axis as per risk stratification. Systemic chemotherapy was administered in 12 (52.17%) patients (11-PB and 1-PC) with EP (etoposide and carboplatin) being the most common regimen (30.43%). The median number of cycles administered was 6 (range 3−6). After a median follow-up of 26.87 months, death and recurrence were observed in 2 and 10 patients (local recurrence-34.78% and spinal drop metastases- 26.09%) respectively. Median RFS was noted to be 2.33 years, 14.29 years and 6.76 years in patients of PB, PPTID and PC respectively. The 2 and 3 year actuarial RFS rates in the entire cohort were respectively 71.6% and 57.9%. Salvage treatment was offered in 6 patients. Median overall survival was not reached. On univariate analysis (Log rank test), age (<18 versus >18 years), sex, histology, extent of surgery (biopsy versus resection) and use of chemotherapy had no significant impact on RFS.
Conclusion: Maximal safe resection followed by radiation therapy is the mainstay of treatment in pineal parenchymal tumor. Radiation volume encompasses the craniospinal axis in pinealoblastoma and the tumor bed with margin in pineocytoma. Platinum based combination chemotherapy should be added in adjuvant treatment in pinealoblastoma.
No conflict of interest.

3329 POSTER

Prognostic value of pseudoprogression after stereotactic reirradiation in locally recurrent glioblastoma patients

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Background: We assessed the prognostic impact of pseudoprogression in locally recurrent glioblastoma patients re-irradiated with frameless stereotactic radiotherapy (SRT).
Material and Methods: Between September 2009 and December 2011, 37 patients with recurrent glioblastoma were treated with CyberKnife in our department. All patients had unresectable, recurrent disease and were previously treated with conformal radiotherapy. The gross tumor volume (GTV) was delineated based on the contrast enhancing lesion on T1-weihgted magnetic resonance images (MRI). A 3 mm margin was added to GTV for defining the planning target volume (PTV). The median fraction number was 5 fractions (range, 1 to 5), and the median total delivered dose was 30 Gy (range, 14 to 32 Gy). The median volume of the GTV was 24 cc (range, 2 to 81cc). The interval between the primary radiotherapy and SRT ranged from 5 months to 45 months (median 15 months).
Results: The median follow was 20 months. The first MRI evaluation revealed that five patients had regression, 14 had stable disease, and 8 had progression. Another 7 patients had progression in their first MRI however they had regression in the follow-up and were diagnosed as pseudoprogression. Three patients died of disease in their first month of follow up. The median overall survival was 10.6 months in median (range, 1.1 to 20 months). The median progression free survival was 7.9 months (range, 7.4 to 13.3 months). The median overall survival for patients with pseudoprogression, regression, stable disease, and progression was 20 months, 13.7 months, 10.4 months, and 7 months respectively. Patients with pseudoprogression had a significantly longer overall survival compared to patients with regression, stable or progressive disease ($p = 0.01$).
Conclusion: In this retrospective cohort, SRT seems to be effective in patients with locally recurrent glioblastoma. We also found that patients with pseudoprogression after SRT had longer overall survival.
No conflict of interest.

3330 POSTER

NG2/CSPG4 promotes resistance to therapy in glioblastoma multiforme

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Background: The CSPG4/NG2 proteoglycan has been shown to be a marker of an aggressive proliferative phenotype, and as a potential marker of treatment resistant cells in GBM, and it may play a functional role in this resistance. However, this has not yet been demonstrated in cell lines derived from fresh surgical tissue. We sought to determine whether CSPG4 plays a role in treatment resistance in freshly derived cell lines.
Methods: Glioblastoma cell lines were derived using the Cambridge Protocol, and were exposed to ionising radiation, temozolomide and carmustine, the main therapies used in GBM. The proportion of live cells expressing CSPG4 was assessed by flow cytometry. Cell lines were FACS sorted, and the survival of positive and negative cells assessed by the MTT assay. To investigate a functional role of CSPG4, shRNA knockdown cell lines were generated before exposure to the therapeutic agents.
Results: CSPG4+ cells were enriched after exposure to all therapeutic modalities, and expression of CSPG4 correlated with survival of cell lines after therapy. FACS sorting confirmed that CSPG4+ cells are more resistant than CSPG4- cells, and growth curve analysis demonstrated long-term expansion of CSPG4+, but not CSPG4-, cells over a long period of time. shRNA knockdown demonstrated that cells were less proliferative and more sensitive to therapy.
Conclusion: CSPG4 is a reliable marker of therapy resistant cells in glioblastoma, and appears to play a functional role in this resistance. The exact mechanisms are under investigation, but targeting of CSPG4 may be beneficial in overcoming treatment resistance.
No conflict of interest.

3331 POSTER

Long-term outcome fractionated stereotactic radiotherapy and radiosurgery for treatment of symptomatic cavernous sinus meningioma: a 15-year experience

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Background: To evaluate the clinical results and radiological local control of symptomatic cavernous sinus meningioma patients treated with fractionated stereotactic radiotherapy (FSRT) or stereotactic radiosurgery (SRS).
Material and Methods: Retrospective cohort study evaluating 89 patients with symptomatic cavernous sinus meningiomas treated with SRS (36%) or FSRS (64%) from January 1994 to March 2007. Neurosurgical partial resection or biopsy was performed in 29.2% of the patients previously to radiotherapy. The single SRS dose was 14 Gy and the FSRT dose, 50.4−54 Gy fractionated in 1.8−2 Gy/dose.
Results: The follow-up period ranged from 36 to 129 months (median 73 months). Improvement in individual symptoms was the same regardless of treatment given, and Clinical improvement occurred in 41.6% of patients and radiological in 48.3%. Approximately 43% of the patients presented radiologically stable disease. The recurrence-free survival was 98.8%, 92.3%, and 92.3%, respectively, in 5, 10, and 15 years. Disease progression occurred in four patients (4.49%). No statistically significant association was observed between the radiotherapeutic method and symptom improvement ($p > 0.05$).
Conclusions: Both FSRT and SRS were equally safe and effective for the management of symptomatic cavernous sinus meningioma patients. There was clinical improvement in 41.6% of the patients and radiological stabilization or lesion regression of the lesion in 92.1%. The 15-year progression-free survival was 92.3%.
No conflict of interest.

3332 POSTER

Initial results of stereotactic linear accelerator based irradiation for pituitary adenoma

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Background: Radiotherapy is an efficient treatment for recurrent pituitary adenomas. Stereotactic linear accelerator based radiosurgery (LINAC) have been used in our Institution since 2008. The purpose of this analysis was to evaluate the initial results in control rate after radiosurgery or fractionated stereotatic radiotherapy in pituitary adenoma.
Material and Method: From september 2008 to July 2011, 36 patients were treated with fractionated stereotatic radiotherapy (FSR) or radiosurgery (RS) for pituitary adenomas. Tumor control was defined as normalization of basal hormonal levels and lack of progression of adenoma assessed by imaging studies. Follow-up included MRI and hormone evaluation.
Results: Twenty patients had nonfunctioning (NF) and sixteen had functional adenomas (acromegaly in ten and Cushing's disease in six cases). The median age was 44 years (range 17−72), with 29 females and 7 males. The median follow-up was 31 months (range 8−53). All patients received radiotherapy postoperatively for residual disease. All acromegaly patients were resistant to octreotide and cabergoline treatment. Mean total dose was 50.4 Gy for fractionated stereotactic radiotherapy ($n = 25$), and 20 Gy for radiosurgery ($n = 11$: 3 with Cushing's disease, 5 with acromegaly and 3 with NF). Twenty patients had stable disease based on MRI, while 15 had a reduction of tumor volume after 12 months. Regarding hormonal control, three of the six Cushing patients achieved normal urinary cortisol and midnight salivary cortisol levels after radiotherapy, one of them treated by RS. Although all patients were resistant to octreotide/cabergoline before radiotherapy, 3 of them obtained normal IGF-1 levels under medical treatment after irradiation and one patients with aggressive and invasive tumor showed normal IGF-1 levels without drug besides hypopituitarism.
Conclusions: Stereotatic radiotherapy is effective and safe in the treatment of pituitary adenomas to improve local control and can improve the hormonal control, with or without medical treatment.
No conflict of interest.

3333 POSTER

The incidence of brain metastases in correlation to dominant hemisphere and different brain lobes

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Purpose: Blood flow to the brain varies according to the dominance and functionality of each brain lobe. We hypothesized that this greater blood flow would lead to an increase in seeding of metastases to areas within the dominant lobe when compared to the nondominant lobe.
Methods: This is a single institution retrospective study of 190 patients (pts) who underwent SRS for 382 metastatic brain lesions from January 2007 through December 2012. All pts underwent single fraction LINAC-based SRS via 6 MV photon using either noncoplanar conformal fixed beams (68%) or dynamic conformal arcs (32%) prescribed to 100% of the planning

target volume (PTV) of which 13, 17, and 6% underwent surgery, whole brain radiotherapy (WBRT), or both, respectively. The median prescribed dose and PTV were 21 Gy (range 15−25) and 2cc (0.1−32). The median Dmax (dose to isocenter) and Dmin were 26.5 and 21 Gy, respectively. All patients had an ECOG performance status $\leqslant$2. The cohort consisted of Hispanics (39%), Caucasians (31%), African Americans (29%), and Asians (1%); 50% of the cohort was male. Histologies included lung (52%), breast (20%), renal (14%), and other malignancies (14%).
Results: The median follow-up for the entire cohort was 5.5 months (ms); however, the median follow-up intervals for survivors vs. expired pts were 12.8 ms (4–94.4ms) vs. 5 ms (1−60). The incidence of brain metastases in the different brain lobes were: 43%, 24%, 12%, 11.5%, and 9.5%, for frontal lobe, parietal lobe, cerebellum, temporal lobe, and occipital lobe, respectively. The incidence of brain metastases in the dominant hemisphere was 97% ($p = 0.01$). The LC for the entire cohort was 88%. The actuarial overall survival (OS) was 26%. No patients experienced RTOG grade $\geqslant$3 toxicities. Breast cancer pts had a longer median actuarial OS (9 ms) vs. other histologies (5 ms). Chi-square analysis showed that metastectomy prior to SRS was a statistically significant predictor for better LC ($p < 0.0001$).
Conclusion: Our data reveal increased seeding of brain metastases to the dominant brain hemisphere and brain lobes with higher blood flow.
No conflict of interest.

3334 POSTER

The number of brain metastases should not be used as a decisive factor to select patients for radiosurgery or not

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Background: Radiosurgery is an accepted treatment modality for selected patients with 1 to 3 brain metastases (BM). It is also well known that patients with a single brain metastasis have a better prognosis than those with multiple BM. However, the impact of the number of BM among patients with multiple brain lesions is unclear. Is the prognostic significance of the number of lesions sufficient to withhold radiosurgery for patients with more than 3 BM? In order to assess this question we analyzed our experience following Gamma Knife radiosurgery (GK) in patients with multiple BM.
Material and Methods: Of the 1365 consecutive BM patients treated in the Gamma Knife Center Tilburg between June 1, 2002 and June 20, 2011, 806 had multiple lesions. There were no differences between the groups of patients with 2 or 3 as compared to 4 or more BM for gender, ($P = 0.35$), age ($P = 0.062$), primary tumor (NSCLC or not; $P = 0.42$) and primary tumor control ($P = 0.60$). Prior WBRT was more common among patients with 4 or more BM ($P = 0.046$).
Results: The likelihood to develop distant recurrences in the brain was higher among the patients with more than 3 BM, 42 as compared to 33%, ($P = 0.014$). However, this difference did not translate into a significant difference in survival following GK. The median survival was 6.2 months for patients with 4 or more BM as compared to 7.2 months for patients with 2 to 3 BM, a non-significant difference ($P = 0.23$). The management of distant recurrences in the brain did not differ significantly between the two groups, ($P = 0.73$).
Conclusions: The number of BM in the patients treated with GK did not have an impact on the survival. In our opinion, the number of BM cannot be used as a decisive factor to select which patients should be offered GK for their BM and which should not.
No conflict of interest.

3335 POSTER

Outcomes of fractionated stereotactic radiotherapy for skull base meningiomas

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Background: The management of skull base meningioma (SBM) is a challenging proposition because SBM often involves cranial nerves. Preserving cranial nerve functions, fractionated stereotactic radiotherapy (FSRT) is more effective than other treatments; i.e. surgery, radiosurgery and hypofractionated stereotactic radiotherapy. The response criteria in SBM is indefinite for its irregular shape. The purpose of this study is to evaluate the safety and efficacy of FSRT and the morphologic change to FSRT.
Material and Methods: Consecutive 28 patients with SBMs were treated with FSRT using Novalis system between March 2007 and November 2011 at Kyoto University Hospital. 21 patients received FSRT following open surgery. 18 patients had WHO grade I meningiomas, one had WHO grade II, two had unknown grade meningioma. Other 7 patients were clinically diagnosed as meningioma based on radiological findings. 21 and 7 patients were treated by multiple dynamic conformal arc and IMRT technique, respectively. The youngest 11 years old patient was received 47.6 Gy in the 1.7 Gy fraction size, and the prescribed dose of the other 27 patients was ranged from 50.4 to 52.2 Gy in the 1.8 Gy franction size. The longest diameter and the short-axis diameter of tumor were measured to evaluate the morphologic change.
Results: The median follow up time was 38 months. All patients had completed the planned FSRT without severe acute adverse events. The 3 year local control and overall survival rates were both 100%. One patient died due to tumor hemorrhage after 42 months from the beginning of FSRT. The other 27 patients were alive with local control during follow-up periods. No patients developed progression of cranial nerve symptoms. All of the longest diameters coincided with the dural attachment. 95% confidence intervals of reduction ratio of the longest diameter and the short-axis diameter were respectively (0.92–1.00) and (0.79–0.95), and there was a significant difference between them.($p = 0.0045$).
Conclusion: Our results demonstrate that FSRT for SBM bring about good local control with preserving cranial nerve functions in limited patients and follow-up. Difference in reduction ratios of the longest diameter and the short-axis diameter may show that it is insufficient to evaluate response to radiotherapy only by the longest diameter.
No conflict of interest.

3336 POSTER

Can fractionated stereotactic re-irradiation improve the outcome in patients with recurrent glioblastoma? Single institutional experience

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Background: Glioblastoma (GBM) is the most common malignant primary brain tumour in adults. Tumour control and survival have improved with the use of radiotherapy (RT) plus concomitant and adjuvant TMZ, but the prognosis remains poor. In most cases recurrence occurs within 7−9 months and up to 90% in close proximity to the resection cavity or the target volume of postoperative RT. Currently, many approaches are available for the salvage treatment of patients with recurrent GBM, including resection, re-irrradiation or systemic agents, but no standard of care exists.
Materials and Methods: This is a retrospective analysis of twenty-four patients with recurrent GBM treated with hypofractionated radiation therapy (HFRT) at our department. After primary therapy, the recurrences were defined as 'in-field', 'marginal' or outside the radiation field. Indication for re-irradiation was evaluated by interdisciplinary neurooncology team and based on: patient clinical condition, lesion location and spread of disease. All patients were treated with multiple noncoplanar beams with a total dose of 25 Gy in 5 consecutive fractions, prescribed to the 70% isodose line.
Results: Of 95 consecutive patients with newly diagnosed GBM treated between 2007 and 2012 with conventional adjuvant chemo-radiation therapy at our department, 24 underwent salvage RT at recurrence. At the time of data analysis, 77 out 95 patients had died and the tumour progression was the primary cause of death in 74 patients. Among 18 patients still alive, 11 were in stable disease and 7 in course of systemic salvage therapy. Recurrence occurred 'in-field' in 59 patients (73%), at RT field margin in 8 patients (9%) and 'out-field' in 14 patients (17%). Salvage RT was performed in 15 of 68 patients with regional or marginal progression and in 9 of 13 patients with distant recurrence. The median time interval between primary RT and salvage RT was 8.8 months (range, 6−54 months). Overall, patients undergoing salvage RT showed a longer survival, with a median survival of 27.3 vs 10.4 months ($p = 0.00149$). Median OS from salvage RT was 10 months (range 4−42 months). In salvage RT patients, KPS ($p = 0.03$) and MGMT methylation status ($p = 0.02$) were statistically correlated with OS. No patients demonstrated clinically significant acute morbidity, and all patients were able to complete the prescribed radiation dose without interruption. Neurological deterioration occurred in two patients at 1 and 3 months after re-irradiation and was managed successfully with dexamethasone.
Conclusion: The current literature suggests that HFRT is effective and safe in recurrent glioblastoma after conventional chemo-radiation treatment. Until prospective randomized trials consolidate these results, the decisions for salvage treatment will remain individual and should be based on multidisciplinary analysis of each patient.
No conflict of interest.

3337 POSTER

Hypofractionated chemoradiotherapy with temozolomide as an appropriate treatment option for glioblastoma patients with poor prognostic features

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Background: Since high-risk GBM patients showed median OS of less than 1 year, clinical benefit of the 6-week postoperative treatment for the high-risk patients has been questioned. This study evaluated the feasibility and safety of hypofractionated radiotherapy (RT) with concomitant temozolomide (TMZ) for glioblastoma (GBM) patients with poor prognostic features.
Material and Methods: From Feb 2007 to Dec 2011, 33 patients with pathologically confirmed GBM received hypofractionated concurrent chemoradiotherapy (CRT) with TMZ, with or without adjuvant TMZ. The patients were either $\geqslant$70 years or <70 years with one or more risk factors (pre-RT ECOG score $\geqslant$3, stereotactic biopsy only, or immediate disease progression after surgical procedure). The median radiation dose was 45 Gy (range, 30 to 45 Gy) with a fraction size of 3 Gy.
Results: With the median age of 66.0 years, 18 patients (54.5%) showed poor performance status (ECOG $\geqslant$3) before starting CRT and 16 patients (48.5%) received stereotactic biopsy only. The median overall survival (OS) and progression-free survival (PFS) were 10.6 months and 4.4 months, respectively. Pre- and post-RT poor performance status (ECOG $\geqslant$3) (HR 3.12, 95% CI 1.21–8.07 and HR 4.51, 95% CI 1.44–14.12, respectively) and no early pseudoprogression (PsPD) (HR 5.43, 95% CI 1.58–18.61) were associated with poor OS. In PFS, post-RT performance status (ECOG $\geqslant$3) (HR 2.97, 95% CI 1.15–7.62) and extent of tumor (HR 2.50, 95% CI 1.05–5.96) were statistically significant. While acute neurologic symptoms during the CRT were reported in 5 patients (15.2%), there was no treatment-related aggravation in performance status with acceptable toxicity profiles.
Conclusion: We suggest a reasonable and well-tolerated therapeutic approach of hypofractionated concurrent CRT with TMZ in high-risk GBM patients. Despite the presence of one or more poor prognostic features in the patient cohort, the median OS comparable to previous studies was remarkable. Maintenance of good performance status before and after concurrent CRT will be beneficial for better prognosis.
No conflict of interest.

3338 POSTER

Hypo-fractionated radiation therapy compared to standard treatment regimen for glioblastoma: Local control and toxicity

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Background: The standard treatment today is maximal surgical resection followed by concomitant chemo-radiation therapy followed by adjuvant TMZ, with median overall survival of 14.6 months and 2-year survival rate of 26.5%. Despite the progress in neurosurgery, radiotherapy and oncology, the prognosis still result poor. In order to reduce the long time of standard treatment, in our institute we investigated the effects of hypofractionated radiation therapy (HFRT). For comparison, a group of 95 patients with similar characteristics and treated with Stupp protocol was retrospectively selected.
Materials and Methods: 67 patients affected by glioblastoma (GBM) underwent surgical resection were treated between October 2005 and December 2011 with HFRT followed or not by adjuvant chemotherapy with temozolomide (6−12 cycles). HFRT (5 Gy/fraction/day) was delivered to a total dose of 25 Gy in 5 fractions, dose prescribed at the 70% isodose. All patients received a non-contrast CT scan and MRI for treatment planning. After image fusion, the target volume was defined by the contrast-enhanced tumour edges on axial T1 and FLAIR sequences by consensus agreement of the neurosurgeon, neuroradiologist, and radiation oncologist. Treatment planning was performed to cover the 100% of planning target volume by 25 Gy, with maximum dose of 35.7 Gy. For treatment delivery, all patients received an portal image prior to each treatment fraction. Sex, age, type of surgery, Karnofsky performance status (KPS), Recursive Partitioning Analysis (RPA) classification, time between surgery and initiation of radiotherapy were analysed as potential prognostic factors for survival using the univariate log-rank method.
Results: All patients have completed the treatment protocol. Median age was 64.5 years (range 41–82 yrs) with 31 females (46%) and 36 males (54%). Median KPS at time of treatment was 80. The surgery was gross total in 38 patients and subtotal in 14 patients; 15 patients underwent only biopsy. The patients characteristics of the two groups of patients are similar. With mean follow-up of 14.9 months (range 3−62 months), the median overall survival and median progression- free survival were 12.43 and 6.9 months, respectively. No grade 3−4 acute or late neurotoxicity was observed. Post-treatment median KPS was 90 (range 70–100). The overall tolerance of patients to HFRT was not different from that for conventional radiotherapy. Not statistically significant difference in terms of overall survival between HFRT group and Stupp protocol group was reported (p 0.12).
Conclusions: The HFRT can be used for patients with GBM, resulting in favourable overall survival, low rates of toxicity and satisfying QoL. Future investigations are needed to determine the optimal fractionation for GBM.
No conflict of interest.

3339 POSTER

Efficacy of bevacizumab on radiation necrosis of the brain diagnosed by positron emission tomography with 11C-methionine

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Background: We reasoned that bevacizumab might be a new effective treatment of cerebral radiation necrosis because its ability to block vascular endothelial growth factor, although accurate diagnosis of radiation necrosis remains controversial. In this study, we examined to differentiate radiation necrosis from recurrent malignant brain tumor by positron emission tomography (PET) with 11C-methionine (MET), and evaluated the efficacy of bevacizumab for the treatment of radiation necrosis.
Material and Methods: 10 patients with malignant brain tumors (6 Glioblastoma, 1 anaplastic oligodendroglioma, 2 metastatic brain tumor, and 1 primary central nervous system lymphoma) were treated with bevacizumab for their symptomatic cerebral radiation necrosis on a 5 mg/kg biweekly, for a maximum total of 6 cycles. Radiation necrosis was diagnosed on the basis of the cut off value of lesion/normal tissue ratios (L/N ratio) on MET-PET. We evaluated the efficacy of bevacizumab treatment by MRI studies, MET-PET and 11C-choline (CHO)-PET, Karnofsky performance status (KPS), adverse events, and clinical courses before and after bevacizumab treatment completion.
Results: Seven patients showed significant clinical improvement in terms of neurologic symptoms expressed by KPS. Post-treatment MRI performed after bevacizumab therapy showed a reduction significantly in all 10 patients in both the MRI post-gadolinium and T2-weighted sequence (median reduction rate was 69.6% and 67.1%, respectively). PET imaging after bevacizumab therapy revealed that the median reduction rate of L/N ratio on CHO-PET was much higher than that of L/N ratio on MET-PET (62.1% and 22.9%, respectively). Bevacizumab-related adverse events of grade 1 or 2 occurred in three patients. During the median follow-up period of 16 months (range, 7−25), radiation necrosis recurred in four patients and the newly tumor lesion appeared in seven patients. All newly tumor lesion was appeared as an intraparenchymal newly enhanced lesion distant from the original tumor site. The 1-year tumor-progression-free survival rates from the completion of bevacizumab treatment were 40.0%. The 1-year survival rates from the completion of bevacizumab treatment were 70.0%.
Conclusions: We concluded that MET-PET could be useful for diagnosing radiation necrosis, and that bevacizumab could alleviate symptomatic radiation necrosis significantly by the restoration of blood–brain barrier and the associated brain edema.
No conflict of interest.

3340 POSTER

RTOG compared to EORTC volume recommendations in high grade glioma: Acute toxicity and integral dose

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Background: Radiotherapy for high grade glioma could be delivered either in single phase (EORTC guidelines) or two phases (RTOG guidelines). We aim to compare the target integral dose and the acute toxicity of radiotherapy in both techniques.
Material and Methods: Patients with high grade glioma eligible for full course of adjuvant radiotherapy during the year 2011 were enrolled in this study. Volumes were contoured for both techniques, the one phase (Gross tumor volume (GTV) with 3 cm margin 60 Gy) and 2 phases' techniques (Edema with 2 cm margin 46 Gy and GTV with 1 cm margin 14 Gy). Decision regarding treatment technique was individualized based on the volumes of the PTVs and its distance from the critical structures. Patients were seen weekly during treatment. Acute toxicity was documented according to the CTCAE version 4.

Results: 42 patients were included and contoured for both techniques. The target integral dose was statistically significant higher with one phase technique (32.1 Gy/L) compared to two phases technique (27.8 Gy/L) P = 0.004. Treatment was actually delivered in one phase in 23 patients and in 2 phases in 19 patients. Patients with larger tumor received treatment more in 2 phases. There was no statistically significant difference in the target integral dose and the acute toxicity profile between the 2 groups. Patients with higher treatment volume and higher target integer dose (>30 Gy/L) had more acute toxicity regardless of the treatment technique.
Conclusions: One phase technique leads to higher target integral dose. Higher target integral dose (>30 Gy/L) is associated with higher acute toxicity. Treating all patients with single phase technique may lead to unjustified increase in the acute toxicity and treatment technique should be individualized based on the tumor size and location.
No conflict of interest.

3341 POSTER

Impact of glycemia on survival in glioblastoma patients

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Background: Hyperglycemia has been associated with worse survival in glioblastoma (GBM) patients. This study aims to assess whether there is an independent association between glycemia and survival in GBM patients treated with radiotherapy (RT) and temozolomide (TMZ).
Materials and Methods: This was a retrospective chart review of GBM patients treated radically with RT and TMZ chemotherapy between 2004 and 2010. We calculated a time-weighted mean (TWM) glucose based on glucose values from diagnosis to 4 weeks after completion of RT and investigated the association of these values with survival, accounting for confounding factors including time weighted mean dexamethasone dose, age, body mass index (BMI), pre-existing diabetes and performance status.
Results: In total, 277 patients with a mean age of 55 years (18−77 years) with a mean body mass index of $26.7 \pm 4.9\ kg/m^2$ were evaluated. Patient performance status was ECOG 0−1 in 89%. Time-weighted mean daily dexamethasone dose was 6.7 mg (0–32.9 mg). After a median follow up of 15 months (1–104 months), the median survival was 15 months. The median TWM glucose from diagnosis to 4 weeks after completing RT was 6.5 mmol/L. For patients with a mean glucose $\leqslant$6.5 mmol/L and >6.5 mmol/L, the median survival was 20 months and 14 months, respectively. On univariable analysis, the following variables were associated with survival: TWM glucose, TWM dexamethasone dose, age, BMI and ECOG performance status. On multivariable analysis, TWM glucose remained an independent predictor of survival such that patients with mean glucose >6.5 mmol/L had an adjusted hazard ratio of 1.7 ($p < 0.0003$). Other independent predictors included the following: TWM daily dexamethasone dose ($p < 0.0001$), BMI ($p = 0.01$), and age ($p = 0.0005$).
Conclusions: This analysis suggests that glycemia is an independent prognostic factor for survival in patients with GBM treated with RT and TMZ, and proposes a biologically-important glycemic threshold for risk. Specifically, lower glucose levels, even below 6.5 mmol/L, were associated with better survival in our study, warranting prospective study of intensive glycemic intervention for patients with GBM.
Conflict of interest: *Other substantive relationships: N. Laperriere − honorariums from Merck, Roche, and Eisai*

3342 POSTER

The incidence and clinical feature of brain metastasis from non-small cell lung cancer, and their associations with EGFR mutation

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Background: Molecular diagnosis had made a great impact on classification of various tumors, including non-small cell lung cancer (NSCLC). Mutation of epidermal growth factor receptor (EGFR) correlates to remarkable response of NSCLC with tyrosine kinase inhibitors (TKIs). We previously reported the favorable control of brain metastases (BMs) with TKIs in EGRF-mutant cases. The aim of this study is to clarify the incidence and clinical feature of BMs and their differences owing to EGFR mutation.
Materials and Methods: We investigated the clinical data of 853 consecutive Asian patients with NSCLC who diagnosed between Apr. 2008 and Jan. 2013 in our institution retrospectively. The EGFR mutation status and brain MRIs were evaluated before initiating treatment in all cases. The incidence of BMs, survival of patients after BMs (OSaBM), and their association with EGFR mutations were investigated. The differences of OSaBM owing to patients' age, Karnofsky performance status (KPS), number and maximum size of BMs were also evaluated.
Results: EGFR mutations were found in 245 cases (28.7%); L858R in 137, Ex19 deletion (Ex19del) in 98, G719X in 5, and L861Q in 5. BMs existed in 121 cases (14.2% of all cases) at diagnosis of lung disease. Additionally, 59 patients (6.9%) developed BMs during their disease course. NSCLC with EGFR mutation more frequently developed BMs (27.8%) in compared with those without mutation (18.4%, $p = 0.002$). The incidence of BMs was higher in cases with Ex19del (34.7%) than those with L858R (22.6%, $p = 0.030$). From a different viewpoint, EGFR mutation was observed in 37.8% of BMs from NSCLC. EGFR mutation correlated not only with better survival after diagnosis of lung disease (not reached vs. 51.9m, $p < 0.0001$) but also with better OSaBM (22.4m vs. 8.0m, $p < 0.0001$). There was no significant difference in OSaBM between L858R and Ex19del. Good KPS ($\geqslant$70%) at BMs was significantly correlated with better OSaBM, regardless of EGFR mutation status ($p = 0.0003$ in mutant and $p = 0.005$ in wild cases). Number of BMs was significant prognostic factor of BMs in EGFR wild cases ($p = 0.039$) but not in mutant ones ($p = 0.134$). Leptomeningeal dissemination was significantly correlated with poor OSaBM in EGFR wild cases (3.0m with dissemination vs. 11.5m without dissemination, $p = 0.0007$), but not in mutant cases (12.3m vs. 25.6m, $p = 0.189$).
Conclusions: Nearly 40% of BMs from NSCLC harbored EGFR mutation and showed favorable outcome regardless of the number of brain lesions.
No conflict of interest.

3343 POSTER

Association of health-related quality of life and neurocognitive function with progression free survival and progressive disease in patients with glioblastoma: A review of the literature

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Background: Glioblastoma (GBM) is the most common malignant primary brain tumor. As disease burden is increasingly of interest in GBM trials, investigators now consider sustaining patient function as a critical treatment outcome. However, it remains unclear how the timing and extent of changes in health-related quality of life (HRQoL) and neurocognitive function (NCF) are associated with progressive disease (PD) or progression free survival (PFS).
Material and Methods: Literature searches were conducted for relevant English-language studies in the Embase®, PsycINFO®, and MEDLINE® databases (01/01/2002 through 12/10/2012). Searches included terms for GBM and brain cancer, quality of life, NCF, and disease survival and progression. Reference lists of included studies were also examined. All studies returned from the literature search were screened by abstract, and a sampling of studies were selected based on their perceived relevance.
Results: Eighty-eight studies were identified as potentially relevant, of which 25 were selected for full-text review. Of these, 4 GBM studies reported data regarding the association of PD or PFS with HRQoL, as measured by the EORTC QLQ-C30 and QLQ-BN20, and 4 studies with NCF, as measured by the MMSE or a battery of NCF tests. With regard to HRQoL: One study reported improved HRQoL scores (in global health status and several functioning scales) prior to disease progression; 1 study reported that HRQoL improvements were more common in patients with a partial or complete response than in those with PD; and 2 studies reported that HRQoL declined at the time of disease progression. With regard to NCF: Two studies (in GBM and brain metastases) reported declines in NCF at PD; 1 study in GBM reported that NCF improved prior to progression; and 1 study in high-grade glioma indicated that higher baseline NCF scores predicted better overall survival but not PFS.
Conclusions: The findings of this review in GBM and brain cancer studies provide evidence of an association between changes in HRQoL and NCF and disease progression or PFS.
Conflict of interest: *Ownership: Ravelo is an employee of Genentech. Abrey is an employee of Roche. Both own stock in Roche.*

Table 1 (abstract 3344). Correlation cognitive classification and PFS.

Cognitive classification	Working memory [% patients]	Attention [% patients]	Verbal and figural memory [% patients]	Verbal fluency/ Language [% patients]	Summary scale [% patients]
improved	34	20	23	23	23
stable	54	46	49	54	63
declined	11	34	29	23	14
p-value for correlation with PFS	0.685	0.015*	0.583	0.158	0.365

*significant on the level of <0.05

3344 POSTER

The prognostic value of cognition in patients with glioblastoma multiforme

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Purpose In patients with glioblastoma multiforme (GBM) progressive disease leads sooner or later to cognitive decline. In this study we evaluated if two cognitive assessments performed early in the treatment course have a prognostic significance for predicting progression free survival (PFS).
Methods: We assessed the cognition of 35 patients with GBM using the program NeuroCogFX with four subscales (working memory, attention, verbal and figural memory, verbal fluency) and summary scale. Baseline evaluation was done at initiation of radiotherapy (11−57 days after diagnosis) and second evaluation three months later (82–117 days after baseline). Results in subscales were categorized in 'declined', 'stable' and 'improved'. Tumor progression was based on MRI scans.
Results: The patients (12 women, 23 men) were in median 54 years old (21−75 years). The majority (63%) showed stable cognitive results, 23% improved and 14% decreased in the summary scale of cognition. The median PFS was 11 months (2.6–27.4 months). An improvement of attention correlated significantly with longer PFS (p = 0.015) whereas the other three cognitive subscales and the summary scale were not associated with PFS (see table 1).
Conclusion: Our data show evidence, that an increase or decrease of attention scales in patients with GBM is associated with the duration of PFS.
No conflict of interest.

3345 POSTER

Prognostic implications of clinical, radiologic, & pathologic markers in recurrent and non-recurrent meningiomas Grade I. Identification of alterations associated with tumor recurrence risk and disease progression

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Background: Most meningiomas are slow growing tumors, but in spite of complete surgical removal, the recurrence rate at 5 years is 5%, rising to 19% in long-term follow-up. However, there are no markers predictive of this evolution.
We study 140 specimens of meningiomas: 29 non recurrent & 57 recurrent in one, two or three times, related with clinical, radiological and pathologic prognosis factors.
Material and Methods: Age, gender, tumor size, Glasgow index recovery & neuroradiologic images were obtained from medical records. Growth fraction (ki 67 index) & progesterone receptors (PR), were assessed by immunohistochemistry (IHC) staining.
Results: Patients with good recovery according to Glasgow index show a lower recurrence rate (p = 0.036). There is a higher probability of recurrence among bigger tumors (>5 cm) (p = 0.257). A heterogeneous neuroimage occurs in the majority of recurrent cases (p = 0.008). Convexity meningiomas show the lowest rate of recurrence as compared with parasagital and basal ones. High levels of PR expression are associated with good recovery.
Conclusions: In our series, Glasgow index, size >5 cm, and heterogeneous neuroimage, are associated with recurrence risk of meningiomas. High levels of PR expression & convexity location occur more frequently in non-recurrent cases.
No conflict of interest.

3346 POSTER

Leptomeningeal metastases from solid tumors − retrospective review of a single institution

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Background: Leptomeningeal metastases (LM) from solid tumors are a rare but devastating complication due to the high incidence of neurological morbidity and mortality. Their incidence appears to be increasing. Neurologic signs and symptoms are the hallmark of LM. Intrathecal chemotherapy (ITC) is the standard of care for LM. However, overall response is low with a median survival of 7−24 weeks, questioning the benefit of this therapy.
Material and Methods: We performed a retrospective review that included all patients (pts) with solid tumors and LM diagnosed by cerebrospinal fluid (CSF) cytology from January 2000 to April 2013. Our main objectives were to characterize the initial signs and symptoms of LM and determine the overall survival (OS) of our pts. Primary brain tumors were not included. OS was estimated using Kaplan–Meier methodology.
Results: Sixty-three cases were reviewed. Median age at LM diagnosis was 56 y (26−81). 75% were females. The primary tumor was breast cancer (56%), lung cancer (20%), melanoma (5%), cervical cancer (5%), gastric cancer (5%), unknow origin (3%), endometrial cancer (2%), prostate cancer (2%), rectal cancer (1%).
Ninety percent had previously diagnosed metastatic disease treated with systemic chemotherapy (CT). Seventy-six percent of pts with LM presented with central nervous system signs and symptoms, 21% with cranial neuropathies and 21% with spinal signs and symptoms (a combination of two sites was seen in 16% of pts). ITC (methotrexate and/or cytosine arabinoside) was administered in 43 pts; 14 pts received radiation therapy to the neuroaxis; 21 pts were treated with systemic CT. The Kaplan–Meier estimates of 1-month, 3-month, 5-month and 12-month OS were 77%, 41%, 25% and 16% respectively (pts treated with ITC); and 45%, 10%, 5% and 0% (pts not treated with ITC). Breast cancer pts had a longer OS than pts with other primaries.
Conclusions: In our series, neurological manifestations prompt the diagnosis of LM, confirming that the diagnosis of LM requires a high index of suspicion. Pts treated with ITC, had a better OS, suggesting that ITC is a valid therapeutic option when feasible. Breast cancer pts, the majority, as expected, appear to have a better prognosis in the setting of LM.
No conflict of interest.

3347 POSTER

Resveratrol effects on cell viability, morphology and migration in cancer stem cell lines from glioblastoma multiforme

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Background: Glioblastoma multiforme (GBM) is a grade IV astrocytoma and the most common malignant brain tumor. Current therapies provide a median survival of 12−15 months after diagnosis, due to the high recurrence rate. The failure of current therapies may be due to the presence within tumor of cells characterized by enhanced self-renewal capacity, multilineage differentiation potential and elevated invasive behavior, called glioma stem cells (GSCs). The development of novel GSC-targeted therapies plays a crucial role in order to eradicate this tumor.
Resveratrol (RV) is a polyphenolic phytoalexin, found in fruits and vegetables, possessing a variety of biological activities, including antioxidant, anti-inflammatory and antineoplastic properties. Many studies have highlighted

its antiproliferative and proapoptotic effects on several type of cancers, including GBM. Moreover, RV is able to reverse temozolomide resistance, to induce the acquisition of a long-lasting differentiated phenotype and to reduce tumor invasion in GBM cell lines. RV represents an attractive agent for the treatment of brain cancers because of its minimal toxicity and blood–brain barrier permeability.
Material and Methods: In this study, we analyzed the effects of RV exposure (24−48−72 h) on cell viability, using MTT assay, and cell morphology in four GSC lines isolated from GBM (GBM2, GBM7, G179, GliNS2). Furthermore, we performed the analysis of cell migration through Wound Healing assay after RV administration for 48−72−96 h.
Results: Results showed that response to RV exposure was heterogeneous among GSC lines. Cell viability was significantly reduced only in GBM2 and G179 cell lines (70% of reduction at 72 h treatment), while GBM7 and GliNS2 were resistant. The analysis of morphology did not highlight any relevant modification in cellular shape after RV administration, except for GBM2 line which showed mild changes in morphology after 48 and 72 hours of treatment. With regards to cell migration, RV strongly reduced cellular motility in all cell lines.
Conclusions: GBM treatment with RV could represent a new interesting therapeutical approach in order to defeat the cancer stem compartment, providing a novel GSC-targeted therapy.
No conflict of interest.

3348 POSTER

Application of intraoperative magnetic resonance imaging and functional neuronavigation in microsurgery for gliomas encroaching both sides of cerebra

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Objective: The microsurgery for glioma located on corpus callosum gliomas encroaching both sides of cerebra is one of the most difficult surgeries in brain because of its bigger volume and adjacent to many important structures.
Thereby, the safe total removing and low deficit rate is hard to get with the routine surgical methods. With the using of the intraoperative magnetic resonance imaging (iMRI) and functional neuronavigation, many difficult operations were done and the good results were got. To explore the advantages and the application foreground of in microsurgery for corpus callosum gliomas encroaching both sides of cerebra and to sum up the operation strategy of corpus callosum gliomas, we deducted this study.
Methods: Retrospective analysis of 74 cases (male:female = 46:28) for corpus callosum gliomas encroaching both sides of cerebra from January 2009 through May 2011 were done. The patients were divided into two groups: A (iMRI) including 56 and B (functional neuronavigation uniquely) 18 cases. The clinical symptoms of both groups before and post operation were compared and the the gross total resection,the postoperative neurological deficit, the Karnofsky (KPS), the rate survived for over 1 year were also analyzed perspectively.
Results: The pathology result shows low grade glioma account for 33.8% (25/74) and hige grade glioma was 66.2% (49/74) in this series. The gross total resection rate of group A was 91.1%, the B group was 55.6%. The preoperative KPS was 50−90 (78±6), and the post operation was 50−90 (82.2±13.5). Compare the post operative KPS in the different groups showed that A group got 60−90 (84.2±10.6), and B group was 50−90 (81.4±8.8). The early postoperative neurological deficit was found of 3.6% in group A, and 16.7% in group B. The follow up were 5−40 months, 1 year survive was 93.3% for A group and 84.6% for B group. The long-term postoperative neurological deficit was noticed of 8.9% in A group, and 15.4% in B group.
Conclusion: The use of imaging guided surgery (IGS) with iMRI and functional neuronavigation are both effective methods to improve the total resection and reduce the postoperative neurological deficits for the large acrossing midline glioms. Meanwhile the 1 year survive rate was higher in the iMRI and functional neuronavigation assisted operation group than the functional neuronavigation unique one.
No conflict of interest.

3349 POSTER

Incidence of brain metastases in patients treated with bevacizumab

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Background: Metastasis to the brain is a frequent complication in certain tumor entities, including non-squamous non-small cell lung cancer (nsNSCLC), and HER2-positive and triple-negative breast cancer. Antiangiogenic therapy with bevacizumab has been investigated in a number of phase III trials in patients with advanced disease who generally had a large tumor burden and metastatic disease at treatment onset. As there are (mainly preclinical) indications that angiogenesis may be crucial for metastatic outgrowth via an early, mandatory angiogenic switch in the colonized organ and as brain metastases are among the most important prognosis limitating factors, it would be interesting to analyze a potential effect of bevacizumab on the development of brain metastases in randomised controlled trials.
Material and Methods: We performed a retrospective analysis of the incidence of brain metastases as first site of recurrence in the AVAIL (nsNSCLC, n = 1043 patients), AVADO (HER2-negative breast cancer, n = 736), and AVEREL (HER2-positive breast cancer, n = 424) randomized clinical trials. Importantly, pre-existing brain metastases where an exclusion criterion at study enrollment in all of these trials due to safety reasons. This setting may bias for patients with a metastatic pattern not involving the brain, but allowed a determination of the effects of bevacizumab on the development of new metastases during and after therapy.
Results: In the AVAIL trial, 20/347 patients (5.8%) in the placebo group developed brain metastases as first site of relapse, but only 18/696 patients (2.6%) in the bevacizumab group (hazard ratio (HR) 0.36; CI, 0.19–0.68, p = 0.001). The median time to brain progression was prolonged under bevacizumab therapy (237 vs. 137 days). The effect of bevacizumab was even stronger when the first 6 months of therapy where analyzed, which cover the average time of bevacizumab exposure in this study: during that time, 3.5% developed brain metastases as site of first relapse in the placebo group, but only 0.9% in the bevacizumab group (p = 0.002). In breast cancer patients, effects did not reach statistical significance for the single studies, likely due to a low number of brain metastases as site of first relapse: In the AVADO trial, the HR was 0.60 (p = 0.19), and in the AVEREL trial, the HR was 0.73 (p = 0.19).
Conclusions: Bevacizumab might prevent the formation of brain metastases in nsNSCLC, especially during drug exposure.
Conflict of interest: *Advisory board: Roche AG. Corporate-sponsored research: Roche AG*

3350 POSTER

Phase I dose escalating study of 2B3-101, glutathione PEGylated liposomal doxorubicin, in patients with solid tumors and brain metastases or recurrent malignant glioma

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Background: Without active delivery across the blood–brain barrier, the efficacy of doxorubicin in the treatment of brain tumors or metastases is limited. Therefore, 2B3-101, glutathione PEGylated liposomal doxorubicin, has been developed as a brain-targeted chemotherapy. In preclinical studies, 2B3-101 showed a 5-fold enhanced delivery of doxorubicin to the brain compared to pegylated liposomal doxorubicin (Caelyx®, Doxil®), and improved survival of mice with glioblastoma.
Methods: Patients with either brain metastases from solid tumors or recurrent malignant gliomas have been treated with 2B3-101 by a 90 min IV infusion q21d to assess (1) the safety, tolerability and MTD and (2) the PK and preliminary anti-tumor efficacy of 2B3-101. Antitumor activity was determined by brain MRIs and body CTs, according to RANO or RECIST criteria. Doses were escalated using a modified Fibonacci scheme in cohorts of 3−6 patients each.
Results: So far, 25 patients have received 2B3-101 at doses of 5−60 mg/m^2, without DLTs. 15 patients had brain metastases from solid tumors, and 10 patients had recurrent malignant gliomas WHO grade IV (7) or III (3). 24 patients had received ⩾3 prior therapies.
No cardiac or CNS toxicity was observed. At doses of ⩾40 mg/m^2, the observed adverse events ⩾ grade II (CTCAE v.4.0) were: neutropenia (46%), leucopenia (46%), thrombocytopenia (8%), mucositis (8%), and PPE (31%). Grade I−II infusion reactions were observed in 6/25 patients. All events were transient and manageable with standard treatments. The PK data show non-linear exposure of 2B3-101 without signs of accumulation with repeat dosing. Due to 1 case of thrombocytopenia grade IV at

60 mg/m^2 the cohort was expanded to 6 patients. In the absence of DLTs the study proceeded to 70 mg/m^2.

At doses of $\geqslant$40 mg/m^2, 8 of the 11 patients evaluated to date have demonstrated either stable disease (7 patients) or a partial response (1 melanoma patient) of their pretreated intracranial disease after 2 cycles. 3 out of 4 progressive glioblastoma patients showed stable disease after 2 cycles. In addition, 2B3-101 has been shown to act on extracranial disease in a patient with SCLC (65% reduction after 4 cycles).

Conclusions: 2B3-101 is safe and well tolerated up to 60 mg/m^2 q21d in both brain metastases from solid tumors and recurrent malignant gliomas and demonstrates preliminary antitumor activity in brain metastases.

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Conflict of interest: *Corporate-sponsored research: to-BBB technologies B.V. Other substantive relationships: to-BBB technologies B.V.*

3351 POSTER

Bevacizumab for recurrent glioblastoma, observations on patient outcome in the Belgian Medical Need Program

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Background: Bevacizumab (BEV), a monoclonal antibody targeted against the vascular endothelial growth factor has anti-tumor activity in patients (pts) with recurrent glioblastoma (rGBM).

Patients and Methods: Between Nov 2010 and Feb 2013, a total of 309 pts with rGBM were enrolled at 15 centers participating in the Belgian medical need program on BEV for rGBM (median No. of pts per center: 19, range 5−46). BEV was administered at a dose of 10 mg/kg every 2 wks.

Results: Baseline pts characteristics: 61% M, 39% F; median age 54 y (range 16−82); ethnicity: 91% Caucasian, 6% Arabic/North-African; 41% had $\geqslant$1 neurosurgical resection; all pts had failed RT and temozolomide and 71% had failed $\geqslant$1 prior therapy for recurrent disease; baseline WHO-PS 0/1/2/3: respectively 10, 67, 19 and 4%; 66% of pts used corticosteroid at baseline. At the time of analysis (28 Feb 2013), BEV treatment was ongoing in 42 pts. A median of 8 BEV cycles were administered per pt (range 1−53). BEV was stopped in 85% of pts because of PD and in 6.8% because of adverse-events (AE). Overall BEV was well tolerated. Hypertension (12%), proteinuria (8.4%), thrombocytopenia (4.2%) and thrombo-embolic events (3.2%) were the most frequently encountered AE. The best objective tumor response (investigator assessment according to RANO criteria): 9 CR (3%), 70 PR (26%), 112 SD (42%), and 77 PD (29%). Out of the 205 pts using corticosteroids at baseline, 71 (34%) decreased their corticosteroid dosing during BEV and 33 (16%) stopped corticosteroid treatment completel. The WHO-PS improved in 57 pts (18%) and 138 (45%) experienced a stabilization for $\geqslant$6 wks during BEV. Median and 6-mths rates (with 95% CI) for PFS 13.9 wks (13−15) and 29% (24−35), for OS 27 wks (23−31) and 54% (48−60). Baseline WHO-PS (0−1 vs. 2−3) was the only baseline characteristic that correlated with PFS and OS (Log Rank $p < 0.01$; HR of. 58 [95% CI. 43-.78] and. 53 [95% CI. 38-.73] for PFS and OS respectively). Pts with a baseline WHO-PS of 0−1 had a significantly lower chance for immediate tumor progression or decline of their WHO-PS (Fisher's exact test two-tailed P value: 0.01 and 0.03 respectively).

Conclusions: Notwithstanding the poor prognosis baseline characteristics of the population treated in this MNP, BEV was well tolerated and demonstrated anti-tumor activity, a corticoid sparing effect, and a beneficial effect on the WHO-PS in a meaningful subgroup of pts legitimating this MNP in the absence of alternative treatment options.

No conflict of interest.

3352 POSTER

Clinical and genetic factors associated with severe myelotoxicity during radiation therapy (RT) plus temozolomide (TMZ) in glioblastoma (GBM) patients: A prospective observational study

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Background: TMZ administered daily with RT for six weeks, followed by adjuvant TMZ for six cycles is the standard therapy for newly diagnosed GBM. A few case reports and small series studies have reported severe myelotoxicity developing during TMZ+RT. We performed a prospective study to analyze the incidence of early severe myelotoxicity and its possible clinical and genetic factors.

Patients and Methods: From November 2010 to July 2012 newly diagnosed GBM patients beginning treatment with RT (2 Gy/die for 30 days) plus continuous daily TMZ (75 mg/m^2/day for 42 days) were enrolled. They met the following criteria: pathologically proven GBM, age $\geqslant$18 years, ECOG PS 0−2, adequate blood cell counts before starting TMZ+RT. Grading of haematological toxicity was based on the NCI CTCAE v. 4.0. Clinical factors from all patients were recorded. Fisher's exact test was performed to compare frequency distribution of clinical factors between GBM patients with and without myelosuppression. Methylation status and polymorphic variants of MGMT gene in peripheral blood mononuclear cells, and polymorphic genetic variants of genes involved in the pharmacokinetics and pharmacodinamics of TMZ were analyzed by DMET Plus GeneChip array. For genetic analyses the patients with toxicity were matched (1:2) for age, ECOG PS, anticonvulsants and proton pump inhibitors with patients without myelotoxicity.

Results: We enrolled 87 consecutive GBM patients, 32 females and 55 males; the average age was 60 years. During TMZ+RT, 4 patients (5%) showed grade 3−4 myelotoxicity with a median duration of 255 days. Predictor factors of severe myelotoxicity were: female sex (4/4 pts with toxicity vs 28/83 pts without toxicity, $p = 0.01$), pre-treatment platelet count $\leqslant$300,000/mm^3 (2/4 vs 7/83, $p = 0.05$); anticonvulsants, proton pump inhibitors, age and pre-treatment WBC were not associated with myelotoxicity. Methylated MGMT promoter in haematopoietic cell system (4/4 vs 0/9, $p = 0.001$) and specific polymorphic variants of the cytochrome P450 oxidoreductase and methionine adenosyltransferase 1A genes ($p = 0.007$) were also associated with myelotoxicity.

Conclusions: We suggest that both clinical and genetic factors might simultaneously be associated with severe myelosuppression developed during TMZ+RT. Patients with these factors should be followed more accurately during the concomitant treatment.

No conflict of interest.

3353 POSTER

Bevacizumab-irinotecan versus procarbazine-lomustine-vincristine in recurrent high-grade astrocytomas − retrospective analysis of one center

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Background: High-grade astrocytomas (HGA) are the most common malignant primary central nervous system (CNS) tumors in adults. Standard-of-care therapy includes surgical resection, radiotherapy and temozolomide, but nearly all patients experience disease progression. Second-line options include procarbazine-lomustine-vincristine (PCV) and bevacizumab-irinotecan (BI). The purpose of this study is to compare response rate, survival times and toxicities between these two options.

Material and Methods: Retrospective analysis of HGA patients treated at our center with PCV or BI, after progression with temozolomide, between 2004 and 2012. Response to therapy was evaluated according to the Macdonald Criteria. Overall Survival (OS) and Progression-Free Survival (PFS) were assessed via Kaplan–Meier method and the multivariate analysis was performed using Cox Regression.

Results: Among 61 patients, 41 were treated with BI, and 20 with PCV. The majority were male (67.2%, n = 41), with a median age of 52 years (34−61) and a median follow-up of 17 months. The most common histology was glioblastoma multiforme (90.2%, n = 55) and 63.9% (n = 39) were submitted to complete macroscopic resection. It was possible to assess response in 58 patients (39 BI and 19 PCV). The median number of cycles in BI and PCV was 9.0 and 2.0, respectively. In the BI group 74.4% had some

response to treatment − 35.9% (n = 14) had complete/partial response and 38.5% (n = 15) stable disease. In contrast, only 21.1% (n = 4) in the PCV group showed response. Median PFS with BI was superior to PCV (5 months, 95% CI, 3.8−6.2 vs. 3 months, 95% CI, 1.6−4.4; p = 0.119), with a 9 month PFS of 33.5% and 13.1%, respectively. Median OS was also longer in the BI group (31 months, 95% CI, 19.6–42.4 vs. 16 months, 95% CI, 14.6–17.4; p < 0.001) and these differences retained statistical significance even in multivariate analysis (p = 0.002; HR 3.74; 95% CI, 3.74–1.59). Male gender was associated with worse prognosis in multivariate analysis (p = 0.026; HR 2.63; 95% CI, 1.12–6.18). The PCV group had a worse toxicity profile than the BI group (grade 3−4: 55% vs. 17.1%; p = 0.002; grade 1−2: 90% vs. 65.9%; p = 0.044).
Conclusions: In our series, patients with recurrent HGA treated with BI showed higher response rates, almost twice the OS and lower degree of toxicity in comparison to the PCV group, which agrees with current knowledge. Nevertheless, our results must be interpreted with caution given the small sample size.
No conflict of interest.

3354 POSTER

Axitinib for the treatment of recurrent glioblastoma − early results from a randomized phase II trial

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Introduction: Glioblastoma (GBM) is characterized by profound tumor related neo-angiogenesis and intracranial peri-lesional edema. GBM express high levels of the vascular endothelial growth factor (VEGF) and frequently carry an amplified copy number of the VEGFR2 gene. Axitinib (Inlyta®) is a small molecule tyrosine kinase inhibitor with specificity for the VEGF-receptors, approved for pts who failed 1 prior therapy for advanced renal cell cancer.
Patients and Methods: The AxiG protocol (ClinicalTrials.gov Identifier: NCT01562197) is an ongoing open label, controlled, multi-center, phase II clinical trial in which pts with recurrent GBM are randomized to treatment with axitinib (5 mg BID) or the physicians best choice of alternative therapy.
Results: Between Sep 2011 and Apr 2013, 22 pts were treated (11 pts with axitinib [5M/6F], and 11 pts, with bevacizumab). Baseline characteristics for axitinib treated pts: median age 55 y (range 42−80); all pts failed prior surgery, RT and temozolomide; 3, 5 and 3 pts had a WHO-PS of 0, 1 and 2, respectively; 9/11pts were on corticosteroids. Overall axitinib was well tolerated; treatment related AEs consisted of: hoarseness (9 pts [8x gr1, 1x gr2]), fatigue (6 pts [2x gr1, 3x gr2, 1x gr3], thrombocytopenia (2pt, gr1), arterial hypertension (3pts, gr2), mucositis (3pts, gr2), diarrhea (3pts; 1x gr1, 2x gr2), hypothyroidism (2pt; gr1), and rash (1pt, gr1). Axitinib dosing was interrupted in 4 pts, and subsequently dose reduced in 3; axitinib was escalated to 7 mg BID in 1 pt. The best overall tumor response for axitinib treated patients (RANO criteria): 1 CR, 6 PR, 1 SD and 3 PD (BORR 64%, DCR 72%). A significant decrease of maximal tumoral uptake (SUVmax/BG) on [18F]FET-PET was documented in 4/5 pts at the time of response on MRI. Analysis of MRS, CBV and CBF measurements is ongoing. Corticosteroids could be stopped in 3, and tapered in 5 pts. After a median follow-up of 45 wks (95% CI 5−73), the median PFS and OS for pts treated on the axitinib- vs. control-arm are respectively 15- (95% CI 8−22) vs. 14.2- (95% CI 2−26) and 45- (95% CI 0–106) vs. 17 wks (95% CI 0−54); 6-mths PFS and OS rates are respectively 42 vs. 23% and 59 vs. 50%.
Conclusion: Early results from this ongoing randomized phase II clinical trial indicate that axitinib has single agent anti-tumor activity and can be safely administered to patients with recurrent GBM who failed prior therapy with RT and temozolomide.
Conflict of interest: *Corporate-sponsored research: Pfizer resaerch grant*

3355 POSTER

Growth kinetics of low-grade glioma before and after treatment with CCNU alone

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Background: Previous studies have reported that low-grade gliomas (LGG) grow continuously and that temozolomide and PCV have an impact in their growth kinetics. No data exists on the impact of CCNU alone. The aim of this study was to evaluate the effect of first-line CCNU alone chemotherapy.
Material and Methods: The mean tumor diameter (MTD) of LGG was evaluated on serial magnetic resonance images before (n = 28), during, and after (n = 36) treatment with neoadjuvant CCNU.
Results: Before CCNU onset, MTD increased linearly over time (range 2.1 to 4.9 mm/year). During treatment with CCNU alone, 91% of patients experienced a decrease of MTD. After CCNU discontinuation, 28 of 33 patients who responded, an ongoing decrease of MTD was observed. Unresponsive tumors resumed their progressive growth within a year.
Conclusion: Our results confirmed that CCNU alone is an effective treatment for progressive LGG and its pattern of MTD decrease is comparable with previous study using Temozolomide and PCV chemotherapy.
No conflict of interest.

3356 POSTER

A randomized phase II trial of hydroxyurea ± imatinib in the treatment of recurrent or progressive meningiomas

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Background: Hydroxyurea (HU) is amongst the most widely used salvage therapies in progressive meningiomas after surgery, radiosurgery, and radiotherapy. Platelet-derived growth factor receptors (PDGF-R) are expressed in virtually all meningiomas. Imatinib sensitizes transformed cells to the cytotoxic effects of chemotherapeutic agents that interfere with DNA metabolism. The combination of HU with Imatinib yielded intriguing results in recurrent malignant glioma. The current trial addressed the activity of this association against meningioma.
Methods: Patients with recurrent or progressive WHO grade I−III meningioma, without therapeutic indication for surgery, radiotherapy or stereotactic radiosurgery, aged 18−75 years, ECOG performance status (PS) 0−2 and not on enzyme-inducing anti-epileptic drugs (EIAED) were randomized to receive HU 500 mg BID ± Imatinib 400 mg QD. Treatment was administered until progression, unacceptable toxicity, or patient's refusal. The primary endpoint was progression-free survival rate at 6 months (PFS-6).
Results: Between September 2009 and June 2011, 15 eligible patients were randomized to receive, HU+Imatinb (N = 7; Arm A) or HU alone (N = 8; Arm B). Afterwards the trial was prematurely closed due to slow enrollment. Patients' characteristics were (A/B): median age 68/68, median PS 1/1, grade 1: 1/1; grade 2: 4/5, grade 3: 1/0, unknown: 1/2, second surgery: 6/6, three or more surgeries: 4/ 1, biopsy: 1/0; radiotherapy: 6/5, radiosurgery: 1/3. All arm A patients progressed within 6 months while 4/8 are currently progression-free in arm B. PFS-6 and median PFS (A/B) was 0%/75% and 4/15.4 months. Two arm A and 4 arm B patients are alive. Median and 2-y OS (A/B) were: 6.5/21.8 months; 14.3%/62.5%. No objective response was observed; 4 arm A and 8 arm B patients had stable disease. Median number of cycles (A/B) was 4 (range 2−7) and 11 (range 4−14). Main G3−4 toxicities were: G3 neutropenia in 1/0, G4 headache in 1/1 and G3 vomiting in 1/0.
Conclusion: This study confirmed that HU is an active and well tolerated agent in recurrent meningioma. Conversely, the addition of imatinib may have a detrimental effect. However due to the small number of patients included in this study, no firm conclusion can be drawn.
No conflict of interest.

3357 POSTER

Concomitant radio-chemotherapy with CCNU after radical removal of newly diagnosed glioblastoma: Preliminary results of a single center retrospective study

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Background: When given concurrently with radiotherapy, Temozolomide has led to improved survival in GBM patients raising the possibility of radiation potentiation of Temozolomide. This study was conducted to determine the relative contribution of concomitant CCNU in patients with newly-diagnosed GBM.
Material and Methods: We identified all patients operated on for a supratentorial GBM and further treated with radiotherapy and CCNU

based chemotherapy either in a concomitant and adjuvant (group 1) or adjuvant only (group 2) setting. The primary endpoints of this study were progression-free survival (PFS), overall survival (OS) and the secondary endpoint was the toxicity.
Results: Forty-two patients (group 1, n = 20; group 2, n = 22) were included in this study. The two arms were well balanced according to their baseline characteristics (including age, KPS). The median follow-up was 15.7 months (95% CI, 12 to inf months). A borderline statistically difference (p = 0.07) was observed according to the PFS between two groups (12 vs 8 months). The median survival OS was 19 months (95% CI 14.1 and 24.7 months) with RT plus CCNU and 11.6 months (95% CI 11.2 and 17.2 months) with adjuvant group, P = 0.09 by the log-rank test. Hematological toxicity was absent during concomitant chemo-radiation and mild (9%) in adjuvant therapy.
Conclusions: Concurrent and adjuvant CCNU is associated with improved survival compared to adjuvant CCNU alone. These results highlight the contribution of CCNU in the radiation effect when given concomitantly.
No conflict of interest.

3358 POSTER

Stem-like glioblastoma cells can be targeted with a novel radiomimetic agent with dual roles in DNA double strand break induction and homologous recombination inhibition

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Background: Glioblastoma (GBM) is a malignant tumour known to limit the efficacy of ionizing radiation (IR) and alkylating-based drug treatment. In GBM cells, the DNA damage response cascade serves as a key radioresistance mechanism, promoting cell-cycle arrest and DNA repair to restore genomic integrity and ensure cell-survival. Hence patients undergoing DNA damage-based therapies are likely to relapse or even be refractory to further treatment. In this study, we introduce a new radiomimetic agent, which achieves DNA damage induced-apoptosis by eliciting lethal DNA double strand breaks (DSB) and blocking the error-free homologous recombination (HR) repair pathway.
Material and Methods: Primary glioma initiating cell (GIC) cultures were established from GBM patients using a serum-free media supplemented with essential growth factors. Surface markers (CD133, EphA3, etc) and neurosphere assay validated the multipotency of GICs while proliferation and colony formation assay confirmed radioresistant survival after IR treatment.
Results: Among 40 different therapeutic agents investigated, only salinomycin showed potential anti-cancer activity. The agent induces DNA strand breakage that is identical to IR but with a higher DNA damage efficacy in which >80% of the GIC population undergoes apoptosis. Cell-cycle profiling showed salinomycin retards GICs at late-S phase instead of G_2/M as seen with IR treatment. The agent did not affect Brca1 and RPA recruitment to the DNA damage site which is essential for HR initiation. However, immunofluorescence analysis of downstream HR components showed absence of Rad51 foci. Western blotting indicated salinomycin targets HR by degrading Rad51 protein which is required for DNA strand invasion. In agreement with its specificity, salinomycin treatment did not alter non-homologous end joining repair that represents the other major DNA DSB repair pathway. In a murine model, the median survival of mice following receipt of GIC with or without IR treatment prior to intracranial engraftment was 103 days and 102 days respectively. In contrast, pre-treated with salinomycin significantly inhibited tumour growth (mice median survival = 133 days).
Conclusions: Current treatment strategies rely on excessive lethal DNA DSB to achieve apoptosis can be easily overcome by DNA DSB repair. Our data demonstrate not only proof-of-principle that HR is essential for GIC genome integrity and survival, and consequently must be targeted to successfully achieve DNA damage-induced apoptosis, but also identify a new radiomimetic analogue with functions in DNA DSB induction and HR inhibition.
No conflict of interest.

3359 POSTER

MGMT promoter hypermethylation is present in grade II/III gliomas and GBM in the absence of IDH mutations

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Introduction: There is a high rate of IDH1/2 mutations in low grade gliomas and in high grade gliomas deriving from them. IDH mutation is an early event in gliomagenesis and independently confers a better prognosis in Grade III and IV tumours. Mutated IDH is believed to predispose glioma cells to DNA hypermethylation because the abnormal IDH product 2 hydroxyglutarate (2-HG) is known to inhibit histone demethylation. Methylation of the MGMT gene promoter silences its expression and improves outcome in patients treated with temozolomide (TMZ) chemotherapy. We compared the expression of mutated IDH and hypermethylated MGMT in a cohort of glioma patients.
Method: 88 samples from 71 patients were identified: 15 WHO Grade 2 gliomas, 29 Grade 3 gliomas and 27 Grade 4 GBM. 31 samples were excluded due to insufficient sample for DNA extraction. For immunohistochemistry, sections were stained with anti-IDH1R132H antibody. For sequencing, DNA was extracted from fresh, frozen tissue. Sanger sequencing of the R132 region of IDH1 and the R172 region of IDH2 was performed. MGMT methylation status was assessed by methylation specific PCR.
Results: We found a high rate of IDH1 mutations in lower grade lesions (grade II & III) (23/43) (53%) and a low rate in GBMs (2/28) (7%). Both grade II gliomas and anaplastic astrocytomas show a statistically different distribution of IDH1 mutation load compared to GBMs ($p < 0.0001$; $p = 0.0021$ respectively). For grade II/III gliomas, 96% (22/23) of IDH mutations are associated with MGMT hypermethylation and 55% (6/11) of IDH mutation negative samples showed MGMT hypermethylation ($p = 0.008$). In the GBM cohort, both samples with IDH mutations show MGMT hypermethylation 100% (2/2) with 54% (14/26) of IDH mutation negative samples showing hypermethylation ($p = 0.5$). In this cohort, the difference in % methylation in grade II/III, 32/43, [74%] and GBM, 16/28, [57%]), did not achieve significance ($p = 0.2$).
Conclusion: In our cohort the difference in MGMT hypermethylation between gradeII/III glioma and GBM is non-significant. IDH mutations are overrepresented and significantly associated with MGMT hypermethylation in grade II/III gliomas compared with GBM. However there is a proportion of IDH negative cases with MGMT hypermethylation in all grades. This suggests that alternate epigenetic mechanisms apart from 2HG-mediated inhibition of histone demethylation may be acting to silence MGMT expression in these cases.
No conflict of interest.

3360 POSTER

Proliferation and microvascular density predict survival in patients with brain metastases of non-small cell lung cancer

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Background: Non-small cell lung cancer (NSCLC) is the most frequent cause of brain metastases (BM). Survival upon diagnosis of BM is variable and established prognostic scores do not include tissue-based parameters. We studied the prognostic value of proliferation, angiogenesis and hypoxia in NSCLC BM.
Methods: All patients treated with neuro-surgery as first line therapy for newly diagnosed NSCLC BM between 01/1990 and 02/2011, were identified from the Neuro-Biobank, Medical University of Vienna. We determined microvascular density (MVD), Ki67 tumor cell proliferation index and hypoxia-inducible factor 1 alpha (HIF1a) score using immunohistochemistry and standard protocols. Clinical and demographic data were retrieved by chart review. We performed statistical correlations including survival analyses using log-rank test and Cox-regression.
Results: BM specimens of 210 patients were available for analysis (133 male (63.3%), 77 female (36.7%), median age at diagnosis of BM 56 (range 31−78). 38/210 (18.1%) patients had squamous and 172/210 (81.9%) non-squamous histology of the primary tumour. Median overall survival (OS) from first diagnosis of BM was 8.0 months (range 0.0–

158.0). Diagnosis specific graded prognostic assessment (DS-GPA) groups showed statistically significant correlation with survival (class 1: 19 months; class 2: 8 months; class 3: 5 months; class 4: 1 month; $p < 0.001$; log rank test). Patients receiving adjuvant whole brain radiation therapy (WBRT) after surgery had a significantly improved survival (6 vs 11 months; $p = 0.039$; log rank test). Median MVD was 71.5 (range 7–298), median ki67 39.1% (range 3−97%) and median HIF1a index was 60.0 (range 0–250). Neither Ki67, MVD nor HIF1a index of the primary tumour showed correlation with time till first occurrence of BM. At univariate survival analysis, patients with low MVD (8 vs. 11 months; $p = 0.045$; log rank test), high HIF1a index (7 months vs. 13 months; $p = 0.027$; log rank test) and high Ki67 (6 months vs. 11 months; $p = 0.005$; log rank test) had an impaired OS. In multivariate analysis, DS-GPA ($p < 0.001$), Ki67 ($p < 0.001$), MVD ($p = 0.008$) and adjuvant WBRT ($p = 0.049$) remained statistically significant.
Conclusion: Ki67 proliferation index and MVD of BM are independent predictors of survival in NSCLC BM patients and should be included in disease- and BM-specific prognostic scores.
No conflict of interest.

3361 POSTER

The immunohistochemical expression of c-Met is an independent predictor of survival in patients with glioblastoma multiforme

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Background and Aims: Because the outcome of glioblastoma multiforme (GBM) remains dismal, there is an urgent need for a better molecular characterisation of this malignancy. The aim of this study was to investigate the prognostic impact of the expression of c-Met a receptor tyrosine kinase implicated in expression growth, survival, motility/migration, and invasion in GMB patients managed according to the established diagnostic and therapeutic protocols.
Methods: Between May 2003 and March 2011, a total of 69 patients (33 males and 36 females; mean age: 52.2±12.9 years, age range: 23−81 years) referred to our Department for the surgical removal of GBM were evaluated immunohistochemically for c-Met expression. Progression-free survival (PFS) and overall survival (OS) served as the main outcome measures.
Results: Compared with c-Met− subjects (n = 38), c-Met+ subjects (n = 31) had both a significantly lower OS (15.3±2.3 vs. 22.6±2.5 months, respectively, $p < 0.01$) and PFS (12.3±2.1 vs. 19.1±2.6 months, respectively, $p < 0.05$). After allowance for potential confounders, Cox regression analysis identified c-Met+ as an independent predictors of both OS (hazard ratio = 1.7; 95 % confidence interval = 1.1−1.7, $p < 0.01$) and PFS (hazard ratio = 1.6; 95 % confidence interval = 1.1−2.4, $p < 0.05$).
Conclusions: Our findings suggest that c-Met immunohistochemical expression is an independent predictor of outcomes in patients with GBM treated by standard of care.
No conflict of interest.

3362 POSTER

Microenvironment cues induce invasiveness in acquired temozolomide resistance glioma cells

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Background: Glioblastoma multiforme (GBM) is the most malignant form of primary brain tumours and patients diagnosed with GBM have a median survival time of 15 months, even with surgical resection, chemotherapy and radiotherapy. One key reason that prognosis for GBM patients is so poor is that single tumour cells can infiltrate diffusely into the brain parenchyma by aberrant interactions with the extracellular matrix (ECM) components in the brain, rendering complete surgical removal of tumour cells impossible. Temozolomide (TMZ), the most promising chemotherapeutic drug for glioma, has further been proven to be ineffective for GBM treatment due to intrinsic or acquired chemoresistance of the GBM cells. In this study, we attempted to understand the influence of microenvironment cues from the ECM on GBM cells with acquired TMZ resistance.
Material and Methods: Stable TMZ-resistant U251MG cell lines were generated by stepwise exposure of parental U251MG cells to TMZ, with 15 passages between each step. Reconstituted rat tail collagen I was used as the 3-dimensional cell culture.
Results: We found that TMZ-resistant U251MG cells displayed a different morphology and were more invasive compared to parental cells in the collagen gels. We further showed that the increased invasiveness of TMZ-resistant U251MG cells were due to the ability to form strong adhesions with surrounding collagen fibers, resulting in a stiffer local microenvironment, and increased expression of matrix metalloproteinases (MMPs).
Conclusions: Microenvironment cues are necessary to induce the invasive capability of TMZ-resistant glioma cells. We propose that complementary chemotherapeutic treatment with TMZ for GBM should emphasize on specific targets, particularly from the MMPs pathway, to prevent recurrence from invasive TMZ-resistant glioma cells.
No conflict of interest.

3363 POSTER

Identification of a 19 miRNAs signature distinguishing low grade from high grade gliomas

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Background: Gliomas account for approximately 70% of malignant primary brain tumors diagnosed in adults. They represent a disparate group of tumors for which there are no cure. MicroRNAs (miRNAs) are small non-coding RNAs, of 18 to 25 nucleotides in length, involved in the post transcriptional regulation of gene expression. Low grade (LG) and high grade (HG) gliomas share several morphological characteristics and pathways abnormalities but have a completely different clinical behaviour. We hypothesize that the comparison of the miRNAs profile between LG and HG gliomas may lead to the identification of miRNAs associated with the glioblastoma multiforme (GBMs) aggressive phenotype.
Material and Methods: miRNAs profiling of 8 LG gliomas (WHO grade II), 24 HG gliomas (2 WHO grade III and 22 GBMs) and 4 commercially available normal brain tissues (NBT) was performed by using the Affymetrix GeneChip® miRNA Array 1.0. Data analysis was performed with Partek Genomic Suite software, setting as cut offs a significative p-value $\leqslant 0.01$ and a fold change of 2. A relative quantification method with standard curve using specific stem loop primers was used to validate the 22 miRNA signature identified by array analysis. The prognostic performance of the 19 validated miRNAs was evaluated by using the Tumor Cancer Genome Atlas Network (TCGA) dataset which includes only GBMs.
Results: miRNA profiling of the 32 gliomas and 4 NBT allowed us to identify 60 miRNAs differentially expressed in LG and HG versus NBT; 80 miRNAs differentially expressed in LG versus NBT and 71 miRNAs differentially expressed in HG versus NBT. A signature of 22 miRNAs distinguished HG from LG and NBT. qRT-PCR analysis confirmed differential expression in LG versus HG for 19 out of the 22 miRNAs. We evaluated our signature on the TCGA dataset finding 6 miRNAs differentially expressed in the GBM subclasses identified by the TCGA data dataset (astrocytic, neural, neuromesenchimal, oligoneural and radial glial). Two of those miRNAs were associated with worse overall survival in both univariate and multivariate Cox Regression analysis (HR 1.19 95% CI 1.008–1.406 P = 0.04; and 1.183 95%C 1.018–1.375 P = 0.03).
Conclusions: Our study has led to identifying a subset of miRNAs able to distinguish low grade from high grade gliomas. This informations could be exploited for the development of novel methodological tools for innovative diagnostic and therapeutic approaches for this deadly disease.
No conflict of interest.

3364 POSTER

HOXB7 gene expression and growth of glioblastoma xenografts after treatment with 13-cis retinoic acid and thalidomide

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Background: 13-cis retinoic acid (RA) and thalidomide (THAL) are biological modulators frequently used as sole agents or in the combination

with different chemotherapeutics or radiotherapy in clinical trials in patients with glioblastomas (GBM). However, induction of homeobox (HOX) gene expression such a HOXB7 by RA may activate basic fibroblast growth factor (bFGF) contributing to tumor progression and thereby potentially limiting its efficacy. The purpose was to test if THAL can inhibit RA-induced HOXB7 and bFGF expression and delay growth of glioblastoma xenografts.
Material and Methods: U343 glioblastoma cells were treated in vitro with RA, THAL and their combination. Quantitative real-time PCR was used to determine changes in HOXB7 and bFGF expression. 1.5×10^6 U251 cells were inoculated s. c. into the right hind limb of NMRI-Foxn1^{nu} nude mice. Animals were randomly assigned in 4 groups (7−11 animals/group): control, RA, THAL and RA + THAL and treated daily (Monday-Friday) via intragastric tube with RA (30 mg/kg), THAL (30 mg/kg) or their combination for 18 days. Tumor growth was determined during the whole treatment period. Animals were sacrificed and tumors resected one day after the last treatment. mRNA was isolated from three tumors selected randomly from each group and transcription of HOXB7 was evaluated by real-time PCR with ACTB as reference.
Results: Treatment of U343 cells with RA *in vitro* caused upregulation of HOXB7 and bFGF gene expression which was significantly inhibited by THAL ($p < 0.0001$ for HOXB7; $p = 0.007$ for bFGF). RA or THAL as sole agents did not influence growth of the xenografts while combined treatment caused a significant decrease in tumor volume ($p = 0.0043$). The final tumor volumes were: control = $1.37 \pm 0.2\,cm^3$, RA = $1.38 \pm 0.23\,cm^3$, THAL = $1.43 \pm 0.5\,cm^3$, RA + THAL = $0.69 \pm 0.075\,cm^3$. Hematoxylin and eosin staining of xenografts revealed marked hypocellularity in the case of combined treatment. No significant difference in HOXB7 expression was found between different treatment groups.
Conclusions: THAL inhibited upregulation of HOXB7 and bFGF expression induced by 13-cis RA in U343 glioblastoma cells. Combined treatment caused significant delay in tumor growth albeit without influence on HOXB7 gene expression. These results indicate a complex mechanism of action of THAL in combination with RA. Microarray analysis of global gene transcription in the tumors is ongoing.
No conflict of interest.

3365 POSTER

Preclinical evaluation of the novel anthracycline derivative aldoxorubicin for human glioblastoma chemotherapy

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Background: Glioblastoma multiforme (GBM) is the most common and aggressive of the adult brain tumors with a median survival of 12−14 months despite aggressive surgery, radiotherapy, and the use of the chemotherapeutic drug temozolomide. In this study, we evaluated the preclinical efficacy of a novel albumin-binding prodrug of doxorubicin, aldoxorubicin (also known as INNO-206), for the treatment of GBM in a murine model.
Material and Methods: U87MG human glioma cells (5×10^5) expressing firefly luciferase (U87-luc) were stereotactically implanted in the left striatum of nude mice. After 9 days, mice ($n = 8$ in each group) received either vehicle or aldoxorubicin by tail vein injection once weekly for a total 3 weeks. The first two doses were 75% and the third dose was 50% of the maximum tolerated dose of 32 mg/kg in mice. Tumor growth was monitored weekly using bioluminescence imaging, and survival compared using Kaplan–Meier curves.
Results: Although, the relative difference in average tumor sizes between the control and the treatment group after 7 days of tumor cell implantation was non-significant ($p>0.05$), all control mice developed large tumors (median tumor size 4.7×10^8 bioluminescence units) by day 21 and died within 29 days. In contrast, mice receiving aldoxorubicin displayed near complete tumor regression 21 days after implantation (median tumor size 0.57×10^8 bioluminescence units), and remained alive at day 29. Kaplan–Meier survival curves revealed significantly increased survival for mice treated with aldoxorubicin ($p = 0.0006$).
Conclusions: Using an intracranial murine model for GBM tumor progression, we show that systemic administration of aldoxorubicin induces significant tumor regression and prolongs survival. Unlike doxorubicin which has shown limited efficacy in the treatment of brain tumors, our data support the potential utility of aldoxorubicin for GBM therapy.
Conflict of interest: *Ownership: CytRx Corporation: Daniel Levitt. Corporate-sponsored research: CytRx Corporation-sponsored research in part and reimbursement of meeting expenses: Om Prakash. Other substantive relationships: CytRx Corporation employment: Daniel Levitt and Scott Wieland*

3366 POSTER

MGMT promoter methylation status and MGMT and CD133 immunohistochemical expression as prognostic markers in glioblastoma patients treated with temozolomide plus radiotherapy

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Background: The CD133 antigen is a marker of radio and chemo-resistant stem cell populations in glioblastoma (GBM). The O6-methylguanine DNA methyltransferase (MGMT) enzyme is related with temozolomide (TMZ) resistance. Our propose is to analyze the prognostic significance of the markers in a homogenous group of GBM patients uniformly treated with radiotherapy and TMZ.
Methods: Seventy-eight patients with GBM treated with radiotherapy combined with concomitant and adjuvant TMZ were analyzed for MGMT and CD133. MGMT gene promoter methylation was determined by methylation -specific polymerase chain reaction after bisulfite treatment. MGMT and CD133 expression was assessed immunohistochemically using an automatic quantification system. Overall and progression-free survival was calculated according to the Kaplan–Meier method.
Results: MGMT methylation status was methylated in 43% and unmethylated in 57%. A significant correlation was observed between MGMT promoter methylation and patients' survival, the median OS among patients with methylates MGMT promoter was 19 months compared with 13 months in unmethylated MGMT promoter tumors ($P = 0.031$). No correlation was found between MGMT promoter methylation and MGMT expression, or MGMT expression and survival. In contrast with recent results, CD133 expression was not a predictive mark er in GBM patients. Analyses of possible correlation between CD133 expression and MGMT protein expression or MGMT promoter methylation were negative.
Conclusions: Our results support the hypothesis that MGMT promoter methylation status but not MGMT expression may be a predictive biomarker in the treatment of patients with GBM. In addition, CD133 should not be used for prognostic evaluation of thes e patients. Future studies will be necessary to determine its clinical utility.
No conflict of interest.

3367 POSTER

Nanoparticles releasing zoledronic acid have antitumor activity against experimental models of human glioblastoma

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Background: Tumours localized in the brain are poorly sensitive to treatments for the intrinsic resistance of tumor cells and for the presence of the blood–brain barrier (BBB). The emerging field of cancer nanotechnology holds promise in the use of nanoparticles to allow the crossing of drugs thorough the BBB. Zoledronic acid (ZOL) is commonly used as antiresorptive agent in the treatment of cancer-related bone disease. On the other hands, ZOL has a direct antitumour activity by inducing apoptosis on different cancer cell types, but it accumulates almost exclusively in the bone not reaching tumour cells. Based on this background, our aim was to study the antitumor efficacy of nanoparticles releasing ZOL against human glioblastoma.
Materials and Methods: Self-assembly PEGylated nanoparticles (NPs), based on calcium/phosphate NPs and cationic liposomes, were optimized to achieve NPs easily prepared before use. The targeting of ZOL in the brain was improved by designing NPs functionalized with transferrin (TRF) able to bind specific receptors on endothelial cells of BBB. The in vitro cytotoxic activity of NPs-ZOL was tested on different glioblastoma cell lines (U373, LN229 and U87-MG) by MTT and clonogenic assay. The antitumor efficacy of NPs-ZOL was evaluated in vivo on heterotopic and orthotopic glioblastoma xenografts by injecting luminescent glioblastoma cells and tumor growth analyzed by an imaging system.
Results: NPs-ZOL strongly inhibited the growth of glioblastoma cells showing an IC50 that was ten times lower than ZOL free and, surprisingly, twenty times lower than Temozolomide. Moreover, this new formulation had higher antitumor efficacy than that one caused by ZOL free in mice-bearing glioblastoma tumors implanted intramuscularly in mice. More interestingly, we observed that i.v injected TRF-NPs were able to overcome BBB since fluorescent NPs were detected in the brain of mice bearing glioblastoma.

Finally, preliminary experiments showed that TRF-NPs-ZOL reduce the growth of orthotopic model of U373-MG-LUC xenografts.
Conclusions: The demonstration of NPs-ZOL to brain tumor localization and assessment of antitumor activity of this formulation opens a new scenario in which NPs-ZOLcould have a strong impact for the treatment of brain tumors, for which a paucity of effective treatments exists.
No conflict of interest.

Proffered Papers Session (Sat, 28 Sep)
Lung Cancer − Localised and Metastatic

3400 ORAL

Impact of crizotinib on patient-reported symptoms and global quality of life (QoL) compared with chemotherapy in a phase III study of advanced alk-positive non-small cell lung cancer (NSCLC)

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Background: The main objective of our analysis was to compare patient-reported symptom and global QOL improvement rates between crizotinib and standard-of-care chemotherapy (pemetrexed or docetaxel) in previously treated patients with advanced *ALK*-positive NSCLC in the ongoing PROFILE 1007 study (Pfizer; NCT0093283).
Methods: 172 patients were randomized to crizotinib and 171 to standard-of-care chemotherapy. Patient-reported outcomes were assessed at baseline, on day 1 of each cycle, and at the end of treatment using EORTC QLQ-C30 and lung cancer module QLQ-LC13. Higher scores (range 0–100) indicated higher symptom severity or better functioning/QOL. A clinically meaningful change was defined as a $\geqslant$10-point change from baseline. The percentage of patients classified as having improved ($\geqslant$10-point increase for functioning scales and $\geqslant$10-point reduction for symptoms in average of change from baseline scores across cycles for a patient) or worsened ($\geqslant$10-point reduction for functioning and $\geqslant$10-point increase for symptoms in average of change from baseline scores across cycles) was examined. Relative risk ratios were calculated for improvement rates in key lung cancer symptoms and differences in rates between treatment groups were tested for statistical significance using chi-square tests.
Results: Completion rates at baseline were $\geqslant$90% in each group and scores were well balanced. Relative risk ratios (95% CI) for improvement rates favored the crizotinib versus the chemotherapy arm for the following lung cancer symptoms: cough (1.7 [1.3−2.2]), dyspnea (2.3 [1.5−3.4]), and pain in chest (1.8 [1.3−2.6]). A significantly greater percentage of patients in the crizotinib versus the chemotherapy arm showed improvements for global QOL (42.6% vs. 20.7%; $p < 0.001$), physical functioning (27.2% vs. 11.9%; $p < 0.001$), role functioning (30.9% vs. 14.6%; $p < 0.001$) emotional functioning (37.0% vs. 24.0%; $p < 0.05$), fatigue (46.3% vs. 20.5%; $p < 0.001$), pain (43.8% vs.20.5%; $p < 0.001$), cough (55.3% vs. 33.3%; $p < 0.001$), dyspnea (39.1% vs. 17.3%; $p < 0.001$), pain in chest (40.0% vs. 22.3%; $p < 0.001$), and pain in arm or shoulder (33.5% vs. 19.5%; $p < 0.001$). A significantly higher proportion of patients showed worsening of constipation (44.4% vs. 22.5%; $p < 0.001$) and diarrhea (41.4% vs. 19.2%; $p < 0.001$) with crizotinib compared with chemotherapy.
Conclusion: Treatment with crizotinib led to significantly higher improvement rates in global QOL and key lung cancer symptoms compared with chemotherapy.
Conflict of interest: *Ownership: Keith Wilner, Arlene Reisman and Shrividya Iyer − stock ownership: Pfizer. Advisory board: Vera Hirsh − Pfizer Dong-Wan Kim − Pfizer Benjamin Besse − Pfizer. Corporate-sponsored research: Fiona Blackhall − Pfizer Benjamin Besse − Pfizer. Other substantive relationships: Fiona Blackhall − honoraria: Pfizer Keith Wilner, Arlene Reisman and Shrividya Iyer − employment: Pfizer Alice Shaw − consultancy services: Pfizer, Novartis, Ariad, Chugai, Daiichi-sankyo*

3401 ORAL

Updated results of a first-in-human dose-finding study of the ALK/EGFR inhibitor AP26113 in patients with advanced malignancies

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Background: AP26113 is a novel tyrosine kinase inhibitor (TKI) that potently inhibits mutant activated forms of anaplastic lymphoma kinase (ALK+) and epidermal growth factor receptor (EGFRm), and TKI-resistant forms including L1196M (ALK) and T790M (EGFR). AP26113 does not inhibit native EGFR.
Methods: The dose finding phase (3+3 design) of this phase 1/2 open-label, multicenter study is ongoing in pts with advanced malignancies (except leukemia) refractory to available therapies or for whom no standard treatment exists. Dosing is once daily (QD) or twice daily (BID).
Results: As of 7 March 2013, 49 pts were enrolled: 30 mg (daily dose) n = 3, 60 mg n = 3, 90 mg n = 8, 120 mg n = 13, 180 mg n = 11, 240 mg n = 9, 300 mg n = 2; 59% female, median age 58 yrs; diagnoses: non-small cell lung cancer (NSCLC, n = 42), other (n = 7). 29 pts discontinued: 19 disease progression, 5 adverse event (AE), 4 deaths (2 possibly related: sudden death, hypoxia), 1 withdrawal by subject. The most common AEs were nausea (43%), fatigue (41%), and diarrhea (35%), which were generally grade 1/2 in severity. The most common grade 3/4 treatment-related AE was diarrhea (4%). 2 dose limiting toxicities were observed: grade 3 ALT increase, 240 mg; grade 4 dyspnea, 300 mg. Doses <300 mg are being explored further. 25 pts had ALK+ history (22 NSCLC, 3 other). Among 21 evaluable ALK+ pts, 13 responded. Among ALK+ pts with $\leqslant$1 prior ALK TKI, responses were observed in 2/3 (67%) TKI-naive pts and 11/15 (73%) pts with prior crizotinib therapy. The longest response is 48 wks (ongoing). Among ALK+ NSCLC pts with prior crizotinib only, 10/14 (71%) responded. 4 of 5 ALK+ pts with untreated or progressing CNS lesions at baseline and with follow-up scans had evidence of radiographic improvement in CNS, including 1 pt resistant to crizotinib and LDK378 (overall response = stable disease). 17 pts had EGFRm history (16 NSCLC, 1 SCLC); 15 pts had $\geqslant$1 prior EGFR TKI. Of 12 EGFRm pts with a follow-up scan, 1 pt (prior erlotinib) responded at 120 mg (duration 21 wks, ongoing), 6 pts had stable disease (1 ongoing).
Conclusions: AP26113 has promising anti-tumor activity in pts with ALK+ NSCLC and other ALK+ tumors, with initial evidence of activity in EGFRm pts, and is generally well tolerated. Phase 2 will begin after the recommended phase 2 dose is determined. Cohorts will include: crizotinib-naive NSCLC; crizotinib-resistant NSCLC; EGFR TKI-resistant NSCLC; other tumors. ClinicalTrials.gov NCT01449461.
Conflict of interest: *Advisory board: DR Camidge has participated in an advisory board for ARIAD. Corporate-sponsored research: CJ Langer has participated in corporate-sponsored research (ARIAD). Other substantive relationships: NI Narasimhan, DJ Dorer, and J Zhang are employees of and hold stock/stock options in ARIAD. AT Shaw has been a consultant/advisor for ARIAD. GJ Weiss has participated in a speaker's bureau for Pfizer.*

3402 ORAL

Pemetrexed (PEM) and cisplatin (CIS) with concurrent thoracic radiation after PEM+CIS induction in patients (pts) with unresectable locally advanced (LA) nonsquamous non-small cell lung cancer (NS-NSCLC): primary results of a phase II study

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Background: Concurrent chemo- and radiotherapy (CT+RT) is standard of care for most pts with unresectable LA NSCLC, but no standard regimen has been established. PEM synergizes with ionizing radiation and CIS in preclinical models. PEM+CIS doublets showed efficacy and

favourable toxicity profiles in Phase I/II studies of NS-NSCLC. This single-arm multicenter Phase II study investigated efficacy and safety of PEM+CIS induction followed by full-dose PEM+CIS plus concurrent RT in pts with LA NS-NSCLC.

Materials and Methods: Pts with unresectable Stage IIIA/IIIB NS-NSCLC, ECOG performance status (PS) 0−1 and forced expiratory volume (FEV) >50% of predicted normal FEV received two 21-day cycles of PEM 500 mg/m^2 + CIS 75 mg/m^2 on Day 1. Pts who had not progressed, had no residual neurological toxicity >Grade(G) 2, PS 0−1 and lung V20 <35% then received 2 cycles of the same full-dose PEM+CIS regimen plus concurrent thoracic RT of 2 Gy/fraction, 5d/wk for 7wks (66 Gy total). All pts received vitamin supplementation/dexamethasone prophylaxis as per PEM-label. Primary endpoint was the 1 yr progression-free survival (PFS) rate. A minimum of 53 events was required to provide 90% power to demonstrate an improvement of the 1 yr PFS rate from 45% (historical data) to 60% at a 2-sided alpha level of 5%, resulting in a sample size of 88 pts assuming 10% dropouts. Secondary data presented include tumor response and toxicity.

Results: 90 pts were enrolled in 4 countries: median age 61 yrs, male/female 57%/43%, ECOG PS 0/1 66%/34%, mean (SD) FEV 2.3 (0.62)L, adenocarcinoma 90%, Stage IIIA/IIIB 36%/62% (2 pts had Stage IV and discontinued before starting RT). 75 pts (83.3%) completed induction CT and started concurrent CT+RT. 63 of the 75 pts (84.0%) received all 4 CT cycles and full RT of 66 Gy. Median PEM+CIS dose intensities were >97% during concurrent CT+RT, median RT dose was 66 Gy (range 18−66 Gy). The 1 yr PFS rate was 51.3% (95% CI 42.0–60.5). After a median follow-up of 24 months, median PFS was 10.6 months (95% CI 8.6–17.3). Response data are shown as table. One pt died from study-drug related toxicity (enteritis) during Cycle 4. Four pts discontinued due to non-fatal drug- or radiation related adverse events, 1 on induction CT (renal failure), 3 on concurrent CT+RT (hypoacusis, 2x radiation esophagitis). During induction CT, 18.9% of pts reported G3/4 CTCAEs, only neutropenia (2.2%) and syncope (2.2%) were reported by >1 pt. During concurrent CT+RT, 41.3% of 75 pts reported G3/4 CTCAEs, mainly esophagitis (12.0%), neutropenia (10.7%) and leukopenia (9.3%). One pt experienced G3 mucositis and 1 pt showed G3 acute pneumonitis.

Conclusions: In this study of PEM+CIS induction followed by full-dose PEM+CIS with concurrent thoracic RT, the 1 yr PFS rate (51.3%) was in the same range as previously observed with other CIS-based induction CT followed by CT+RT (40−50%). Of note, 7 pts had CR. Main G3/4 toxicities during concurrent CT+RT included esophagitis, neutropenia and leukopenia.

Conflict of interest: *Ownership: None. Advisory board: Yes: Lilly, Roche, Boeringher, Astra-Zeneca, Celgene. Board of directors: No. Corporate-sponsored research: Yes, this study (Eli Lilly). Other substantive relationships: None.*

Table: Best tumor response in 90 patients

Best tumor response	n	(%)
CR	7	(7.8)
PR	46	(51.1)
SD	17	(18.9)
PD	12	(13.3)
NE	8	(8.9)
RR (CR+PR)	53	(58.9; 95% CI 48.0–69.2)
DCR (CR+PR+SD)	70	(77.8; 95% CI 67.8–85.9)

3403 ORAL

Treatment compliance of customized postoperative chemotherapy after NSCLC resection: A toxicity/safety analysis of SCAT (Spanish Customized Adjuvant Therapy) trial − Spanish Lung Cancer Group/GECP

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Background: Adjuvant platinum-based CT improves outcomes in resected NSCLC with nodal involvement but is still insufficient to provide optimal survival. Better risk selection or customized selected therapy needs to be explored. mRNA BRCA1 levels are prognostic in early NSCLC and could be a predictive marker for CT activity. In advanced disease patients with low BRCA1 benefit from cisplatin doublets meanwhile p with high levels attained longer survival with taxanes. Customization is feasible in adjuvant setting (tissue availability). Compliance is a key issue in adjuvant setting.

Methods: Phase III trial testing 4 cycles non-selected vs selected adjuvant CT. Entry criteria: NSCLC, R0 resection, pN1 or pN2, KI >70, recovered from surgery, adequate hematologic, renal and liver functions, no prior CT or RT, age >18 y, informed consent. Stratification: N1 vs N2, histology (squamous vs non-squamous), resection (lobectomy vs pneumonectomy). Central lab mRNA BRCA1 levels and quartile distribution. Primary end-point: DFS. Secondary end-points: OS, toxicity, recurrence pattern. Design: R: 1:3. Control treatment: Cis-Docetaxel (CD). Experimental arm: Q1: Cis-Gemcitabine (CG); Q2−3: Cis-Docetaxel; Q4: Docetaxel (D). PORT in pN2 patients. Analysis adjuvant CT toxicity profile (CTC-AE) and treatment compliance between arms.

Results: 461 included p; 108 control arm, 353 experimental arm. mRNA BRCA1 expression: Q1 162, Q2−3 98, Q4 93. M/F ratio: 82.5/17.5%. Median age: 62 (range 36−80). PS 0/1/2: 55.9/43.1/1%. Histology: Adenocarcinoma 47.5%, Squamous 44.1%. Stages: IIA/IIB/IIIA: 11.1/38.4/50.2%. Surgical procedure: Lobectomy 72.1%; Pneumonectomy 27.9%. Overall low levels BRCA1: 43.8%. Toxicity/compliance assessed in 297 p. G3−4 AE: Neutropenic fever: CD 10% vs D 4.4% vs CG 0%. ($p = 0.0056$); Nausea/vomits: CG 11.1% vs CD 10.4% vs D 0%. ($p = 0.0198$); Hypersensitivity: D 5.97% (NS). Dose-reduction: 34.24% control vs 18.30% experimental ($p = 0.0044$). Full 4 cycles CT compliance: CD control 80.83%, CG 91.2%, CD experimental 79.2%, D 88.1% ($p = 0.052$). PORT compliance 55.31% of planned cases.

Conclusions: Majority of resected NSCLC showed low levels expression BRCA1. Safety profiles differences observed between treatment schedules: neutropenic fever (CD), nausea/vomits (CG). Customized treatment requires less dose-reductions. Trend to poor compliance with Cis-Doc. Low compliance for PORT.

No conflict of interest.

3404 ORAL

Resistance training in patients with radically treated respiratory cancer: A prospective randomized multi-center study (REINFORCE)

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Background: Patients with respiratory cancer improve their post-radical treatment exercise capacity, muscle strength and quality of life (QOL) by conventional resistance training (CRT). Whole body vibration (WBV) is proposed as an alternative to CRT.

Aim: To investigate by a RCT with a 2-tier design, the effect of radical treatment and of 2 post-treatment resistance training programs on functional and maximal exercise capacity, muscle strength and QoL, as measured respectively by the 6 minutes walking distance (6MWD), Wmax, Quadriceps Force (QF), and scores for physical functioning (PF), fatigue (F), pain (P) and dyspnoea (D).

Methods: Patients with clinical stage I−IIIB (non-)small cell lung cancer (N- SCLC) or I−II mesothelioma were evaluated before (M1) and after (M2) completion of either radical surgery (RS) +/− platin-based chemotherapy (PCT) or radiotherapy (RT) or RT +/− PCT, and were randomized to either to usual care (UC), CRT or WBV. 6MWD (primary endpoint), Wmax, QF and PF, F, P and D were measured at M1, M2 and 12 weeks (w) after intervention (M3). A minimal clinical important difference (MCID) in 6MWD was considered 54 m. Within and in-between treatment arm changes in 6MWD were estimated using a linear and logistic regression model.

Results: Of the 121 patients evaluated at M1, 70 were randomized to UC: n = 24, CRT: n = 24 and WBV: n = 22. M1-characteristics were well balanced: male 73%, median age 62 y (29−79); median BMI 25 kg/m^2 (16−42); 40% had COPD, 91% NSCLC and 60% stage I−II. 48% had RS and 6% RT as sole therapy, 46% a combination of RS or RT with PCT and/or PORT; 19% had a pneumonectomy. A median of 28 CRT-sessions (10−36) and 23 WBV-sessions (0−37) were attended with a median M2-M3 interval of 14 w (9−30). Radical treatment significantly decreased all variables at M2: Δ6MWD: 20 m (−295–130); ΔWmax: −18 Watt (−119−34); ΔQF: −12 Nm (−117–102); ΔPF: −7 points (−60−40); ΔF: 2 points (−29−30), ΔP: 1 point (−8−8) and ΔD: 1 point (−7−8), $p < 0.05$ to M2. 6MWD at M3 increased with 95 m (58–132) in CRT ($p < 0.0001$), 37 m (−1−76) in WBV ($p = 0.06$) and 1 m (−34−36) in UC (CRT vs. UC $p = 0.0006$ and WBV vs. UC $p = 0.16$). A significant increase of Wmax and PF in both CRT and WBV

was seen at M3 ($p < 0.05$). Only QF increased significantly ($p = 0.0009$) after CRT and D significantly decreased in WBV patients ($p = 0.009$). M3 values did not significantly exceed M1 ones with either intervention. In multivariate analysis, RS was independently associated with the likelihood to reach the MCID of 6 MWD (OR: 15.6 (1.87 −129, 8) ($p = 0.011$).
Conclusions: Exercise capacity, muscle strength and QOL significantly decrease by any radical treatment and are restored by resistance training. WBV does not substitute for CRT. Surgically treated patients benefit most. CRT should be offered to patients with radically treated lung cancer and mesothelioma. Supported by a research grant of IWT-TBM the Clinical Research Fund of Ghent University Hospital). (clintrials.gov NCT00752700)
No conflict of interest.

3405 ORAL

Radical surgery as treatment option in advanced NSCLC − a retrospective analyses of 80 NSCLC patients of the TYROL lung cancer registry

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Introduction: In various advanced tumors (e.g. melanoma, colorectal carcinoma, sarcoma), metasasectomy is part of standard treatment for selected patients. The clinical significance of metastasectomy in advanced non-small-cell lung cancer (NSCLC) is still unclear, and scientific evidence is limited. We present a retrospective analysis in 80 advanced NSCLC patients, who underwent radical metastasectomy in an either synchronous or metachronous setting.
Methods: In the TYROL (Twenty Years Retrospective of Lung) Cancer Registry, >2500 lung cancer cases are documented, and 80 patients were subjected to radical surgery in an advanced stage of disease. Using SPSS statistics, clinical characteristics were analyzed descriptively, and outcome in stratified subgroups was calculated by event-time analyses.
Results: 58 patients (73%) were male; at time of palliative surgery, median age was 62 years (range: 36−82). 24/44 evaluable cases were smokers (55%), 10/44 former smokers (23%), and 3/44 never smokers (7%). 37/48 (77%) were in favorable ECOG PS 0−1. Histologically, 41/80 patients had adenocarcinoma (51%), 21 (26%) squamous, 7 adenosquamous (9%) and 11 (14%) other carcinoma. 37/80 (46%) had surgery, the rest combined modality treatment (20 chemotherapy, 12 radiotherapy, 11 chemo- & radiotherapy). 28 (35%) underwent radical resection of primary tumor and limited metastasis ('synchronous'), whereas 52 (65%) had later resection of metastasis ('metachronous': singular pulmonal [n = 17]; pulmonal & mediastinal [12]; brain [12]; 5 renal/suprarenal [5]; liver, chest wall, soft tissue [2 each]). At last follow-up, 46 were dead (58%). Median PFS and OS from palliative resection were 12.1 months and 33.4 months, respectively. In patients with metachronous metastasectomy, PFS was inferior if the interval was <2 years from primary surgery (5.9 vs. 37.9 months; $p < 0.001$) and anemia was present (5.1 vs. 14.9 months, $P = 0.001$). Likewise, OS was inferior in case of an interval <2 years (20.7 vs. 57 months; $p = 0.002$) and anemia (12.6 vs. 33.4 months, $p < 0.001$).
Conclusion: In selected patients with advanced NSCLC, radical surgery might be an attractive option. Especially patients with a long disease free interval from first treatment to progression and without anemia benefited.
No conflict of interest.

Proffered Papers Session (Sun, 29 Sep)
Lung Cancer − Metastatic

3406 ORAL

Evaluation of protein expression by immunohistochemistry in non-small cell lung cancer (pharmacogenoscan study)

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Background: Platinum-based chemotherapy regimens are the standard treatment of metastatic non-small cell lung cancer (NSCLC). In this study, our objective was to identify proteic biomarkers that may predict a benefit from these treatments.
Methods: The 'Pharmacogenoscan' study (NCT 00222404) included 537 patients with chemotherapy-naive NSCLC from each stage between 2005 and 2010 in 6 hospitals in the Rhône-Alpes-Auvergne region in France. We collected tumor tissue samples and evaluated the expression by immunohistochemistry (IHC) of 8 biomarkers: ERCC1, BRCA1, p53, $p27^{kip1}$, class III β-tubulin (TUBB3), Bax, Fas and FasL. High and low expression marker status was determined by the median of intensity x positivity rate score for each protein. Results were correlated with objective tumor response after 2 or 3 cycles of platinum-based chemotherapy using standard RECIST criteria, progression-free survival (PFS) and overall survival (OS). Given the number of statistical tests, the Bonferroni correction was used.
Results: Two hundred twenty nine patients had a suitable tumor tissue specimen for evaluating the expression of at least one biomarker. Only TUBB3 expression levels were significantly higher in adenocarcinoma tumors ($p=8.10^{-4}$). Tumors with under-expression of ERCC1 were more frequently metastatic (ns). No significant association was found between the level of biomarkers' expression and tumor response or survival (PFS or OS). However, patients with TUBB3-negative and FasL-negative tumors had a tendency towards a better response to platinum-based chemotherapy with respectively 89% vs. 79% objective response rate (ORR) in the TUBB3-positive group (ns) and 90% vs. 81% ORR in the FasL-positive group (ns).
Conclusion: Immunohistochemical biomarkers cannot be recommended as predictors of response to chemotherapy. Our negative results on a large cohort do not allow assigning any prognostic or predictive role of these biomarkers.
No conflict of interest.

3407 ORAL

Does KRAS mutation status predicts for chemoresistance in advanced non-small cell lung cancer (NSCLC)?

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Background: Clinical implications of KRAS mutation status in advanced NSCLC remain unclear. While K-RAS mutation seems to be correlated with resistance to EGFR TKI, its predictive value regarding efficacy of chemotherapy (CT) is debated. We retrospectively explored whether KRAS mutations could impact on tumor response during first line platinum-based CT as well as on progression-free survival (PFS) and overall survival (OS).
Methods: Between June 2009 and June 2012, 340 patients with advanced (stage IIIB/IV) NSCLC were retrospectively reviewed in a single institution (Institut Gustave Roussy). Two hundred and one patients had a biomolecular profile and a platinum-based first line CT. Patients with an unknown mutational status or with actionable abnormalities (i.e. EGFR, PI3K, HER2, BRAF, FGFR4, ERBB4, PTEN, NRAS, and STK11 mutations; as well as HER2, FGFR1, and MET amplification; ALK translocation), were excluded. We retained two groups: patients with an exclusive KRAS mutation (MUT) and patients with wild type KRAS and wild-type EGFR (WT). Multivariate analyses with logistic or Cox model were used.
Results: One hundred and eight patients were studied: 39 in MUT group and 69 in WT group. Radiological presentation before 1st line chemotherapy demonstrated an excess of brain and liver metastases in MUT patients (33% vs. 13%, $p = 0.01$; 21% vs. 7% $p = 0.04$, Fisher). The disease control rate (DCR) of 1st line CT was 76% for MUT vs. 91% for WT group ($p = 0.04$, in uni and multivariate analysis), with no difference for type of platinum-based CT (use of pemetrexed or not). In second line setting, no statistically significant difference was observed on DCR ($p = 0.32$) between MUT and WT. At 24 months there was no statistically significant difference in PFS (4.8 vs. 7.3 months; $p = 0.27$) and in OS (10.3 vs 13.2 months; $p = 0.37$) between MUT and WT in uni and multivariate analysis.
Conclusion: KRAS mutant cancer is probably a different disease with greater incidence of hepatic and cerebral metastasis in advanced setting. KRAS mutant patients showed a lower DCR rate in 1st line platinum-based CT (independently of pemetrexed use or not), but this small difference did not translated in a PFS or OS difference in multivariate analysis.
No conflict of interest.

3408 ORAL

Clinical activity, safety and biomarkers of PD-L1 blockade in non-small cell lung cancer (NSCLC): Additional analyses from a clinical study of the engineered antibody MPDL3280A (anti-PDL1)

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Background: Mutational complexity may be associated with increased tumor immunogenicity. In lung cancer, the antitumor immune response may be inhibited by PD-L1 expression. MPDL3280A, a human monoclonal Ab containing an engineered Fc-domain designed to optimize efficacy and safety, aims to restore tumor-specific T-cell immunity by blocking PD-L1 from binding to its receptors, including PD-1 and B7.1.
Materials and Methods: Pts with squamous or nonsquamous NSCLC received MPDL3280A IV q3w in a Ph I expansion study. Pts were treated for up to 1 y. Objective response rate (ORR) was assessed by RECIST v1.1. Reported ORR includes u/cCR and u/cPR. Cigarette smoking history was captured at baseline.
Results: As of Feb 1, 2013, 53 NSCLC pts were evaluable for safety and treated at doses of 0.03 (n = 1), 1 (n = 1), 10 (n = 10), 15 (n = 19) and 20 mg/kg (n = 22). Pts received treatment for a median duration of 106 days (range 1–450) of MPDL3280A. The incidence of all G3/4 AEs, regardless of attribution, was 34%, including pericardial effusion (6%), dehydration (4%), dyspnea (4%) and fatigue (4%). No G3−5 pneumonitis or diarrhea was reported. 37 NSCLC pts enrolled prior to Jul 1, 2012, were evaluable for efficacy. An ORR of 24% (9/37) was observed in pts with squamous and nonsquamous histologies with a duration of response range of 1+ to 214+ days. All responses were ongoing or improving. Additional pts had delayed responses after apparent radiographic progression (not included in the ORR). The 24-week PFS was 46%. Analysis of biomarker data from archival tumor samples demonstrated a correlation between PD-L1 status and efficacy. Pts with PD-L1-positive tumors showed an ORR of 100% (4/4), while pts who were PD-L1 tumor status-negative had an ORR of 15% (4/26). 84% (31/37) of pts were either former or current smokers, and 16% (6/37) of pts were never smokers. The response rate in the former or current smokers group was 25% (8/31) versus 16% (1/6) in the never smoker group. The median pack year history was 15 pack years for responders versus 5 pack years for pts with PD as best overall response. Updated data will be presented.
Conclusions: Treatment with MPDL3280A was well tolerated, with no pneumonitis-related deaths. Rapid and durable responses were observed, and PD-L1 tumor status correlated with response to MPDL3280A. In addition, preliminary data suggest that the number of responders was numerically higher for former/current smokers versus never smokers.
Conflict of interest: *Advisory board: Roche, Genentech. Corporate-sponsored research: Roche, Genentech. Other substantive relationships: Roche, Genentech*

3409 ORAL

Analysis of overall survival in adenocarcinoma NSCLC patients receiving 2nd line combination treatment with nintedanib (BIBF 1120) + docetaxel in the LUME-Lung 1 trial: A randomized, double-blind, placebo-controlled phase 3 study

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Background: Nintedanib (N) is an oral inhibitor of VEGFR, FGFR, and PDGFR. LUME Lung 1, a placebo (P) controlled phase 3 trial investigated N + docetaxel (D) in locally advanced/metastatic NSCLC patients (pts) progressing after 1st line chemotherapy (NCT00806819).
Methods: Stage IIIB/IV or recurrent NSCLC pts were stratified by histology, ECOG PS, prior bevacizumab and brain metastases, randomized to N 200 mg bid + D 75 mg/m^2 q21d (n = 655) or P + D (n = 659) and treated until progression or unacceptable adverse events (AEs). 1º endpoint was centrally reviewed progression free survival (PFS) analysed after 714 events; the key 2º endpoint was overall survival (OS) analysed hierarchically after 1121 events first in adenocarcinoma (adeno) pts <9 mo since start of 1st line therapy (T<9 mo; identified as a predictive biomarker [ASCO 2013; ESMO 2013]), followed by all adeno pts and then all pts.
Results: 1,314 pts were recruited (658 adeno, 554 squamous, 102 other histology). Pt characteristics were balanced between the arms. N + D significantly prolonged median (m) PFS vs P + D regardless of histology (3.4 vs 2.7 mo, HR 0.79, 95% CI: 0.68–0.92, p = 0.0019) with a trend for improved mOS (10.1 vs 9.1, HR 0.94; CI: 0.83–1.05; p = 0.272). In adeno pts N + D (n = 322) significantly prolonged mOS vs P + D (n = 336) (12.6 vs 10.3 mo, HR 0.83; CI: 0.70–0.99; p = 0.0359). The treatment effect was observed early and was consistently maintained over time (Table). The greatest mOS improvement was observed in T<9 mo adeno pts randomised to N (n = 206) vs P (n = 199) (10.9 vs 7.9 mo, HR 0.75; CI: 0.60–0.92, p = 0.0073). Common non-haematologic AEs (N vs P) in adeno pts were diarrhea (any: 43.4 vs 24.6%; Gr⩾3: 6.3 vs 3.6%) elevated ALT (37.8 vs 9.3%; 11.6 vs 0.9%) and fatigue (30.9 vs 29.4%; 4.7 vs 4.2%). Incidence of CTCAE Gr⩾3 AEs was 75.9 vs 68.5%. Withdrawals due to AEs (20.9 vs 17.7%) were similar in both arms, as were Gr⩾3 hypertension, bleeding and thrombosis.
Conclusions: 2nd line treatment with N + D improved OS for adeno NSCLC pts significantly and consistently over time. AEs were generally manageable with dose reductions and symptomatic treatment.

Table: OS probabilities in adeno pts over time

Time since study start (mo)	N + D (n = 332)			P + D (n = 336)		
	n at risk*	n (%) events*	OS probability	n at risk*	n (%) events*	OS probability
6	230	86 (26.7)	0.729	219	99 (29.5)	0.692
12	163	149 (46.3)	0.527	139	176 (52.4)	0.447
18	113	196 (60.9)	0.374	88	223 (66.4)	0.293
24	72	231 (71.7)	0.257	55	253 (75.3)	0.191

*Cumulative.

Conflict of interest: *Advisory board: Reck M: Lilly, Hoffmann-La Roche, Pfizer, AstraZeneca. von Pawel J: Daiichi-Sankyo, Pfizer, Boehringer. Douillard JY: Boehringer Ingelheim, Roche, AstraZeneca. Corporate-sponsored research: Douillard JY: Merckserono. Other substantive relationships: Barrueco JR: Employee Boehringer Ingelheim Pharmaceuticals Inc., USA. Kaiser R, Hocke J: Boehringer Ingelheim Pharma GmbH & Co KG. Douillard JY: Honoraria for symposia, Roche, AstraZeneca.*

3410 ORAL

MARQUEE: A randomized, double-blind, placebo-controlled, phase 3 trial of tivantinib (ARQ 197) plus erlotinib versus placebo plus erlotinib in previously treated patients with locally advanced or metastatic, non-squamous, non-small-cell lung cancer (NSCLC)

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Background: In a randomized phase 2 study, the combination of tivantinib (T), a selective MET inhibitor, plus erlotinib (E) improved progression-free survival (PFS) and overall survival (OS) compared with placebo (P) plus E in the subset of patients with nonsquamous histology, a population enriched for MET overexpression.
Material and Methods: Patients with locally advanced or metastatic nonsquamous NSCLC previously treated with 1 or 2 lines of systemic therapy, including a platinum-doublet, were stratified by number of prior

therapies, sex, smoking history, and *EGFR* and *KRAS* mutation status, then randomized (1:1) to oral T (360 mg twice daily) + E (150 mg once daily) or P+E until disease progression. Prior treatment with an EGFR inhibitor was not allowed. The primary endpoint was OS, with 1 interim analysis and stopping boundaries for futility and superiority. Secondary and exploratory objectives included PFS, OS in molecular subgroups, and safety.
Results: From Jan 2011 to Jul 2012, 1048 patients were randomized to T+E (n = 526) or P+E (n = 522). Baseline characteristics included median age of 62 y (range, 24−89 y), prior therapies =1 (66%) or 2 (34%), ECOG performance status of 0 (32%) or 1 (68%), *EGFR* mutant (10.4%), and *KRAS* mutant (27.1%), and were well balanced between arms. In Sep 2012, the independent data monitoring committee recommended trial discontinuation because the pre-planned interim analysis crossed the futility boundary. At the Dec 2012 data cutoff, median OS was 8.5 mo (95% confidence interval [CI], 7.1−9.3 mo) in the T+E arm and 7.8 mo (95% CI, 7.0−9.0 mo) in the P+E arm (hazard ratio [HR]=0.98; 95% CI, 0.84–1.15; $P = 0.81$). Median PFS was 3.6 mo (95% CI, 2.8−3.7 mo) in the T+E arm and 1.9 mo (95% CI, 1.9−2.0 mo) in the P+E arm (HR = 0.74; 95% CI, 0.62–0.89; $P < .0001$). Overall response rate (ORR) improved to 10.3% in the T+E arm compared with 6.5% in the P+E arm ($P < .05$). Common adverse events (T+E arm vs P+E arm, respectively) included rash (33.1% vs 37.3%), diarrhea (34.6% vs 41.0%), and asthenia/fatigue (43.5% vs 38.1%), which occurred at similar rates between treatment arms; neutropenia (Grade 3/4: 10.0% vs 1.0%) was more common with tivantinib.
Conclusions: Addition of tivantinib to erlotinib did not achieve the primary endpoint of improved OS. However, the combination is well tolerated and biologically active with substantial improvement in PFS and ORR. Analysis of molecular subgroups, including MET expression, is ongoing.
Conflict of interest: *Ownership: D Shuster: stock ownership in Daiichi Sankyo, Inc.; B Schwartz: stock ownership in ArQule, Inc. Advisory board: F Barlesi: Daiichi Sankyo, Inc. and Roche; J von Pawel: Daiichi Sankyo, Inc. and Pfizer; A Sandler: Daiichi Sankyo, Inc. and Genentech/Roche (competitor); G Scagliotti: Eli Lilly, AstraZeneca, Doche, Pfizer. Corporate-sponsored research: R Ramlau: Arqule, Inc.; D Shuster: Daiichi Sankyo, Inc.; A Sandler: Daiichi Sankyo, Inc. and Genentech/Roche. Other substantive relationships: F Barlesi: Daiichi Sankyo, Inc. (sponsored presentation); D Shuster: Employee of Daiichi Sankyo, Inc.; A Sandler: Speakers bureau − Genentech/Roche; B Schwartz: Employee of ArQule Inc.*

3411 ORAL

Safety and efficacy profile of crizotinib in the French Temporary Authorization for Use (ATU) of crizotinib in patients (pts) with ALK-positive (+) advanced NSCLC

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Background: Crizotinib is a selective tyrosine kinase inhibitor of MET, ALK and ROS1 approved in the US on Aug 2011 for advanced ALK+ NSCLC and in Europe on Oct 2012 for previously treated advanced ALK+ NSCLC. The ATU program is an exceptional measure allowing drug availability before Marketing Authorisation Approval. We report the efficacy and safety data of crizotinib in ALK+ NSCLC pts included in a French ATU. ALK testing was performed by genetics platforms funded by French National Cancer Institute.
Methods: The ATU included pts not eligible for a clinical trial with advanced ALK+ NSCLC (assessed by FISH or immunohistochemistry [IHC]) or other ALK+ tumors. Pts received 250 mg bid crizotinib until disease progression or intolerance. The clinicians were asked to provide data on efficacy and tolerance of crizotinib every 3 months. Data cut-off for the present analysis was Oct 13th, 2012 for efficacy and demographic data and July 12th, 2012 for safety.
Results: From Dec. 1st, 2010 to Oct. 13th, 2012, 254 pts were included in the ATU, among whom 241 metastatic NSCLC pts with a median age of 57 (17−87). Baseline characteristics: 50.2% females, PS 0/1/2/3 (%): 30/46/16/8, 31% with brain metastases; 2%, 45%, 27%, 26% of pts received 0, 1, 2 and ⩾3 previous lines of therapy (up to 6), respectively. Discrepancies between IHC and FISH ALK tests were observed in 12 (7.5%) pts. Median duration of treatment for all pts (not mature) was 3.25 months (range 0.03 months − 14.0 months). 91 pts were assessable for response with CR: 4.4%, PR: 61.5%, SD: 29.7% and PD: 4.4%. 187 pts were assessable for toxicity. Most frequent reported AEs were visual disturbances (n = 15), neutropenia (n = 12), edema (n = 8), nausea (n = 8) and diarrhea (n = 7). Five serious AEs related to hepatitis were observed. Treatment was permanently discontinued for toxicity in 9 pts. Final safety and efficacy are being evaluated, including response rates for PS 3 pts, heavily pretreated pts and pts with brain metastases.
Conclusions: These interim results of efficacy and toxicity of crizotinib in ALK-positive advanced NSCLC patients in routine clinical practice do not differ from data previously reported in clinical trials. Updated results will be presented at the meeting.
Conflict of interest: *Advisory board: Pfizer: M. Perol,J. Cadranel, D. Planchard, E. Dansin, D. Moro-Sibilot, B.Besse,. Board of directors: Pfizer: A. Buturuga. Corporate-sponsored research: Pfizer*

Poster Discussion Session and Poster Session (Sun, 29 Sep)
Lung Cancer

3412 POSTER DISCUSSION

Impact of crizotinib on patient-reported general health status compared with single-agent chemotherapy in a phase III study of advanced ALK-positive non-small cell lung cancer (NSCLC)

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Background: The present analysis compares patient-reported general health status between crizotinib and standard-of-care chemotherapy (pemetrexed or docetaxel) in previously treated patients with advanced *ALK*-positive NSCLC.
Material and Methods: Patients in the ongoing PROFILE 1007 study (Pfizer; NCT00932893) were randomized to crizotinib (n = 172) or chemotherapy (n = 171). Patient-reported outcomes were assessed at baseline, on day 1 of each cycle, and at the end of treatment using EQ-5D, a standardized measure of health status that consists of a descriptive system comprising 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression rated at 3 levels (no, some, or extreme problems) and a single index score for health status (range 0 [dead] to 1 [full health]) calculated using a standard algorithm. In addition, a visual analog scale (VAS) measured self-rated health status from '0' (worst imaginable) to '100' (best imaginable). Descriptive statistics were reported. Repeated measures mixed-effects analyses were performed to compare overall index and change from baseline VAS scores between the treatments, controlling for baseline.
Results: Completion rates at baseline were ⩾85% in each group. The mean (SD) scores at baseline were comparable between crizotinib and chemotherapy for the VAS (64.09 [21.04] vs 66.76 [20.74]) and the EQ-5D index scores (0.72 [0.25]) vs (0.69 [0.26]). The proportion of patients reporting the presence of a problem at baseline for crizotinib and chemotherapy, respectively, were: mobility (31% vs 32%), self-care (9% vs 14%), usual activities (51% vs 52%), pain (62% vs 67%), and anxiety/depression (49% vs 57%). The overall mean (SD) EQ-5D index scores on treatment were significantly greater ($p < 0.001$) for crizotinib (0.82 [0.01]) compared with chemotherapy (0.73 [0.02]). A statistically significant ($p < 0.05$) improvement in VAS score was observed early and maintained (cycles 2−15) in the crizotinib arm compared with no significant change in the chemotherapy arm. A significantly greater overall improvement from baseline was observed in VAS scores in the crizotinib arm compared with chemotherapy (4.68 vs −6.06; $p < 0.001$).
Conclusion: Treatment with crizotinib leads to a significantly greater improvement in general health status compared with chemotherapy in previously treated patients with advanced *ALK*-positive NSCLC.
Conflict of interest: *Ownership: Keith Wilner, Arlene Reisman and Shrividya Iyer − stock ownership with Pfizer Inc. Advisory board: Vera Hirsh − Pfizer Canada Dong-Wan Kim − Pfizer Inc Benjamin Besse − Pfizer Inc. Corporate-sponsored research: Fiona Blackhall − Pfizer Inc Benjamin*

Besse − Pfizer Inc. Other substantive relationships: Fiona Blackhall − received honoraria from Pfizer Inc Keith Wilner, Arlene Reisman and Shrividya Iyer − employed by Pfizer Inc Alice Shaw − consultancy for Pfizer Inc, Novartis, Ariad, Chugai, Daiichi-sankyo

3413 POSTER DISCUSSION

Clinical experience with crizotinib in patients (pts) with advanced ALK+ non-small cell lung cancer (NSCLC) and brain metastases

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Background: Crizotinib is an oral tyrosine kinase inhibitor targeting ALK and is approved in several countries for the treatment of advanced *ALK+* NSCLC. PROFILE 1005 (NCT00932451; Pfizer) is a large ongoing global open-label, single-arm phase II study of crizotinib in pts with *ALK+* NSCLC who have received ⩾1 treatment regimen for advanced/metastatic disease. PROFILE 1007 (NCT00923893; Pfizer) is a global randomized phase III study that compared crizotinib with standard chemotherapy as second-line therapy for advanced *ALK+* NSCLC (Shaw et al, ESMO 2012). To evaluate the clinical outcomes of pts with brain metastases on crizotinib, we conducted a retrospective analysis of pooled data from these studies.
Materials and Methods: Pts with previously treated advanced *ALK+* NSCLC enrolled in either PROFILE 1005 or PROFILE 1007 (and randomized to crizotinib) were included in this analysis. Baseline (BL) brain imaging was required in both studies, and if brain metastases were detected, subsequent brain imaging was required at 6-week intervals. Otherwise, imaging to assess brain metastasis on treatment was performed as clinically indicated. Tumor assessments were evaluated by investigators based on RECIST. The starting dose of crizotinib was 250 mg BID. Three subgroups of pts were evaluated: those with untreated (no prior radiotherapy) asymptomatic brain metastases at BL, those with previously treated asymptomatic brain metastases at BL, and those without detectable brain metastases at BL.
Results: Of 980 pts included in this analysis, 120 had untreated asymptomatic brain metastases at BL. Among these 120 pts, 112 were evaluable for systemic response, 111 for intracranial (IC) response, and 109 for both types of response. 6/111 had complete IC responses and 4/111 had partial IC responses, for an IC ORR of 9%; 78/111 pts (70%) had stable IC disease (SICD). The systemic ORR was 41% (46/112). 54/109 pts had IC responses that matched or exceeded their systemic response. 42/109 pts (39%) had a better systemic than IC response, of whom 27/42 (64%) had SICD ⩾3 months. Additional data on pts with IC responses (e.g., the number, size, and location of lesions) and summaries of pt subgroups with untreated, treated, or no brain metastases at BL will be presented.
Conclusions: Crizotinib appeared to provide clinical benefit in pts who had untreated asymptomatic brain metastases at BL, with an IC disease control rate of nearly 80% in evaluable pts.
Conflict of interest: *Ownership: S Martin Shreeve, Robin Wiltshire and Paulina Selaru − stock ownership: Pfizer. Advisory board: Benjamin Solomon − Pfizer Gregory Riely − Ariad, Chugai, Novartis, Abbott, Foundation Medicine, Celgene. Corporate-sponsored research: Sai-Hong Ou − Pfizer Benjamin Solomon − Pfizer Gregory Riely − Novartis, Chugai, GSK, BMS, Infinity, Pfizer, Merck, Millennium. Other substantive relationships: Sai-Hong Ou − speakers bureau: Pfizer Daniel Costa − consulting: Pfizer S Martin Shreeve, Robin Wiltshire and Paulina Selaru − employment: Pfizer*

3414 POSTER DISCUSSION

Pooled analysis of the European (EUR) and Chinese (Ch) BRCA1-RAP80 Expression Customization (BREC) randomized trials of customized therapy in advanced non-small-cell lung cancer (NSCLC) patients (p) (NCT00617656/GECP-BREC and ChiCTR-TRC-12001860)

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Background: Findings from the SLCG phase II customized chemotherapy trial (NCT00883480) showed that RAP80, a component of the BRCA1 complex, influenced outcome both in p with low BRCA1 expression treated with cisplatin (cis)/gemcitabine (gem) and in p with intermediate/high BRCA1 levels treated with cis/docetaxel (doc) or with doc alone. Together with the French Lung Cancer Group, the SLCG performed a prospective, randomized phase III trial comparing non-customized cis/doc with customized therapy in metastatic NSCLC p. A parallel phase II study was carried out in China under the auspices of the SLCG.
Material and Methods: Randomization to the control or experimental arm was 1:1 in the EUR and 1:3 in the Ch trial. p in the control arm receive cis/doc; p in the experimental arm received treatment according to their BRCA1 and RAP80 levels: p with low RAP80, regardless of BRCA1 levels, cis/gem; p with intermediate/high RAP80 and low/intermediate BRCA1, cis/doc; p with intermediate/high RAP80 and high BRCA1, doc alone. The primary endpoint was progression-free survival (PFS).
Results: 382 p are evaluable for PFS and overall survival (OS). PFS was 5.46 months (m) in the control and 3.91 m in the experimental arm (P = 0.08). OS was 11.91 m in the control and 9.64 m in the experimental arm (P = 0.05). Response rate was 34.9% in the control and 28.9% in the experimental arm (P = 0.23). In the multivariate analysis including PS, treatment arm, BRCA1, RAP80, histology, smoking status and metastatic site, only treatment with doc alone was associated with an increased risk of progression (HR, 2.15; P<0.001).
Conclusions: Negative results may be due to the poor predictive capacity of RAP80 and the inclusion of doc alone as a treatment in the experimental arm. In addition, doc/cis may not be the ideal combination for the control arm.
No conflict of interest.

3415 POSTER DISCUSSION

GAIN-(L): Efficacy, safety and biomarker analysis of RG7160 (GA201), a novel dual-acting monoclonal antibody (mAb) designed to enhance antibody-dependent cellular cytotoxicity (ADCC), in combination with 1st line cisplatin and pemetrexed in metastatic non-squamous NSCLC

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Background: GA201, a humanized, engineered IgG1 anti-Epidermal Growth Factor Receptor (EGFR) mAb designed to enhance ADCC, has shown promising clinical activity in phase I and in the neoadjuvant treatment of head and neck cancer. This phase II study (NCT01185847) aimed to demonstrate evidence of superior activity of GA201 added to cisplatin and pemetrexed versus chemotherapy alone in terms of PFS in non-squamous NSCLC.
Methods: In this open-label, multicenter, phase II study, non-squamous NSCLC patients (pts) who had not received prior chemotherapy were randomized (2:1) to treatment arm A to receive GA201 (1400 mg IV on day 1 and 8 then q2-weekly) in combination with cisplatin (75 mg/m^2 IV) and pemetrexed (500 mg/m^2 IV) on day 1 q3-weekly for a maximum of 6 cycles followed by GA201 monotherapy until progression or withdrawal, or arm B to receive chemotherapy alone. Data cut off was 9 months after enrolling the last patient.
Results: 41 pts (15 female) and 21 pts (3) with performance status 0−1 were enrolled in arms A and B respectively. PFS HR was 0.92 (95% CI 0.51, 1.66) for 77% of events. Median PFS (Investigator reported) was

5.4 months (95% CI 4.1, 6.5) in arm A versus 6.0 (95% CI 3.7, 8.1) in arm B. Consistent results were observed with independent review. Median overall survival (OS) (52%) was 9.0 months (95% CI 6.6, 13.5) in arm A versus 11.1 (95% CI 9.0,·) in arm B. Most common adverse events (AEs − all grades) included rash (85% in arm A and 19% in arm B), hypomagnesaemia (63 and 19% respectively), nausea (54 and 52% respectively) and infusion-related reactions (49% in arm A only). AEs of ⩾ grade 3 included rash (49% in arm A only), neutropenia (22 and 33% respectively), hypomagnesaemia (15 and 5% respectively), fatigue (15% in arm A only), infusion-related reactions (7% in arm A only) and pulmonary embolism (7 and 5% respectively). Median time to improvement of rash grade 3 was 15 days (range 3−37). AEs led to treatment discontinuation for 24% of pts in arm A (15% discontinued for rash) and 10% in arm B. Analysis of immune cell densities in the tumor at baseline showed a potential positive correlation of CD16+CD3 cells with improved OS.

Conclusion: The study was negative with respect to the primary efficacy endpoint (PFS). In a recent updated analysis of OS, 12 pts (29%) are censored in the GA201 arm with survival times of 13−20 months. Biomarker analysis showed encouraging data for CD16+CD3 combination associated with GA201 clinical efficacy.

Conflict of interest: *Advisory board: Roche/Genentech. Corporate-sponsored research: Roche/Genentech. Other substantive relationships: Honoraria Roche*

3416 POSTER DISCUSSION

Ganetespib in combination with docetaxel versus docetaxel alone in second line adenocarcinoma patients with KRAS mutations and elevated LDH levels

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Background: Heat shock protein 90 chaperone function is critical for the biological effects of many oncoproteins. Ganetespib (G) is a highly potent 2nd generation Hsp90 inhibitor with a favorable safety profile and synergistic activity with docetaxel (D) in NSCLC xenografts. G has shown single-agent clinical activity in NSCLC patients with tumors harboring ELM4-ALK translocations and KRAS mutations (mKRAS).

Methods: We conducted a randomized, international open-label study of D with or without G (Galaxy-1) in patients with advanced lung adenocarcinoma, one prior systemic therapy, and ECOG PS 0/1. D was given at 75 mg/m^2 on Day 1 of a three-week cycle in both arms. In the combination arm, G was given at 150 mg/m^2 on days 1 and 15. The co-primary endpoints were PFS in patients with elevated LDH (eLDH) levels, or tumors harboring KRAS mutation. Key secondary endpoints were OS and PFS in all adenocarcinoma patients. Target enrollment was 240 adenocarcinoma patients, including 120 eLDH and 80 mKRAS patients. Statistical tests are 1-sided.

Results: Enrollment of 254 adenocarcinoma patients, including 63 mKRAS and 77 eLDH patients, completed in November 2012; enrollment of mKRAS and eLDH patients continues in order to reach recruitment target. In all adenocarcinoma patients, baseline characteristics were balanced between the two arms (median age 60 years, males 57%, PS 0 41% and never-smokers 25%). Median number of cycles delivered were 5 and 4 for D+G and D, respectively. Grade 3/4 adverse events for the D+G and D alone arms were: neutropenia 38% vs. 37%; fatigue 4% vs. 3; anemia 7% vs. 6%; diarrhea 3% vs. 0; fever with neutropenia 8% vs. 2%.

At the time of abstract submission OS HR in the all adenocarcinoma population was 0.69 (90% CI 0.48 to 0.99, p = 0.093). In the mKRAS group OS HR was 0.63 (90% CI 0.31 to 1.28, p = 0.14), and in the eLDH group OS HR was 0.57 (90% CI 0.32 to 1.01, p = 0.05). The PFS HR in the all adenocarcinoma population was 0.70 (90% CI 0.53 to 0.94, p = 0.012). In the mKRAS group the PFS HR was 0.93 (90% CI 0.53 to 1.65, p = 0.58), and in the eLDH group PFS HR was 0.82 (90% CI 0.50 to 1.35, p = 0.75). Updated mKRAS and eLDH results, including ORR, PFS and OS, will be presented at the meeting.

Conclusions: Treatment with D+G showed a favorable safety profile. Encouraging survival improvement was observed in the combination arm in all adenocarcinoma patients, including mKRAS and eLDH patients.

Conflict of interest: *Ownership: Yes. Advisory board: Yes. Board of directors: Yes. Corporate-sponsored research: Yes*

3417 POSTER DISCUSSION

Key survival prognostic factors in NSCLC based on patient reported outcomes of global factors and thoracic symptoms using the LCSS: results of the 622 patient AP-QL trial

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Background: Reliable prognostic factors assist better trial design and appropriate personalization of care. Clinical factors and molecular testing are commonly used for these purposes but no patient reported outcome (PRO) is routinely used, as performance status is not patient rated.

Methods: This prospective study enlisted 622 patients receiving initial docetaxel-based chemotherapy (80% with cisplatin or carboplatin) and correlated PROs from an electronic LCSS format (eLCSS-QL) every 3 weeks with survival outcomes. The eLCSS-QL requires <3 minutes; it is simple and inexpensive to perform especially with electronic assistance and has high patient and staff acceptance.

Results: Survival and baseline PRO data were available for 96% of patients (70% male; 65% adenocarcinoma; medians: KPS = 90; ECOG = 1, with 27% having ECOG 0 PS); Stages: IV (72%), IIIB (28%). Survival: 12.8 months median; 52% at 1 year. Survival results were analyzed for differences in PRO scores at baseline, assessing survival according to whether patients scored baseline PROs at less than the median (negative finding) or greater than the median (positive finding) for the 3 NSCLC thoracic symptoms (dyspnea, cough, pain) and the 3 LCSS global items (see table). Survival differences for baseline PRO values above or below medians for each global item varied by about 4 months, while differences for the thoracic symptoms were about 2 months on average. Individual symptoms are found only in subsets of patients, while all patients have scores for global factors.

Parameter	Median value at baseline	Survival advantage if baseline value is above the median	p
Dyspnea	78%	2.1 Months	0.33
Cough	75%	1.3 Months	0.26
Pain	81%	2.6 Months	0.05
Symptom distress	68%	3.6 Months	<0.003
Quality of life	60%	4.3 Months	<0.003
Activity level	66%	4.4 Months	0.0006

Conclusions: PRO findings at baseline have strong predictive properties, with global items such as quality of life exceeding any thoracic symptom. An index of these PRO factors is now under analysis. For unselected patients, these parameters can equal or exceed prognostic separations identified by molecular alterations. These results show the value of PRO factors and the need for evaluating global factors as well as symptoms. Use of these factors can assist better trial design and analysis, and can aid in personalizing therapeutic decision making based on individual likelihood of risk and benefit.

Conflict of interest: *Corporate-sponsored research: Sanofi*

3418 POSTER DISCUSSION

Retrospective evaluation of the futility analysis in LUME Lung 2, a randomized, double-blind, placebo-controlled phase 3 trial of nintedanib (BIBF 1120) in combination with pemetrexed in NSCLC patients progressing after one prior first line chemotherapy

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Background: LUME Lung 2 was a placebo (PB) controlled phase 3 trial (NCT00806819) of 2nd line nintedanib (N) + pemetrexed (PM) in patients (pts) with advanced/metastatic non-squamous NSCLC. Based on results of a planned futility analysis conducted by the Data Monitoring Committee (DMC), the trial was halted prior to planned completion (no safety concerns).
Methods: Pts with Stage IIIB/IV or recurrent NSCLC were randomised to N 200 mg po bid + PM 500 mg/m^2 iv q21d (n = 353) or PB + PM (n = 360). 1º endpoint was centrally reviewed progression free survival (PFS). The pre-planned DMC analysis used investigator reviewed PFS data (14 Mar 2011; 345 [48%] events) and met futility criteria as defined in the DMC charter. Based on the DMC recommendation to stop the study, ongoing pts were unblinded and follow-up was continued per amended protocol. Using the final study data (9 Jul 2012) a retrospective evaluation of statistical factors such as conditional and predictive power over time was performed for both investigator and centrally reviewed data.
Results: 713/1300 planned pts were entered. Pt characteristics were balanced. Analysis of the 1º endpoint (9 Jul 2012 data) showed a statistically significant improved PFS by central independent review favoring N + PM (median 4.4 vs 3.6 mo, HR 0.83; CI: 0.7–0.99, p = 0.0435). This was confirmed in a follow-up analysis (15 Feb 2013 data, median 4.4 vs 3.4 mo HR 0.84; CI: 0.7–1.00, p = 0.0506). Retrospective analysis of the statistical factors leading to the futility results confirmed that based on investigator reviewed PFS the criteria defined in the DMC charter were met at the time of the original DMC analysis (13.3% conditional and 21.6% predictive power). When analyzed at other times, however, these statistical measures remained above the pre-defined futility criteria. When centrally reviewed PFS was analysed over the same period of time, fluctuations in the statistical measures were noted but remained above the pre-defined futility criteria.
Conclusions: The 1º endpoint was met even though the study was stopped prior to planned completion. Retrospective investigations suggest that had the DMC analysis been performed at another time point or had centrally reviewed data been used, the outcome of the futility analysis may have been different. In general, futility analyses should be repeated at different time points during the study and potential discordances between investigator and centrally assessed PFS need to be considered.
No conflict of interest information specified.

3419 POSTER DISCUSSION

Updated analysis and secondary endpoints with L-BLP25 in unresectable stage III non-small cell lung cancer in the phase III START study

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Background: START is a phase III trial of MUC1-specific cancer immunotherapy L-BLP25 in patients (pts) with stage III unresectable non-small cell lung cancer who did not progress after primary chemoradiotherapy (CRT). While the primary objective of overall survival (OS) prolongation was not met, pre-defined subgroup analyses revealed a clinically meaningful prolongation of OS in pts previously treated with concurrent CRT. Sensitivity analyses suggested the observed treatment effect was underestimated due to a clinical hold. L-BLP25 was well tolerated, with no safety concerns identified. Here we report pre-defined subgroup analyses for secondary endpoints. Updated OS data, available in Q3 2013, also will be presented.
Materials and Methods: From Jan 2007 to Nov 2011, 1513 patients with unresectable stage III NSCLC who did not progress after CRT were randomized (2:1; double-blind) to L-BLP25 (806 μg lipopeptide) or placebo (PBO) SC weekly x 8 then Q6 weeks until disease progression or withdrawal. Cyclophosphamide 300 mg/m^2 x 1 or saline was given 3 days prior to first L-BLP25/PBO dose. Primary endpoint was OS. Secondary endpoints were time to symptom progression (TTSP) (measured by the lung cancer symptom scale, LCSS) and time to progression (TTP).
Results: The primary analysis population (n = 1239) was defined prospectively to try to account for the clinical hold. L-BLP25 extended TTSP and TTP compared with PBO. Analyses of TTSP and TTP in pre-defined subgroups were conducted. In line with OS data, L-BLP25 treatment effects on TTSP and TTP were more pronounced in patients with prior concurrent (n = 806) vs. sequential (n = 433) CRT. For pts with concurrent CRT, TTSP was 16.4 m (L-BLP25) vs. 11.4 m (PBO) (HR 0.81, 95% CI 0.67–0.97, p = 0.023) whilst for pts with sequential CRT, TTSP was 12.3 m (L-BLP25) vs. 11.4 m (PBO) (HR 0.92, 95% CI 0.73–1.17, p = 0.493). Similarly, TTP was 11.9 m (L-BLP25) vs. 9.4 m (PBO) (HR 0.85, 95% CI 0.71–1.02, p = 0.078) for concurrent CRT and 7.7 m (L-BLP25) vs. 7.4 m (PBO) for sequential CRT (HR 0.91, 95% CI 0.72–1.15, p = 0.437). Time to event analysis of each of the 9 single LCSS variables was consistent with the overall TTSP results.
Conclusions: While the primary objective of the trial to prolong survival time significantly was not met, detailed secondary endpoint analyses of pre-defined subgroups support a potential benefit of L-BLP25 in patients receiving prior concurrent CRT (Sponsor, Merck KGaA; ClinicalTrials.gov number, NCT00409188).
Conflict of interest: *Ownership: AS owns stock in Merck KGaA and the license provider of L-BLP25, Oncothyreon, Inc. Advisory board: NT is on Merck Serono advisory boards, and received speaker fees and travel payments for advisory speaker work with Merck Serono. Corporate-sponsored research: MS has received research funding from EMD Serono. PM has received reimbursement of time as a START Trial International Steering Committee Member. Other substantive relationships: FS has an uncompensated consultant/advisory relationship with Merck. CB has a consultant/advisory relationship with Merck Serono and Merck KGaA, and has received honoraria from Merck Serono and Merck KGaA. CH and AS are permanent employees of the trial sponsor (Merck KGaA, Merck Serono).*

3420 POSTER DISCUSSION

Phase IB study to evaluate the efficacy and tolerability of olaparib (AZD2281) plus gefitinib in patients with epidermal growth factor receptor (EGFR) mutation positive advanced non-small-cell lung cancer (NSCLC) patients (pts). (NCT=1513174/GECP-GOAL)

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Background: Progression-free survival (PFS) and response rate (RR) to EGFR tyrosine kinase inhibitors (TKIs) vary in pts with NSCLC driven by EGFR mutations, suggesting that other genetic alterations may influence oncogene addiction. In our experience, high BRCA1 mRNA expression negatively influenced PFS among EGFR mutant pts treated with erlotinib. We hypothesized that since olaparib can attenuate and/or prevent BRCA1 expression, the addition of olaparib to gefitinib could improve PFS in these pts.
Methods: This is a Phase IB dose escalation study to identify the maximum tolerated dose (MTD), dose limiting toxicity (DLT), pharmacokinetics (PK), and clinical activity of orally administered olaparib in combination with gefitinib in EGFR mutant advanced NSCLC. In a standard 3+3 design

based on toxicity, pts were treated with gefitinib 250 mg once daily plus olaparib at escalating doses ranging from 100 mg BID to 250 mg TDS during a 28-day cycle.
Results: 22 pts have been included across four dose levels of olaparib: 100 mg BID (3), 200 mg BID (6), 200 mg TDS (6) and 250 mg TDS (7). Median age, 65 (range 39−84); male, 6 pts; PS 0−1, 19 pts; EGFR TKI treatment-naive, 14 p; T790M positive (69%), 9 of 13 pts analyzed. Toxicities: anemia (66.6%), leucopenia (33.3%), nausea (33.3%), diarrhea (33.3%), asthenia (27.7%), rash (22.2%) vomiting (11%), decreased appetite (16%), and hyperlipasemia (5.5%). Most toxicities were G1−2; G3 drug-related events included leucopenia (1) and anemia (3). No DLT at dose levels 1, 2, and 3; 2 DLT at dose level 4 (G3 anemia and repeated blood transfusion within 4−6 weeks). Few dose reductions or interruptions for both drugs were needed. 1 pts died due to pulmonary embolism unrelated to study treatment. 19 pts were evaluated for response: Partial responses (PR) were observed in 8 pts (42%), all EGFR TKI-naive; stable disease (SD) in 8 pts (42%), most previously treated; progressive disease (PD) in 2 pts (10.5%), all previously treated. Durable PR and SD were observed in both EGFR TKI-naive and previously treated pts.11 pts are still on treatment.
Conclusions: This phase IB trial of gefitinib plus olaparib, confirms the tolerability of the combination and the activity seen warrants further exploration in treatment-naive patients. The final recommended dose of olaparib is expected to be either 200 mg BID or 200 mg TDS. A phase II randomized trial in treatment-naive EGFR-mutant advanced NSCLC is planned in 2013.
No conflict of interest.

3421 POSTER DISCUSSION

Tissue biomarker analysis in PROSE, a randomized proteomic stratified phase III study of second line erlotinib (E) versus chemotherapy (CT) in patients with inoperable non-small cell lung cancer (NSCLC)

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Background: Improved PFS in first line E-treated pts is associated with EGFR sensitizing mutations. However, a test for optimizing treatment in pts with wild-type or unknown EGFR mutation status in second line setting is of clinical value. PROSE is a multicenter prospective randomized biomarker validation trial, designed to evaluate the ability of VeriStrat (VS) serum protein test to predict survival in 2nd line metastatic NSCLC pts treated with E or CT. It is the first completed prospective randomized biomarker validation trial following the MARVEL design.
Methods: 285 pts, stratified by performance status, smoking habits, and blinded pre-treatment VS classification were randomized in a 1:1 fashion to receive E or CT at standard doses. Primary endpoint was overall survival (OS) having as the primary hypothesis a significant interaction between VS status and treatment. Sample size was calculated based on an estimated 65%/35% VeriStrat Good (VSG):VeriStrat Poor (VSP) ratio, and hazard ratio (HR) for interaction of 2.35, with a 2-sided α=0.05 and 90% power.
Results: 263 (129 CT, 134 E) were included in the primary analysis as per protocol: 68% of pts in CT arm and 72% in E arm were classified as VSG. The analysis was performed reaching 226 events. The primary objective was met with a significant interaction between treatment and VS classification (p-value for interaction 0.037). Pts in the VSP group performed worse on E compared to CT (HR: 1.72, 95% CI: 1.08–2.74); there was no significantly different OS between treatments in the VSG group (HR: 1.09, 95% CI:0.79–1.50). Data in subgroup analyses in pts with wild-type EGFR, positive K-RAS mutation status and by histology will be presented.
Conclusions: The results suggest that VS status is predictive of differential OS benefit for E versus CT in the second line setting. The ongoing subgroup analysis will clarify whether VS has prognostic and predictive value independently from other validated variables such as EGFR and K-RAS mutations.
Conflict of interest: *Other substantive relationships: Heinrich Roder*

3422 POSTER DISCUSSION

Safe introduction of VATS in the Netherlands: First results of a nation-wide audit

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Background: In 2006 video-assisted thoracic surgery (VATS) was introduced for anatomical parenchymal resections (segmentectomy, (bi)lobectomy, pneumonectomy) of non-small cell lung cancer (NSCLC) in the Netherlands. Implementation was realised by the formation of dedicated teams and formulating minimum volume requirements. The main objective of this study was to compare surgical outcome between VATS and thoracotomy.
Material and Methods: Patients who underwent resection for NSCLC in 2012 were included in a nation-wide, web-based prospective database, the Dutch Lung Surgery Audit. Patients were stratified in two groups, those who underwent thoracotomy versus those in whom resection was performed by VATS. Patient, tumour and treatment characteristics, as well as outcome, were compared between the two groups using Chi-square tests and multivariate analysis.
Results: The preliminary results comprise 1.580 patients treated in 42 hospitals with general thoracic surgeons. Patient characteristics were similar for the VATS and thoracotomy group, though more advanced tumour stages were found in the thoracotomy group. Near 75% of lobectomies and a small minority of more extensive parenchymal resections (bilobectomies, pneumonectomies) were performed by VATS. For lobectomies, a similar number of resected N1 and N2 lymph nodes were found in both groups. There was no significant difference in 30-day mortality (VATS: 1.6% vs thoracotomy: 3.1%) or reintervention rate (VATS: 4.1% vs thoracotomy: 5.1%). Extensive blood loss was small in both groups. Pneumothorax and air leakage longer than 5 days were more common in the VATS group, although this was not associated with a prolonged length of stay (mean: 6 versus 8 days).
Conclusions: Since its introduction in the Netherlands, the number of resections for NSCLC performed by VATS procedure increased rapidly. Although variation in patient selection criteria does not allow a direct comparison of outcomes between the two techniques, this study suggests that there has been a safe introduction of VATS for the treatment of NSCLC in the Netherlands.
No conflict of interest.

3423 POSTER DISCUSSION

Functional outcome after pulmonary metastasectomy: Video-assisted thoracoscopic surgery versus thoracotomy

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Background: Today, pulmonary metastasectomy is performed as a routine part of clinical practice. Thoracic surgeons use a thoracotomy or a video-assisted thoracoscopic (VATS) approach to enter the thorax and remove oligometastic disease. To a lack of randomized controlled trials it is not clear which approach yields a better postoperative recovery. The main goal of this study is to compare the functional recovery after pulmonary metastatectomy for two distinct surgical approaches (i.e. VATS and thoracotomy) used in current clinical practice.
Material and Methods: From April 2006 to December 2011, 100 eligible patients treated for pulmonary metastasis, were identified through a prospective database incorporated in a multidisciplinary care path for oncological thoracic surgery in the Netherlands Cancer Institute. Patient-, tumour-, treatment- and outcome characteristics were collected. Quality of life (QoL) and painscores were evaluated pre-operative, 1, 3 and 6 months postoperative using the SF-36 questionnaire and a visual analogue scale (VAS), respectively.
Results: QoL 6 months postoperative revealed a physical and mental performance comparable to baseline. Linear regression analysis showed no significant differences in QoL scores 6 months postoperative between the two surgical approaches. No difference in pain, direct postoperative

and 6 months postoperative, between thoracotomy and VATS group was revealed (resp. $p = 0.087$ and $p = 0.402$). Short term outcome showed that VATS is associated with shorter hospital stay ($p<0.001$), shorter duration of chest drainage ($p<0.001$), and shorter duration of epidural analgesia ($p<0.001$).
Conclusion: No differences were found in QoL or painscores 6 months postoperative between the thoracotomy and VATS group. Though, a VATS approach has advantages in short-term outcome: shorter hospital stay, shorter duration of chest drainage and of epidural analgesia.
No conflict of interest.

Poster Session (Sun, 29 Sep)
Lung Cancer − Localised/Local Regional

3424 POSTER

Characterisation of the tumour microenvironment in non-small cell lung cancer

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Background: This study set out to characterise the number and localisation of T cells, CD8+ T cells, FOXP3+ T regulatory cells and macrophages in the tumour microenvironment of Non-Small Cell Lung Cancer (NSCLC) and determine whether the number of immune cells is associated with survival.
Methods: Immunohistochemistry was carried out on 32 resected NSCLC tumours using CD3, CD8, FOXP3 and CD68 antibodies to detect T cells, CD8+ T cells, FOXP3+ T regulatory cells and macrophages respectively. The number of immune cells in the tumour islets (intratumoural), tumour stroma, tumour islets and stroma (total) was quantified using a microscope. The number of immune cells was correlated with the clinicopathological data (including survival) of patients.
Results: The number of CD3+ cells was highest in both the stroma and tumour; followed by CD8+ cells, CD68+ cells and FOXP3+ cells. Stage II was associated with a higher number of intratumoural CD3+, CD8+ and FOXP3+ cells compared to stage I. The number of stromal, intratumoural and total immune cells detected using one antibody correlated with the number of stromal, intratumoural and total immune cells respectively detected using the other antibodies. The number of immune cells was not associated with survival using either univariate or multivariate analysis.
Conclusions: The number of immune cells was not associated with survival. The prognostic value of immune cells in the tumour microenvironment of NSCLC should be further investigated in a larger study.
No conflict of interest.

3425 POSTER

Venom present in *Heteractis magnifica* induces apoptosis in human lung cancer A549 cells

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Background: Lung cancer is a major cause of cancer deaths through the word but the complexity of apoptosis resistance in lung cancer is becoming apparent. This study defined important roles for inducing apoptosis in A549 human lung cancer cell line with sea anemone venom.
Material and Methods: Cytotoxicity induced by *H. magnifica* venom was investigated through two colorimetric bioassays, the MTT assay (metabolic viability) and the Crystal violet assay (Cell number) on human lung cancer A549 cell line. Apoptosis was also assayed, via annexin V-flourescein isothiocyanate and propidium iodide (PI) staining followed by flow cytometric analysis. Cell cycle progression and mitochondria membrane potential were studied via flow cytometry following PI and JC-1 staining respectively.
Results: This study shows that chemo-preventive action of venom from *H. magnifica* might be due to its ability to induce apoptosis and cell cycle arrest. *H. magnifica* venom inhibited the growth of A549 cells line in a concentration dependent manner. The venom at 40 μg/ml on A549 cell line induced 32.2% apoptosis compared to 2.2% in untreated cells. Caspase 3/7 assay and JC-1staining were conducted to detect increases in the levels of apoptosis-regulating proteins and mitochondrial membrane potential, respectively.
Conclusions: The findings of this study indicate that the crude extracts from *H. magnifica* induce apoptosis in A549 human lung cancer cell line and that is phenomenon is mediated via both the death receptor-mediated and mitochondria-mediated apoptotic pathway. Thus, novel compounds from *H. magnifica* may be developed as effective treatments for lung cancer.
No conflict of interest.

3426 POSTER

Metabolic activity measured by FDG-PET predicts pathological response in locally advanced NSCLC undergoing trimodality treatment

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Background: Pathological response (pCR) after induction chemoradiation for locally advanced NSCLC is an important prognostic factor. Patients with a pCR or less than 10% vital tumor cells (pR10) have superior outcomes compared to those with >10% vital cells. Post-induction surgery in these patients is questionable. We evaluated whether changes in metabolic activity can predict pCR or pR10 following induction chemoradiation in patients with superior sulcus tumors (SST). Furthermore, we investigated whether the use of post-induction SUV_{peak} (i.e. SUV of a 1cc sphere with highest FDG activity concentration) increases sensitivity of pCR prediction.
Methods: In this prospective cohort study all consecutive patients with SST between January 2010 and January 2012 were included. Routine clinical pre- and post-induction FDG-PET/CT scans were evaluated. FDG uptake was expressed as $SUV_{max,}$ SUV_{TTL} (tumor-to-liver ratio = tumor SUV_{max} / liver SUV_{mean}), SUV_{peak} and SUV_{PTL} (peak-to-liver ratio = tumor SUV_{peak}/liver SUV_{mean}). First, a single pathologist assessed all parts of the tumor for maximal vital tumor cell percentage per cm^2 (C%) and overall residual tumor percentage (T%). Next, tumor regions corresponding to the postinduction SUV_{peak} regions were designated. Then, changes in SUV_{max} and SUV_{TTL} were correlated with T%. Post-induction SUV_{peak} and SUV_{PTL} were correlated with the corresponding C%.
Results: FDG-PET/CT scans from 8 out of 31 treated patients were not usable due to absent postinduction scans or unstandardized PET scans. Sixteen patients had less than 10% remaining vital tumor of which 8 had a pCR. The area under the ROC curve (AUC) for predicting pCR was 0.78 for SUV_{max} ($P = 0.054$) and 0.90 for SUV_{TTL} ($P = 0.007$). The optimal cutoff value for reduction in SUV_{max} was 67% and 77% for SUV_{TTL}. At this cutoff value, sensitivity and specificity was 83% and 70% for SUV_{max} and 83% and 85% for SUV_{TTL}. The AUC for predicting pR10 was 0.96 for SUV_{max} ($P = 0.002$) and 0.96 for SUV_{TTL} ($P = 0.002$). The optimal cutoff value for reduction in SUVmax was 55% and 47% for SUV_{TTL}. At this cutoff value, sensitivity and specificity was 85% and 100% for SUV_{max} and 100% and 83% for SUV_{TTL}. The use of SUV_{peak} and SUV_{PTL} did not improve sensitivity of the prediction of pCR and pR10.
Conclusions: Changes in metabolic activity measured by FDG-PET/CT may predict pathological response in patients with locally advanced NSCLC. The post-induction SUV_{peak} did not improve sensitivity. These findings need confirmation in larger cohorts.
No conflict of interest.

3427 POSTER

A phase II study of cisplatin and oral vinorelbine concomitantly with radiotherapy in locally advanced non-small-cell lung cancer treatment: Primary objective and safety results

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Background: Cisplatin (CDDP) plus oral Vinorelbine (OV) as induction and concomitant regimen with radiotherapy (RT) has shown good efficacy outcomes and safety profile (Vokes, Fournel, Krzakowski). The objective of this study was to evaluate the effectiveness and toxicities of the combination

of CDDP and OV given at full doses concomitantly with RT in locally advanced (LA) non-small-cell lung cancer (NSCLC).
Material and Methods: Between February 2010 and December 2011, 48 chemo-naive patients (p) with histologically confirmed unresectable stage IIIA/IIIB LA NSCLC were treated. Treatment consisted of 4 cycles (cy) of OV 60 mg/m^2 on days 1 and 8 and CDDP 80 mg/m^2 every 3 weeks plus RT 66 Gy starting on day 1, cy 2. The primary objective is the ORR using RECIST 1.0. A standard Fleming two stage design was used. The sample size calculated with a type 1 error of 0.05 and type 2 error of 0.01, taking P_0 20% and P_1 40%.
Results: Patient's characteristics were: Median age 61 years (range 34−72); ⩾65 y 42%; males 89.6%; PS0 42%/PS1 58%; smokers 52%; adenocarcinoma 30%/squamous 64%; stage IIIA 46%/IIIB 54%. Median of days between initial diagnosis and study start was 28 days. 75% p completed the treatment as per protocol. Relative dose intensities of OV and CDDP were 97%/98%, respectively. 14.7% of cy were delayed, 11.8% due to toxicity. Dose of day 8 OV was canceled or delayed in 8.2% of cy. Hematological toxicities (% p): grade (g) 3/4 neutropenia 33.3%; g3 anemia 12.5%; g3/4 thrombocytopenia 16.6%; febrile neutropenia concomitant during CT-RT 14.6%. Non-hematological toxicities (% p): g3 esophagitis 12.5%; g3 dyspnea 4.2%, g3 vomiting 4.2%, g3−4 infection 4.2%. 2 treatment-related deaths were reported, both during cycle 1. 42 p (87.5%) received RT, 7.1% under 60 Gy, 23.8% with RT delays or interruptions due to adverse events. 44 p were evaluable for response. ORR 77.3% [95% CI, 62.2–88.5], DCR 88.6% [CR 2 p (4.5%), PR 32 p (72.7%), SD 5 p (11.4%)]. Median follow-up 6.6 months (range 0.47–23.5). Median OS and TTP not reached. Median PFS 13.3 months (95% CI, 6.4–20.2).
Conclusions: This prospective phase II trial shows that the schedule of CDDP plus OV concomitant with RT from 2nd cy obtains a good efficacy with an acceptable safety profile.
No conflict of interest.

3428 POSTER

Adjuvant treatment of completely resected stage IB−IIIA non-small-cell lung cancer − a retrospective study with cisplatin or carboplatin and oral vinorelbine

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Background: Adjuvant chemotherapy is a standardized treatment for early stage non-small-cell lung cancer (NSCLC) patients after complete resection. The most evidence-based data exist for combination of cisplatin (cis) and vinorelbine (vrb), whereas carboplatin (carbo) can be administered as combination partner in cis-unfit patients. To analyze effectiveness and tolerability of platinum-based combination therapy with predominantly oral vrb in daily practice we performed a retrospective study in our hospital.
Material and Methods: Data from 152 patients with completely resected NSCLC (stage IB−IIIA) receiving adjuvant chemotherapy with cis or carbo in combination with intravenous or oral vrb (Navelbine© Oral) between March 2005 and November 2011 were retrospectively analyzed. The primary endpoint was overall survival, secondary endpoints recurrence-free survival and toxicity. Overall survival and recurrence-free survival were estimated with the Kaplan–Meier method.
Results: Patients were on average 61 years old and diagnosed with stage IB (35%), IIA (5%), IIB (38%) or IIIA (22%) NSCLC. 66% of the patients were male, and 93% were former or active smokers. Vrb was predominantly administered orally (89%) and most patients received carbo (74%).
The combination treatment was effective with an estimated 5-year survival of 64% (cis/vrb: 65%, carbo/vrb: 64%) and recurrence-free survival after five years of 60% (cis/vrb: 63%, carbo/vrb: 59%). Toxicities (all grades) related to combination therapy mainly concerned the hematologic system with 70% leukopenia (carbo/vrb: 74%), 32% thrombocytopenia (carbo/vrb: 40%), 40% anemia, 28% neutropenia, and 5% febrile neutropenia. The treatment caused nausea and vomiting in 47% and 23% of the patients (cis/vrb: 59% and 28%), respectively, and fatigue was reported for 23% of the patients. Of note, overall 64% of the patients (carbo/vrb: 71%, cis/vrb: 44%) completed combination therapy with the planned number of cycles.
Conclusions: The results of this retrospective study are in line with clinical trials of cis in combination with intravenous vrb and show that adjuvant chemotherapy of a platinum-based combination therapy with vrb is effective. Carbo was better tolerated than cis resulting in superior treatment compliance and comparable effectiveness.
Conflict of interest: *Corporate-sponsored research: Pierre-Fabre, Freiburg, Germany*

3429 POSTER

Definitive concurrent chemoradiotherapy for patients over 75 years old with locally advanced non-small-cell lung cancer

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Background: Radiotherapy alone is the standard treatment for elderly patients with locally advanced non-small-cell lung cancer (NSCLC). However, curative thoracic radiotherapy with concurrent chemotherapy may be feasible and contribute to longer survival of selected elderly patients with NSCLC. This retrospective study was aimed to evaluate the tolerability and efficacy of concurrent chemoradiotherapy (CCRT) in patients aged 75 years or older.
Material and Methods: We reviewed the records of 28 consecutive stage III NSCLC patients who were 75 years or older when treated with definitive CCRT from 2006 to 2011. The median age was 79 years, with a range of 75 to 87 years. Twenty-two (78.6%) patients exhibited comorbidity. The median number of Eastern Cooperative Oncology Group (ECOG) performance status of the cases at the beginning of treatment was 1, with a range from 0 to 2. The median delivered radiation dose was 60 Gy. Regional lymph nodes were prophylactically irradiated in 25 patients, while involved-field radiation was applied to the other 3. Concurrent chemotherapy regimens were carboplatin plus paclitaxel, cisplatin plus vinorelbine, carboplatin plus docetaxel, carboplatin plus vinorelbine, paclitaxel alone, pemetrexed alone and S1 alone.
Results: The median follow-up time was 16.9 months (1.7–63.5). The median overall survival and progression-free survival were 19.1 (95% CI 11.5–26.8) and 8.1 months (95% CI 7.4−8.8), respectively. One-year and 2-year survival rates were 76.0 and 44.3%, respectively. Nineteen (67.9%) patients could be evaluated for the initial effects of CCRT. The response rate was 84.6%, namely, 22 patients; 3 (11.5%) experienced stable disease and one (3.8%) disease progression for an overall clinical benefit of 96.2%. During the treatment, 9 patients (32.1%) experienced grade 3−4 neutropenia, three patients (10.7%) grade 3 neutropenic fever, one patient (3.6%) grade 3 anaemia, and no patients thrombocytopenia of grade 3 or higher. Grade 3 radiation pneumonitis and grade 3 drug-induced lung injury were observed in 2 (7.1%) and 1 patients (3.6%), respectively. No treatment-related death occurred. Esophagitis or other non-haematological toxicity of grade 3 or higher was not observed.
Conclusion: CCRT was feasible in selected patients aged 75 years or older with locally advanced NSCLC; it may thus have clinical benefit.
No conflict of interest.

Table: Adverse effects due to definitive concurrent chemoradiotherapy

	Grade 3	Grade 4	Grade 5
Neutrophil count decreased	2 (7.1%)	7 (25.0%)	0
Febrile neutropenia	3 (10.7%)	0	0
Anaemia	1 (3.6%)	0	0
Thrombocyte count decreased	0	0	0
Radiation esophagitis	0	0	0
Radiation pneumonitis	2 (7.1%)	0	0

3430 POSTER

Rotational, intensity-modulated radiotherapy for inoperable non-small cell lung cancer: Long term follow-up and toxicity profile

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Purpose: To report mature results of treatment efficacy and toxicity of rotational, intensity-modulated radiotherapy by means of helical tomotherapy for patients with inoperable, non-small cell lung cancer (NSCLC).
Methods: Between Jan 2006 and March 2012, a total of 144 inoperable NSCLC patients were treated on the Tomotherapy HI-ART II system, in the concurrent (n = 75) or sequential/primary (n = 69) (chemo)radiotherapy approach. Concurrent chemoradiotherapy (CCRT) consisted of weekly administrations of cisplatin and docetaxel at 20 mg/m^2 each in combination

with 30 fractions of 2.24 Gy. Radiotherapy schedule for sequential (SCRT) or primary (PRT) treatment consisted of 30 fractions of 2.35 Gy. Toxicity monitoring was performed using the RTOG and NCI CTCAE version 3.0 criteria. Treatment efficacy was evaluated in terms of in-field progression free, metastasis-free and overall survival using the Kaplan–Meier method. Log-rank testing was used for intergroup comparison.

Results: Mean age was 65 years (range,37−85). AJCC 6th edition was used for staging, clinical stages of the 144 patients were as follows: IIB (n = 3), IIIA (n = 55), IIIB (n = 77), IV (n = 9). The rate of acute ⩾grade 3 esophageal and lung toxicity was 9% and 7%. The rate of late ⩾grade 3 esophageal and lung toxicity was 0.7% and 14%. With a median follow-up time of 14.3 months (range, 3−70 months), 64% of patients experienced disease progression. Site of first failure was distant in 32% and locoregional in 26%. The median overall survival was 25 months, with a 1-year and 2-year overall survival of 71% and 45%, respectively. The 1-year and 2-year in-field progression-free survival rate was 78% and 68% with a median time to in-field progression of 14.7 months. The median metastasis-free survival was 21.5 months with 1-year and 2-year rates of 57% and 37%. No significant statistical difference was observed in survival rates between the three different treatment modalities. A trend towards improved metastasis-free survival was observed between CCRT and SCRT ($p = 0.0625$, log-rank).

Conclusion: Moderate hypofractionated radiotherapy by means of helical tomotherapy in patients with inopearbel NSCLC resulted in accepatable acute and late treatment-related toxicity and encouraging survival results.

No conflict of interest.

3431 POSTER

Reliability of small biopsy samples for determining PD-L1 expression in non-small cell lungcarcinoma, compared with resected specimens using immunohistological staining

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Background: Several studies have assessed the expression rate of programmed cell death 1 ligand (PD-L1) in resected specimens of non-small cell lung carcinoma(NSCLC). Although advanced NSCLC is routinely diagnosed by biopsy, expression of PD-L1 in these samples has not been reported.

Materials and Methods: From April 2009 to March 2012, 79 NSCLC patients for whom both resected specimens and biopsy samples for diagnosis were available in our institute were retrospectively enrolled in this study. PD-L1 expression was assessed by immunohistochemistry (IHC) and scored according to hybrid (H) score. Concordance rates for expression of PD-L1 between both the samples were analyzed.

Results: Distribution of disease stage in the patients (52 male, 29 female; median age, 68 years; range, 38−83 years) was stage I in 38, stage II in 8 and stage III in 23. Diagnosis included endobronchial biopsy in 59 cases, transbronchial needle aspiration (TBNA) in 14, and CT-guided needle biopsiy (CTNB) in 6. Positivity rate of PD-L1 in these samples was 45.6% (endobronchial biopsy, n = 27; TBNA, n = 6; CTNB, n = 3) versus 41.8% in resected specimens. Median H-score was 0 (range: 0–170) and mean was 26.7 (standard deviation: 36.2). No association between patient characteristics and expression of PD-L1 was seen. On comparison of biopsy samples and resected specimens, 11 tumors were discordant for expression of PD-L1 and 68 tumors were concordant, giving a concordance rate of 86.1%.

Conclusions: PD-L1 status showed moderate concordance between biopsy samples and resected specimens in NSCLC.

These small samples, even those derived from transbronchial needle aspiration, appeared adequate for assessment of PD-L1 expression.

No conflict of interest.

3432 POSTER

An empirical assessment of non-small cell lung cancer charges by survival

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Background: Non-small cell lung (NSCLC) cancer has a high mortality rate and is costly to treat, but it remains unknown if charges differ between patients who die while receiving treatment compared to those who survive. The objective of this study was to assess the mean charges per patient in those diagnosed with NSCLC by survival status.

Material and Methods: The University of Utah Enterprise Data Warehouse was used to analyze patients ⩾18 years with a diagnosis of NSCLC identified by ICD-9 code (initial diagnosis defined as index date) treated at the Huntsman Cancer institute (HCI) from 2002–2010. The HCI Tumor Registry was used to confirm cases and determine stage and histology at diagnosis. Cancer-related death and date of death were captured from the Utah Population Database. NSCLC-related and other charges (US dollars) were identified by ICD-9 code from index date until death or the end of the study period. Patients who died were matched to survivors based upon the Kaplan–Meier probability of survival at the time of death or end of the study period. A generalized linear model (GLM) with gamma distribution and log link function was used to examine charges by survival status, adjusting for stage, histology, year of diagnosis, cancer treatments, demographics, and comorbidities.

Results: A total of 776 patients were included. There were no differences between deceased patients and survivors in age (mean 66 vs. 65) and sex (male 63% vs. 59%). Compared to survivors, more deceased patients were diagnosed with stage IV disease (58% vs. 25%; $p < 0.001$). Additionally, patients who died had more comorbidities ($p = 0.01$) and greater use of radiation ($p < 0.001$). Mean unadjusted NSCLC-related charges were not significantly higher in deceased patients compared to survivors ($66,533 vs. $58,916; $p = 0.12$), but other charges were ($36,666 vs. $20,924; $p < 0.001$). Results from the GLM indicated deceased patients had a non-significant $8,251 increase in adjusted mean NSCLC-related charges ($p = 0.13$), but a significant $23,521 increase in adjusted mean other charges ($p < 0.001$). Being younger and having more comorbidities were associated with an increase in other charges.

Conclusions: When adjusting for confounders, death was associated with higher other charges, but not NSCLC-related charges. Though potential confounders were included in the analysis, patients who died during treatment may have had more aggressive disease leading to higher utilization of ancillary treatments.

No conflict of interest.

3433 POSTER

Non-small cell lung cancer in women: Description of early stages from the Spanish World07 database

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Background: Lung cancer is showing an increasing incedence amongst women in most european countries in recent years. As no specific information is available about early stages in this particular population, a descriptive analysis from the Spanish WORLD07 database have been performed.

Material and Methods: From 2007 to December 2012 a total of 2101 women with lung cancer have been included in the database. Data are available from 1,759 NSCLC of them and 477 presented with stages I−IIIa (27.1%).

Results: Stage distribution was (percentages are from overall NSCLC patients (p)): I, 218p (12.4%); II, 83p (4.7%); IIIa, 176 (10.0%). Median age was 61.9 years. Of them 60.7% were current smokers and in other 15.8% second hand smoking could be documented. Most patients (76.9%) were post-menopausal.

Surgery was performed in 343p (71.9%) and in 83.5% of these cases a lobectomy was performed. Adjuvant chemotherapy was administered to 148 of the resected p (43.1%) and adjuvant radiotherapy to 67p (19.5%). Chemotherapy schemes included cis or carboplatin in 136 p (92.1%) and mean number of courses given was 3.7. Survival data are currently under analysis.

Conclusions: NSCLC incidence is rapidly increasing in women and data in this specific situation in lacking. The present data show an example from a wide, women-only, case-series that may shed some ling on the topic. Updated data will be presented.

No conflict of interest.

3434 POSTER

FDG-PET parameters as predictors for outcome in non-small cell lung cancer (NSCLC) treated with stereotactic body radiotherapy (SBRT)

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Background: To identify predictive FDG-PET imaging factors for outcomes following SBRT in early stage NSCLC.
Materials and Methods: Patients with inoperable T1 and T2 NSCLC and a baseline FDG PET-CT at a single centre (Leeds St James University Hospital) treated with SBRT for a single tumour between 2009 and 2012 were included. Scans were reported by a single radiologist. Prospective data was collected on a range of FDG-PET parameters (including SUVmax and TLG − Total lesion glycolysis). Patient characteristics and outcome variables including stage, histology, PTV volume, performance status, dose, time interval between PET and SBRT, maximum response to treatment and patterns of failure collected and analysed. The PET parameters were analysed as a continuous variable.
Results: 125 patients (72 female, 53 male), median age 75.2. 94 were T1 and 31 T2. Median follow up 1.19 yrs (range 0.28−3.3). Histology was available in 40 patients.
In assessable patients maximal response to treatment was Complete Response in 19%, Partial Response in 50%, Stable Disease in 14% and Progressive Disease in 11%.
Relapse free survival at 2 years was 55%. Local, regional and distant relapse-free rates were 94%, 89% and 83% respectively. Overall and cause-specific survival at 2 years was 57% and 81% respectively.
Median SUVmax was 9.2 in patients who had a relapse and 7.35 in those without. On multivariate analysis, pre treatment SUVmax predicted for recurrence ($p = 0.005528$), distant metastases ($p = 0.024081$) and overall survival ($p = 0.000253$). This was consistent amongst patients with and without diagnostic pathology. Median SUVmax for patients with and without histology was 5.85 and 7.65 respectively. SUVmax however did not correlate with local or regional relapse.
Stage was a significant predictor for Overall and Relapse free survival, consistent with previous data. Dose of radiation and time interval from PET to SBRT showed no significant correlation with outcome.
Other PET parameters assessed include TLG 20 which correlates with regional relapse, the significance of this is not clear.
Conclusion: This study identifies that SUV max is the strongest FDG-PET parameter to correlate with outcome following SBRT for NSCLC. This is consistent with previously published data. With SBRT an emerging treatment modality for early stage disease, this may have future implications on the use of adjuvant chemotherapy.
No conflict of interest.

3435 POSTER

Adaptive dose escalation in radiotherapy (RT) for locally advanced non-small cell lung cancer (LA-NSCLC) using serial 4D FDG PET/CT scanning: a planning study

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Background: There has been recent interest in dose escalation in LA-NSCLC, with the aim to improve loco-regional control and survival. Attempts to dose escalate CT-defined volumes for radiotherapy (RT) for locally-advanced NSCLC have been limited due to organ at risk (OAR) toxicity. We investigated the potential for adaptive dose-escalation using 4DPET/CT scans acquired prior to and during a course of radical chemo/RT (CRT).
Material and Methods: This single institution study prospectively enrolled patients with NSCLC receiving CRT to a dose $\geqslant$60 Gy, delivered in daily 2 Gy treatments. 4DPET/CT scans were acquired prior to (week 0) and at weeks 2 and 4 during RT. RT was delivered to the patients using the intensity modulated RT (IMRT) plan developed from the week 0 scans. Three alternative dose escalated IMRT plans were developed offline based on the week 0, 2 and 4 scans. The PET avid primary (PET-T) and nodal disease (PET-N) volumes were auto-contoured using the 50%SUVmax metric. PET-T and PET-N were dose escalated to as high as possible while respecting OAR constraints and ensuring coverage of the clinical plan PTV. The D95% of the PET-T and PET-N were calculated and compared between week 0, 2 and 4.
Results: Thirty-two patients were recruited, with 27 completing all scans. Sixteen patients were stage IIIA (60%), 9 were IIIB (33%) and 2 were IIA (7%). Eight patients (30%) had been prescribed a clinical dose of 60 Gy, 17 (63%) had 66 Gy, 1 patient 70 Gy and 1 patient 74 Gy. 25 patients (93%) were boosted successfully above the clinical plan doses at week 0; this reduced to 23 (85%) at week 2 and 20 (74%) at week 4. For all weeks combined, the D95 for PET-T was higher than that delivered to clinical PTV by a median of 16.2 Gy. The D95 for PET-N exceeded that delivered to clinical PTV by 13.4 Gy. The median D95% to the PET-T at week 0, 2 and 4 were 74.4 Gy, 75.3 Gy and 74.1 Gy respectively. The median D95% to PET-N at week 0, 2 and 4 were 74.3 Gy, 71.0 Gy and 69.5 Gy.
Conclusions: Using 4DPET/CT, it is feasible to dose escalate PET avid disease in majority of patients, either at the onset or during RT. Though it was possible to escalate the PET-T to higher doses than PET-N, the nodal disease can still be boosted to significant doses. More patients were successfully dose escalated at the onset of RT, however, mid-RT dose escalation allows the additional potential for adaptation.
No conflict of interest.

3436 POSTER

Local control predicts survival in operable patients receiving stereotactic radiotherapy for early lung cancer: A Japanese–European comparison

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Background: Stereotactic body radiotherapy (SBRT) for early stage lung cancer is increasingly considered standard of care for medically inoperable patients and for patients refusing surgery. This joint analysis aimed at revealing differences in treatment technique and results between a Japanese and a Dutch high-volume stereotactic radiotherapy center.
Material and Methods: Lung cancer patients treated with SBRT for a single lesion (T1−2N0M0) in Osaka (OM) or Groningen (GN) were retrospectively analyzed. Forty to 60 Gy were delivered in 3 to 10 fractions. To correct for differences in planning and dose prescription, all doses were recalculated using collapsed cone or Monte Carlo dose calculation algorithms and expressed as biologically effective dose (BED; alpha/beta = 10) at the margin of the planning target volume (PTV). Survival and local control were analyzed.
Results: Between September 2006 and July 2010, 383 patients were registered (OM, n = 162; GN, n = 221). Patients in GN had a worse WHO performance status (PS) and larger gross tumor volumes (GTV) than in OM ($p < 0.001$). Treatment dose was prescribed at the isoceter in OM, and at the periphery of the PTV in GN. This resulted in a peripheral BED of 102 Gy (+/− 21) and 83 Gy (+/− 5) in GN and OM, respectively. Median follow up was 41 months. At 3 years, actuarial overall survival (OS) was 72% and 52% ($p < 0.001$), and disease specific survival (DSS) was 85% and 76% ($p = 0.1$) for OM and GN respectively. GTV and PS were highly significant prognostic factors for survival. After correction for GTV and PS, OS was no longer significantly different between institutions (HR 0.88; $p = 0.47$). Local control rate at 3 years was better in GN (93% vs 84%, $p < 0.05$) despite larger GTVs; GTV ($p = 0.048$) and BED ($p = 0.014$) were significant factors. While local failure (LF) had a significant effect on OS in operable patients (56/383), that was not observed in inoperable patients: Adjusted for GTV and PS, LF yielded a HR for OS of 7.5 (2−27; $p = 0.003$) for operable and a HR of 1.1 (0.7−1.9; $p = 0.6$) for inoperable patients.
Conclusions: Administration of sufficient dose was confirmed in this international comparison of the European with the Japanese approach towards SBRT. Higher dose yielded better local control, local control in turn was significant for overall survival in operable patients.
This work was supported by the Japan Society for Promotion Science (JSPS) Core-to-Core Program (number 23003).
No conflict of interest.

3437 POSTER

Cost-effectiveness analysis of thoracic radiotherapy in non-operated clinical stage IIIA non-small cell lung cancer

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Background: The aim of this study is to use patient-level data to compare the cost-effectiveness of radiotherapy for non-operated clinical stage IIIa non-small cell lung cancer (NSCLC) patients who were treated with chemotherapy.
Material and Methods: We performed a retrospective cohort study for non-operated clinical stage IIIa NSCLC patients diagnosed in 2007, using data

from the Collaboration Center of Health Information Application (CCHIA). CCHIA is a nation-wide database including cancer registry, death registry, and reimbursement data in Taiwan. We identified patients treated with both chemotherapy and radiotherapy (group A) and those were treated with chemotherapy only (group B). We compared the cost and effectiveness of group A vs group B. Effectiveness was measured as survival from diagnosis to either death or censored on Jan 1st, 2010. We compared the survival and cost (both within 2 years after diagnosis) between group A and group B. We used log-rank test, Cox proportional hazard model, t-test, and Chi-square test for the above statistical analysis. We used the net benefit regression to estimate the incremental cost-effectiveness ratio (ICER, in US dollars/life-years (USD/LY)) of radiotherapy after covariates adjustment including characteristics of patients' demographic, comorbidity, health services' provider, and clinical status.
Results: We identified 39 & 92 patients for group A & B respectively. The distribution of the covariates was not statistically different between both groups. Radiotherapy was associated with insignificantly better survival. Radiotherapy was associated with higher mean incremental costs and mean incremental effectiveness (life-days). The mean cost (2011 USD) and effectiveness (days) (both within 2 years from diagnosis) for group A vs group B were 61200 vs 39466 and 497 vs 472 respectively. The unadjusted ICER was 317392 USD/LY. After covariates adjustment, the net benefit analysis revealed that radiotherapy is not likely to be beneficial unless the willingness-to-pay (WTP) is at least around 130000 USD/LY.
Conclusions: In this population based study, we found that radiotherapy might prolong survival for non-operated clinical stage IIIa NSCLC. However, it may not be cost-effective at common WTP threshold.
No conflict of interest.

3438 POSTER

Evaluation of the usefulness of restricted respiratory interval at the time of radiotherapy for non-small cell lung cancer patient

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Background: It is essential to minimise the movement of tumour due to respiratory movement at the time of respiration controlled radiotherapy of non-small cell lung cancer patient. Accordingly, this study aims to evaluate the usefulness of restricted respiratory interval by comparing and analysing the treatment plans that apply free and restricted respiration interval respectively.
Subjects and Methods: After having conducted training on 9 non-small cell lung cancer patients (tumour n = 10) from April to December 2011 by using 'signal monitored-breathing (guided-breathing)' method for the 'free respiratory interval' measured on the basis of the regular respiratory interval of the patents and 'restricted respiratory interval' that was intentionally reduced, total of 10 CT images for each of the respiration phases were acquired by carrying out 4D CT for treatment planning purpose by using RPM and 4D CT simulator. Visual gross tumour volume (GTV) and internal target volume (ITV) that each of the observer 1 and observer 2 has set were measured and compared on the CT image of each respiratory interval. Moreover, the amplitude of movement of tumour was measured by measuring the center of mass (COM) at the phase of 0% which is the end-inspiration (EI) and at the phase of 50% which is the end-exhalation (EE). In addition, both observers established treatment plan that applied the 2 respiratory intervals, and mean dose to normal lung (MDTNL) was compared and analysed through dose-volume histogram (DVH). Moreover, normal tissue complication probability (NTCP) of the normal lung volume was compared by using dose-volume histogram analysis program (DVH analyzer v.1) and statistical analysis was performed in order to carry out quantitative evaluation of the measured data.
Results: As the result of the analysis of the treatment plan that applied the 'restricted respiratory interval' of the observer 1 and 2, there was reduction rate of 38.75% in the 3D direction movement of the tumour in comparison to the 'free respiratory interval' in the case of the observer 1, while there reduction rate was 41.10% in the case of the observer 2. The results of measurement and comparison of the volumes, GTV and ITV, there was reduction rate of 14.96±9.44% for observer 1 and 19.86±10.62% for observer 2 in the case of GTV, while there was reduction rate of 8.91±5.91% for observer 1 and 15.52±9.01% for observer 2 in the case of ITV. The results of analysis and the reduction rate of MDTNL 3.98±5.62% for observer 1 and 7.62±10.29% for observer 2 in the case of MDTNL, while there was reduction rate of 21.70±28.27% for observer 1 and 37.83±49.93% for observer 2 in the case of NTCP. In addition, the results of analysis of correlation between the resultant values of the 2 observers.
Conclusion: It was possible to verify the usefulness and appropriateness of 'restricted respiratory interval' as the treatment plan that applied 'restricted respiratory interval' illustrated relative reduction in the evaluation factors.
No conflict of interest.

3439 POSTER

Pulmonary imaging changes after radiotherapy in patients with lung cancer or oesophageal carcinoma and its correlation to CTC grade 2 or higher radiation pneumonitis

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Background: To retrospectively analyse risk factors for the Common Terminology Criteria for Adverse Events (CTC AE) V3.0 grade 2 or higher radiation pneumonitis (RP) in lung cancer or oesophageal carcinoma patients with pulmonary imaging changes after radiotherapy.
Material and Methods: From January 2011 to May 2012, 60 patients with lung cancer and 17 patients with esophageal carcinoma had pulmonary imaging changes (interstitial inflammation or interstitial fibrosis) after thoracic radiotherapy with no less than 50 Gy/25f in our department. 41 patients received three-dimensional conformal radiation therapy, 15 patients received intensity-modulated radiation therapy, and 21 patients received volumetric modulated arc therapy. There were 53 male patients and 24 female patients, and the median age was 61 (range 31−77). We analysed clinical and dosimetric risk factors for grade ⩾2 RP.
Results: After the median follow-up time of 14 months (6−23 months), the median time to detection of pulmonary imaging changes after radiotherapy was 2 months (0−6 months), and 79.2% (61/77) of patients had their imaging changes in regions receiving ⩾40 Gy. 50.7% (39/77) of patients had grade ⩾2 RP, and the median time to grade ⩾2 RP after radiotherapy was 1 month (0−5 months). Risk factors of grade ⩾2 RP were pulmonary infection (infection *VS.* non-infection: OR=11.48, $P = 0.000$) and lung cancer (lung cancer *VS.* oesophageal carcinoma: OR=4.51, $P = 0.009$). Dosimetric factors including V_5, V_{10}, V_{20}, V_{40}, volumes and mean doses of ipsilateral, contralateral and total lung were found to be not associated with grade ⩾2 RP. Fungous infection and grade 4−5 RP were much higher in patients with imaging changes exceeded regions receiving ⩾40 Gy than those with imaging changes in regions receiving ⩾40 Gy (62.5% *VS.* 8.2%,$P = 0.000$;37.5% *VS.* 0%,$P = 0.000$).
Conclusions: Pulmonary infection and lung cancer were risk factors of grade ⩾2 RP in patients with pulmonary imaging changes after thoracic radiotherapy, and pulmonary imaging changes were predominantly in regions receiving ⩾40 Gy. Furthermore, patients with imaging changes exceeded regions receiving ⩾40 Gy had much higher possibilities to get fungous infection and grade 4−5 RP.
No conflict of interest.

3440 POSTER

Patterns of failure after stereotactic body radiotherapy for histologically proven stage I non-small-cell lung cancer

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Background: To report patterns of failure after stereotactic body radiotherapy (SBRT) for histologically proven Stage I non-small-cell lung cancer (NSCLC).
Materials and Methods: Between 2003 and 2007, 78 consecutive patients with clinically staged, histologically proven Stage I NSCLC (median age, 79 years; T1N0M0, n = 44; T2N0M0, n = 34) were treated with SBRT at our center in Japan. Twenty-four patients were medically operable but refused surgery, and 54 patients were inoperable because of underlying comorbidities. The histology was adenocarcinoma in 53 patients, squamous cell carcinoma in 23 patients, and others in 2 patients. Stereotactic three-dimensional treatment was performed using non-coplanar, static 4-MV photon beams. Forty-eight Gy in 4 fractions within 4−8 (median = 4) days was prescribed for the isocenter of the planning target volume for all patients. Data were collected and analyzed retrospectively.
Results: Median durations of observation for all patients and survivors as of the final follow-up were 41.1 (range, 2.2–105.9) and 59.9 (range, 9.4–105.9) months, respectively. The 5-year local control, progression-free survival, overall survival, and cause-specific survival were 69.5%, 45.9%, 47.6%, and 63.2%, respectively. Disease progression was observed in 36 patients. The sites of first recurrence were distant only (n = 21), local only

(n = 8), nodal only (n = 5), and nodal and distant (n = 2). First recurrence occurred at a median of 14.0 (range, 4.5–91.5) months, and, in 28 patients (77.8%), first recurrence occurred within 2 years. Finally, after long-term follow-up, local, nodal, and distant failure occurred in 15, 16, and 29 patients, respectively. Local failure occurred at a median 16.4 (range, 5.7–91.5) months, and, in 10 of 15 patients (66.7%), local failure occurred within 2 years. One patient safely underwent salvage surgery and had not developed new recurrence as of the final follow-up (76.5 months). Another patient developed local failure at 91.5 months after SBRT without nodal and distant failure. Univariate analysis showed that a large gross tumor volume was associated with a trend toward high local failure rate, and was a significant factor in cause-specific survival, although no significant factors were correlated with nodal and distant failure.
Conclusions: After SBRT for histologically proven Stage I NSCLC, the predominant pattern of failure was distant failure, followed by local failure. Local failure may occur even after a long-term follow-up. Dose escalation should be considered to prevent local failure, especially for large tumors, as well as systemic chemotherapy to prevent all failures.
No conflict of interest.

3441 POSTER

Stereotactic body radiotherapy (SBRT) for elderly patients with early stage non-small cell lung cancer (NSCLC)

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Background: SBRT is a standard approach for early stage NSCLC, which is applied for elderly patients that cannot tolerate surgery. The aim of this study is to assess the efficacy and safety of SBRT, especially for elderly patients.
Material and Methods: Since December 2006 through June 2010, 130 patients (94 men and 36 women) of early stage NSCLC (cT1a in 51, cT1b in 53, and cT2a in 26 patients without lymph node and distant metastasis) underwent SBRT at our institution. Histological diagnosis was adenocarcinoma in 58, squamous cell carcinoma in 30, and no evidence of malignancy in 42 patients. Tumors were located in the upper or middle lobes in 87 and in the lower lobes in 43. The median diameter of the tumor was 23 mm(11−47 mm), the median gross tumor volume was 4.9 cm^3(0.8–53.7 cm^3), and the median planning target volume was 28.2 cm^3(6.3–140.4 cm^3). Total doses were 48 Gy in 4 fractions at the isocenter. Local control and overall survival rates were calculated by the Kaplan–Meier method. The median follow-up time after SBRT was 37 months (range: 1−73 months). The endpoints were local control rates. Adverse events were scored using Common Terminology Criteria for Adverse Events version 4.0.
Results: The subjects were 78 years old in median (range: 59−90) and contained 56 patients over 80 years old (43%). The 3-year local control rates were 80.5% for all patients, and 85.7%, 81.3%, and 67.1%, for T1a, T1b, and T2a, respectively. Local control and overall survival rates at 3 years were 82.3% and 82.3% for patients under 80 years old and 77.4% and 67.6% for patients over 80. On univariate analysis for local control, only clinical stage was a significant factor ($p = 0.037$), however, age was an insignificant factor ($p = 0.361$). Concerning adverse events, only one 83-year-old patient developed grade-3 radiation pneumonitis, however, completely recovered after steroid therapy. The other grade-2 or more adverse events were grade-2 rib fractures in 3 patients, all of whom were under 80 years of age.
Conclusions: Our study showed that SBRT achieved equivalent local control even for patients over 80 of age with NSCLC to that for under 80. Overall survival for the elderly patients was lower than that for under 80, however, the difference was insignificant. The incidence of adverse events was minimal for the elderly patients. SBRT for early stage NSCLC provided acceptable local control and was safe for patients over 80 years of age as well.
No conflict of interest.

3442 POSTER

Hypofractionated (chemo)radiation delivered with helical tomotherapy allows safe dose escalation in stage III unresectable non small cell lung cancer

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Background: To assess treatment outcome, and toxicity after a moderately escalated hypofractionated radiotherapy delivered with Helical Tomotherapy (HT) in locally advanced stage III unresectable non-small cell lung cancer (NSCLC) combined with sequential or concurrent chemotherapy.
Methods and Materials: Sixty-one eligible patients were treated with combined platinum-based chemotherapy associated with a moderately escalated hypofractionated radiation course delivered with HT. The treatment schedule consisted of 30 daily fractions of 2.25–2.28 Gy each administered in 6 weeks, corresponding to a normalized total dose at 2 Gy per fraction (NTD2) of nearly 70 Gy, applying a/b ratio of 10. The target was considered the gross tumour volume and the clinically proven nodal regions, without elective nodal irradiation. Overall survival and local control were assessed as well as acute and late toxicity using Radiation Therapy Oncology Group (RTOG) grading system.
Results: No Grade $\geqslant$4 acute and late toxicity was reported. Acute Grade 3 treatment-related pneumonitis was detected in 10% of patients. Two patients, both receiving the concurrent schedule, developed a Grade 3 acute esophagitis. The overall incidence of late Grade 3 lung toxicity was 5%. No patients experienced a Grade 3 late esophageal toxicity. The median survival duration was 18 months in the sequential group and 24 months in the concomitant group, with 1-year and 2-year OS rate of 77% and 53% respectively for all patients, 43% of whom were stage IIIB.
Conclusions: Our findings shows that a moderately hypofractionated radiation course delivered with HT is a feasible treatment option for patients with inoperable locally advanced NSCLC receiving chemotherapy (sequentially or concurrently). Hypofractionated radiotherapy with a dedicated technique allows safely dose escalation, minimizing the effect of tumor repopulation that may occur with prolonged treatment time.
No conflict of interest.

3443 POSTER

Pleural lavage cytology is a significant prognostic factor for stage I lung adenocarcinoma patients

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Background: The result of cytological examination of pleural effusion is important for planning of treatment and prediction of the prognosis in non-small cell lung cancer (NSCLC) patients. Previously, we reported that the positive cytology was detected by carrying out pleural lavage cytology (PLC) at the time of thoracotomy for NSCLC patients with no pleural effusion and its prognostic significance was evaluated. Here, re-examination was performed with additional follow-up survey and new knowledge about the significance of PLC was reported.
Material and Methods: Cytology of pleural lavage immediately after thoracotomy was examined in 1317 consecutive patients with NSCLC with no pleural effusion who underwent pulmonary resections from 1987 to 2004 in Kobe University Hospital and Hyogo Cancer Center. The patients who underwent induction therapy, who underwent CT-guided needle biopsy, and who had pleural dissemination confirmed by pathological examination were excluded from this study.
Results: Forty-six of 1317 patients (3.5%) had positive cytological findings. The prognosis of 46 patients was significantly worse compared with the negative cytology group (26% vs 64% for 5-year survival rate, $p < 0.0001$). In 814 of pathologically stage-I patients, eighteen patients were diagnosed as positive with PLC (2.2%) and the prognosis of them was also significantly worse (25% vs 78%, $p < 0.0001$). The recurrence rate of PLC-positive Patients in stage I was 83% (15 of 18 patients).
Conclusions: Positive finding of PLC is associated with a worse prognosis, and the tendency is significant in stage-I patients. These findings suggested the need of PLC in the staging and treatment of NSCLC patients.
No conflict of interest.

3444 POSTER

Treatment possibilities for local recurrence of surgically treated non-small cell lung cancer

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Background: Reoperation in patients previously operated for lung cancer is practically indicated in two cases. The most common reason is recurrence of disease (relapse), and the other reason is, if previous resection was made incomplete. Relapse of disease is related to the level of radicality on primary operation and is also in relation to the characteristics of the primary tumor.
Materials and Methods: The study was retrospective-prospective and included 114 patients with recurrent disease, primarily operated with the clinical stage of Ia − IV. The patients are collected from the database of

the Institute for Lung Diseases, Clinical Center of Serbia and the Institute for Oncology and Radiology of Serbia in Belgrade from year 2002 to 2010. One patient initially had a solitary metastasis in the CNS (stage IV), which was operatively treated in the beginning of treatment. Operative treatment included all kinds of resections, from minimal atypical (wedge) resection through segmental lobectomies, sleeve lobectomies, pneumonectomies, sleeve pneumonectomies, and if necessary resection of the chest wall.
Results: In the study group of 114 patients, in 42(36.84%) patients surgical resection was possible. Because of poor general condition, symptomatic therapy was applied in 14 (12.8%) patients. For other patients, chemotherapy was applied in (33.33%), radiotherapy (13.16%) and combined chemo-radiotherapy (4.39%). In 42 operated patients, the most common type of surgery was resection of the chest wall in 17 (40.48%) patients. Pneumonectomy or intrapericardial pneumonectomy was performed in 13(30.95%) patients. Mediastinal lymphadenectomy was performed in a total of 22(52.38%) patients. Complications occurred in two patients such as empyema and chronic pain, respectively.
Conclusion: The surgery of local recurrence is justified if the extent of primary operation was less than pneumonectomy.
If local recurrence appears in chest wall on the side where primary operation was done we can certainly say that resection of primary tumor which was in contact with parietal pleura was incomplete. Local recurrence such as pathologically changed lymph nodes in mediastinum more often happens when selective lymphadenectomy was done and not systemic.
Local recurrence on bronchial stump and in lung parenchyma is a sign of positive margins of earlier resection. In our patients it was most common when frozen section was not done.
No conflict of interest.

3445 POSTER

Lymphatic permeation status stratifies the prognosis of pathological node positive patients with clinical stage IA lung adenocarcinoma

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Background: Logically, lymph node metastasis in lung cancer is thought to be a result of lymphatic permeation in the primary tumor. However, tumors with pathological node metastasis (pN(+)) are not necessarily show lymphatic permeation in pathological examination. The aim of this study is to analyze the prognostic significance of lymphatic permeation in patients with pN(+).
Material and Methods: The present study included 609 clinical T1N0 lung adenocarcinoma patients that consist of 568 pN(−) and 41 pN(+) patients. The association between the prognosis and pathological findings was retrospectively analyzed.
Results: In the pathological factors, pN(+) patients showed a significant lower lepidic growth component ratio (14.0±17.1% v.s. 50.7±36.6%, P <0.001), higher lymphatic, vessel, and visceral pleural invasion rate (68, 59, and 29 % v.s. 11, 14, and 9%, all P <0.001), respectively. In pN(−) patients, both the univariate and multivariate analysis of recurrence free survival (RFS) revealed that lower lepidic growth component ratio, lymphatic, vessel, and pleural invasion had a significant correlation with a poor prognosis. On the other hand, in pN(+) patients, both the univariate and multivariate analysis of RFS showed that only patients with lymphatic invasion (Ly) had an adverse prognosis ($P = 0.024$ and 0.022). Although RFS in the pN(+) patients was significantly worse compared with pN(−) (5 years RFS rate: 51.2% v.s. 88.6%, P <0.001), RFS in pN(+)/Ly(−) patients was significantly better compare with pN(+)/Ly(+) patients, (5 years RFS rate: 68.8 and 41.9%, $P = 0.024$), which was even close to that in pN(−)/Ly(+) patients.(5 years RFS rate: 68.2%, $P = 0.33$).
Conclusions: Even in patients with pathological lymph node metastasis, lymphatic permeation status in the primary tumor stratified the prognosis of patients with clinical stage IA lung adenocarcinoma.
No conflict of interest.

3446 POSTER

Early stage lung cancer treated only with surgery, impact of the 7th AJCC classification

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Background: With the high recurrence rates observed in early stage non-small cancer (NSLC) the identification of prognostic factors in this population becomes essential. Adjuvant chemotherapy is the standard treatment for stage IB to IIIA patients since the publication of several randomized controled trials in the early 2000s.
Material and Methods: We have retrospectively reviewed a cohort of patients (characteristics resumed in table 1) treated in our center with radical resection for stage I or II NSLC between March 1999 and March 2003. These patients didn't receive adjuvant chemotherapy.
Results: Median overall survival (OS) was 55 months (m) and the survival rate at 5 and 10 years was 51% and 26% respectively. Differences are found using 6th or 7th edition AJCC classification. Patients with stage I had a better overall survival (69 vs. 43 m) and (73 vs. 39m) although the difference was only statistically significant (p<0, 05) using the 7th edition AJCC classification. Differences between stage IA and stage IB were also numerically superior with the 7th edition (76 vs. 59 m) and(91 vs. 54 m) but neither reached statistical significance (p = 0.4 and 0.08). The existence of previous chronic pulmonary obstructive disease (COPD) was prognostic OS 34 vs. 86 months p < 0.001.
Conclusions: There is little doubt that in some patients NSLC is a systemic disease even when the primary tumor is detected at an early stage, but the current AJCC classification improves the identification of a subset of patients with a good prognosis only.
No conflict of interest.

Table: Characteristics of 41 patients

Gender	92% Male
Age (median)	71(52−86)
Smoking status	56% current smokers, 37% former, 5% never
COPD	46%
Pathological staging 6th AJCC	IA: 43% IB:26% IIA: 5% IIB:25%
Pathological staging 7th AJCC	IA: 34% IB:31% IIA:10% IIB:22% IIIA 2.5%
Histology	56% squamous, 39% adenocarcinoma, 5% large cell
Lymphovascular invasion	21%
Grade	17% well differentiated, 57% moderately, 25% undifferentiated

3447 POSTER

Revision of integrated positron emission tomography value by tumor size is not necessary to evaluate malignancy grade of clinical stage IA lung adenocarcinoma

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Background: Maximal standardized uptake value (maxSUV) on positron emission tomography/computed tomography (PET/CT) is reported to be a surrogate marker of tumor malignancy grade in lung adenocarcinoma. Logically, maxSUV should be revised to correct for partial volume effect, ie, small tumors are thought to be underestimated. In this study, we examined whether revision of maxSUV by tumor size is needed in order to clinically evaluate malignancy grade of clinical stage IA lung adenocarcinoma.
Material and Methods: Consecutive 609 patients with clinical stage IA lung adenocarcinoma who had undergone preoperative PET/CT were enrolled in this study. Tumor diameter from high resolution CT was used to revise maxSUV based on outcomes of study using an anthropomorphic body phantom that conformed to National Electrical Manufacturers Association standards. Measured maxSUV (m-maxSUV) and revised maxSUV (r-maxSUV) by tumor size were compared according to pathological tumor malignancy grade and prognosis.
Results: Recovery coefficient (RC) was determined according to tumor size; 0.2, 0.6, 0.8, 0.9 and 1.0 for tumor diameter (mm) of 10−12, 13−17, 18−22, 23−27 and 20-, respectively. r-maxSUV was calculate using the equation: r-maxSUV = m-maxSUV/RC. Median m-maxSUV was significantly lower than r-maxSUV (1.6 vs 2.4). All receiver operating characteristics area under the curve for predicting ly, v, pl, n, high-grade

malignancy (ly, v, pl or n) and tumor recurrence were larger for m-maxSUV than those for r-maxSUV. Cut-off values of m-maxSUV and r-maxSUVfor predicting tumor recurrence were 3.3 and 2.7, respectively. A significant difference in recurrence free survival (RFS) and overall survival (OS) were identified between patients whose adenocarcinoma had m-maxSUV 3.3 or less (n = 471; 5-year RFS, 95.8%, OS, 96.0%) and greater than 3.3 (n = 138; 5-year RFS, 72.5%, OS, 81.9%. We also found significant differences in RFS and OS between patients whose adenocarcinoma had m-maxSUV 2.7 or less (n = 333; 5-year RFS, 96.7%, OS, 96.7%) and greater than 3.3 (n = 276; 5-year RFS, 83.0%, OS, 88.0%.).
Conclusions: Revision of maxSUV by tumor size is not necessary to evaluate malignancy grade of clinical stage IA lung adenocarcinoma.
No conflict of interest.

3448 POSTER

Our experience of surgical management of rare malignant tumours of lungs: Lessons learned

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Background: The problem of surgical treatment of rare malignant tumours of lungs remains so far insufficiently studied and remain difficult task of modern oncology. To rare malignant tumours of lungs carry tumours as epithelial tumours (carcinoid, adenoid-cystic cancer) and no epithelial tumours (sarcoma, giant cell cancer, etc.).
Aims: To analyse results of surgical management of patients with rare lung tumours.
Materials and Methods: From 1963 to 2012 in our division 4078 operations for primary lung cancer were performed. 388 (9.5%) procedures were performed in patients with rare malignant tumours.
Among rare new growths it is necessary to consider as the most widespread epithelial tumour bronchial lung carcinoid (267 patients) which differentiated on typical (90.5%) and atypical (9.5%) options. Adenoid-cystic cancer was in 28 (7.2%) patients, giant cell cancer in 13 patients. Various histologic types of non-epithelial malignant tumours (sarcoma) in 71 patients. Tactics concerning rare malignant tumours was same as in non-small cell cancer of a lung. Organ-preserving operations including bilobectomy and reconstructive bronchial plastic surgeries were a main type of surgical intervention in cases of typical carcinoids and in cases of adenoid-cystic cancer. When scoping resection atypical carcinoid considered as a non-small cell cancer of a lung and observed the modern principles of a cancer therapy. In the malignant non-epithelial tumours, atypical carcinoids and giant cell cancer expanded operations were performed including pneumonectomy, and also a lob- and bilobectomy with removal of lymph nodes from mediastinum. Postoperative complications observed in 41 patients (10.6%). The hospital lethality made 1.5% − 6 patients died. Long-term results after operations in carcinoid includes five-year survival rate 92.1%, ten-year survival rate 84.2%, in adenoid-cystic cancer: 5 years survival rate was 72.2%, more than 10 y − 27.3% survival rate, more than 15 years − 18% survival rate. In patients operated concerning non epithelial tumours in the II−III stage and with metastasises in lymph nodes (N1−2) the long term results were not very comforting, and only patients with first stage of a disease 5 year survival rate was 52%. Results of treatment of giant cell cancer were worse: 7 patients died in terms till 24 months, the others till 36 months. Only 1 patient lived 61 months.
Conclusion: Since majority of rare lung tumours are resistant to chemotherapy and radiotherapy the surgical management remain single curative option. In patients with high-differentiated tumours in T1N0M0 and T2N0M0 stages surgical treatment is rather effective, but in cases of low-differentiated type of a tumour and as when malignance involving mediastinal lymph nodes results more worse and these patients received combined therapy. Major factors of the prognosis are size of tumour, a condition of intra chest lymph nodes and degree of a differentiation of tumour cells. The long-term results of surgical management of rare malignant tumours of lungs testify to correctness of these tactics.
No conflict of interest.

3449 POSTER

Feasibility of bronchoplastic surgery for bronchial carcinoids

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Background: Surgical management of bronchopulmonary carcinoids has evolved significantly over the years. Parenchyma preserving surgery (PPS) has been the preferred management option where ever possible. We share our experience in the management of bronchopulmonary carcinoid tumors at our institute over the last 7 years, with a specific emphasis on parenchyma preserving surgery.
Methods: A retrospective analysis of records of patients diagnosed as bronchopulmonary carcinoid tumors and surgically managed at our institute since 2005 was done to evaluate the outcome of various surgical procedures.
Results: A total of 45 patients with bronchopulmonary carcinoids treated surgically were identified. Among the various surgeries performed, 17 of 45 patients (37.7%) underwent parenchymal preserving surgeries(PPS) − sleeve resection and anastomosis(5), sleeve lobectomy(7), wedge resection (5); while 28 of 45 underwent various parenchymal resection surgeries (PRS) including lobectomy (12), bilobectomy (6) and pneumonectomy (10). 25 patients (8 PPS, 17 PRS) had post operative morbidity, of which 7 patients (3 PPS, 4 PRS) required re-exploration, while 18 patients (5 PPS, 13 PRS) were managed non-operatively. There was no perioperative mortality. One patient had microscopic post margin in PPS group. During follow up (range: 4 months- 80 months), 40/45 patients were doing well(3 − lost to follow-up), with no symptoms or evidence of disease recurrence on bronchoscopy and imaging (including patient microscopic positive margin). Patients with PPS also had a better preservation on lung function in comparison to parenchymal resections on follow up pulmonary function tests.
Conclusion: Parenchyma preserving surgery is feasible in selected patients with bronchopulmonary carcinoids with better preservation of lung function and lesser morbidity.
No conflict of interest.

Treatment	Number of cases
Pneumonectomy	10
Lobectomy	12
Bilobectomy	6
Wedge resection	5
sleeve lobectomy	7
Sleeve resection & Anastomosis	5

3450 POSTER

Is early 18F-FDG PET useful for predicting pathologic response to EGFR-TKI in resectable non-small cell lung cancer?

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Background: The value of neo-adjuvant therapy in patients with resectable non-small cell lung carcinoma (NSCLC) is limited. Recent advances in targeted therapy have provided novel treatment options for NSCLC with promising results. The Epidermal Growth Factor Receptor (EGFR) is over expressed or may harbour activating mutations in adenocarcinoma in particular. Inhibition of EGFR with tyrosine-kinase inhibitor (TKI) therapy has a favourable outcome in advanced stage patients with activating mutations. Metabolic imaging in (advanced) NSCLC has shown to be valuable in response assessment in the setting of targeted therapy. The purpose of this study was to prospectively evaluate the timing of 18F-FDG-PET to measure metabolic response to neoadjuvant erlotinib, in patients with early stage NSCLC.
Patients and Methods: This study was designed as an open-label phase II trial, performed in 4 hospitals in the Netherlands. Patients received preoperative erlotinib 150 mg once daily for 3 weeks. Response evaluation was performed after 1 week and at 3 weeks using an FDG-PET/CT scan. Tumour FDG uptake and changes were measured by standardized uptake values (SUV). Metabolic response was classified using EORTC criteria. Metabolic response was compared to the histopathological response.
Results: From December 2006 until November 2010, 60 patients with NSCLC eligible for surgical resection were enrolled in this study. In 43 patients (18 male, 25 female), repeated FDG-PET/CT scans and histopathologic response monitoring were available. After 1 week the FDG-PET/CT scan showed partial metabolic response in 10 patients (23%). After 3 weeks, 14 patients (33%) showed partial metabolic response. Relative change in SUVmax at early and at late scan were significantly correlated. Histopathologic examination showed a response in 13 patients (>50% necrosis). Early FDG-PET/CT scan showed an AUC of 64.5% in predicting

histopathologic response, late scan showed an AUC of 72%. No significant difference was seen between these curves.
Conclusion: Response monitoring via FDG PET/CT scan can be performed as early as 1 week after intention of erlotinib.
Conflict of interest: *Corporate-sponsored research: This study was supported in part by an unrestricted educational grant from Roche, The Netherlands.*

3451 POSTER

18F-FDG-PET vs CT in predicting histopathological response to EGFR-TKI treatment in resectable non-small cell lung cancer

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Background: In early stage non-small cell lung cancer (NSCLC) treatment is focused on curative surgery. The value of neo-adjuvant therapy is limited. Recent advances in targeted therapy have provided novel treatment options for NSCLC with promising results. The Epidermal Growth Factor Receptor (EGFR) is over expressed or may harbour activating mutations in adenocarcinoma in particular. Inhibition of EGFR with tyrosine-kinase inhibitor (TKI) therapy has a favourable outcome in advanced stage patients with activating mutations. Several studies demonstrated that FDG-PET is able to identify response to treatment and to avoid (continued) ineffective treatment in advanced stage NSCLC. However, CT has been the clinical standard for response evaluation and discussion has been going on the performance of FDG-PET as compared to CT. In this perspective, a phase II study was designed to monitoring histopathologic response of erlotinib using both diagnostic CT and FDG-PET in patients with NSCLC. The objective was to prospectively evaluate radiologic and metabolic response after 3 weeks of neoadjuvant EGFR-TKI treatment and relate the data to histopathologic response.
Patients and Methods: This study was designed as an open-label phase II trial, performed in four hospitals in the Netherlands. Patients received preoperative erlotinib 150 mg once daily for 3 weeks. CT and FDG-PET were performed at baseline and after 3 weeks of treatment. CT was assessed according to the RECIST criteria 1.1. FDG-PET, tumour FDG uptake and changes were measured by standardized uptake values (SUV). Radiologic and metabolic responses were compared to the histopathological response.
Results: From December 2006 until November 2010, 60 patients were enrolled in this study. In 53 patients (22 male, 31 female) the combination of CT, FDG-PET and histopathological evaluation was available for the analysis. Three patients (6%) had a radiologic response. According to EORTC criteria 15 patients (28%) showed metabolic response. In 11 patients histopathologic response ($\geqslant$50% necrosis) was seen. In predicting histopathologic response, CT had a positive predictive value of 66% (CI 21%-94%) and a negative predictive value of 78% (CI 65%-87%). FDG-PET had a positive predictive value of 46% (CI 25%-70%) and a negative predictive value of 84% (CI 70%-93%).
Conclusion: FDG-PET has an advantage over CT as a predictive tool to identify histopathologic response after 3 weeks of EGFR TKI treatment in NSCLC patients.
Conflict of interest: *Corporate-sponsored research: This study was supported in part by an unrestricted educational grant from Roche, The Netherlands.*

3452 POSTER

Community-based evaluation of determinants for outcome of completely resected non-small cell lung cancer (NSCLC) stage IB receiving adjuvant chemotherapy

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Background: The case for adjuvant chemotherapy following microscopically completely resected NSCLC stage IB is not yet fully illuminated. Adjuvant chemotherapy is currently optional for these patients (pts). We reviewed a consecutive group of unselected completely resected stage IB pts according to 6th staging edition in Copenhagen who received adjuvant chemotherapy and examined subgroups for determinants of overall survival (OS) and disease free survival (DFS).
Materials and Methods: Consecutive pts completely resected 2005–2012 received adjuvant i.v. cisplatin 75 mg/m^2 day 1 and i.v. vinorelbine 30 mg/m^2 day 1+ 8 every third week for 4 cycles. 50 variables including patient characteristics, pathology and surgical records, relapse site and survival were collected. 2- and 5-year OS and DFS were calculated using Kaplan–Meier plots. Differences in OS in subgroups were evaluated using Cox regression analysis.
Results: Among totally 69 pts there were 24 males (34%), median age was 63 years (range 40−78 years). 49 pts (70%) had adenocarcinoma, 14 pts (20%) had squamous cell carcinoma, 5 pts (7%) had large cell carcinoma and 2 pt (3%) had mixed type NSCLC. Median tumor size was 31 mm (7−90 mm), 53 pts (76%) had pleural involvement and 6 pts (9 %) had vascular invasion. Median follow-up was 3.4 years (0.35 −7.3 years). 13 pts (19%) had disease recurrence being local in 46%, distant in 31 % and local + distant in 23%. 11 pts (16%) died. Kaplan–Meier estimates of 2-, and 5-year OS were 90% (CI: 80−96) and 82% (CI: 70−90). 2-, and 5-year DFS were 84% (CI: 73−92) and 74% (CI: 62−83). A multivariate Cox regression analysis including gender, age, histology, tumor size, pleural involvement, vascular involvement, and performance status revealed that pts with a tumor size 5 cm or smaller had significant better OS than pts with tumors larger than 5 cm (p = 0.05). Literature reviews from 2003–2012 revealed 4 articles reporting on OS specifically in stage IB receiving adjuvant chemotherapy with 5-year OS ranging from 60−85% (CI: 52−91) [1−4].
Conclusion: It might be anticipated that selected patients included in randomized trials would experience a better OS than unselected community-based similar pts. This was not the case, supporting application of results to routine daily practice in unselected stage IB pts. Only tumor size was significant in multivariate analysis which corroborates with current 7th staging edition. Biomarkers may clarify which pts in 7th edition stage IB may benefit or not from ACT.
No conflict of interest.

3453 POSTER

Online validation of survival-associated biomarkers in non small-cell lung cancer using transcriptomic data of 1,715 patients

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Background: To decipher the molecular basis of lung cancer and to improve treatment strategies we have to identify genes correlated to therapy response and to survival. Here, we present the development of a new, freely available online tool suitable for the real-time meta-analysis of published lung cancer microarray datasets to validate expression based survival associated biomarker candidates.
Materials and Methods: First we have searched the caBIG, GEO and TCGA repositories to identify datasets with published gene expression data and survival information. In this, three GEO platforms(GPL96, GPL570 and GPL3921) were considered as these possess 22,277 common probes, which were used for constructing the database. All together 1,715 NSCLC samples in ten independent datasets were identified, 85% have overall survival and 45% progression free survival info, one-third adenocarcinomas and one-third squamous cell carcinomas. Cox uni- and multivariate analysis, Kaplan–Meier survival plot, and the hazard ratio with 95%confidence intervals and logrank P value are calculated and plotted in R using Bioconductor packages. To assess the prognostic value of a gene, each percentile (of expression) between the lower and upper quartiles are computed and the best performing threshold can be used as the final cutoff in a Cox regression analysis. The complete meta-analysis tool can be accessed online at http://www.kmplot.com/lung/
Results: We used this analysis tool to validate previously published survival associated biomarkers including 21 individual genes and 7 gene expression signatures. Each of the biomarker candidates was investigated in a cohort having similar clinical characteristics as the patients in which they were originally described. Survival was best predicted by CDK1 (HR = 2.56, p<1e-16), CD24 (HR = 2.45, p=3.6e-10) and CADM1 (HR = 0.38, p=7e-12) in adenocarcinomas and by CCNE1 (HR = 2.44, p=4.8e-08) and VEGF (HR = 1.9, p=3.3e-10) in all NSCLC patients. One of the signatures using 139 genes achieved an even higher power (HR = 3.59, p=8.9e-16) in stage I NSCLC patients.
Conclusions: In summary, by utilizing genome-wide microarray datasets we have successfully integrated a large scale database suitable for the *in silico* validation of biomarker candidates. The presented program is a highly valuable tool for lung cancer research groups enabling to promptly validate genes correlated to survival in order to choose the most robust markers for subsequent analyses.
No conflict of interest.

3454 POSTER

Poor prognosis of concurrent KRAS and TP53 mutations in patients with resected non-squamous non-small cell lung cancer (NSCLC)

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Background: *TP53* and *KRAS* mutations are the most frequent genetic alterations in lung adenocarcinomas but their prognostic impact in early-stage NSCLC remains debated. Here, we addressed the prognostic value of *TP53* inactivating mutations regarding concurrent genetic alterations in *EGFR*, *KRAS*, *CDKN2A*, *CCND1*, *CCND3* and *CCNE1*.
Material and Methods: *TP53* mutations were determined in a surgical series of 140 consecutive non-squamous NSCLC prospectively collected. These tumors were characterized for *TP53* (ex 4−10), *EGFR* (ex 18−21) and *KRAS* (ex 2) mutations by direct sequencing, as for *CDKN2A* homozygous deletions and for *CCND1*, *CCND3*, *CCNE1* amplifications by Q-PCR. Prognostic factors were determined using uni- and multivariate Cox-model analyses on overall survival (OS). Then, we addressed the effect of concurrent mutations on prognostic (ie $TP53_m$ and $KRAS_m$) by testing their interaction in Cox models on OS.
Results: After a median follow-up 7.03 years (CI 6. 67–7.57), 72 events occurred. Pts had a median age of 60 years (range 33−85), included 58 females and 82 males, 123 adenocarcinomas and 17 other histologies, 82 stage I, 27 stage II and 31 stage IIIA tumors. Somatic mutations were: 32% *TP53*, 21% *KRAS*, 17% *EGFR*, 6% had concurrent $KRAS_m$-$TP53_m$; amplifications were: 15% *CCND1*, 12% *CCNE1*, 11% *CCND3*; homozygous deletions were 9% *CDKN2A*. In multivariate analysis, prognostic factors were: tumor stage II (HR 2.14; CI 1.17–3.80), tumor stage III (HR 3.62; CI 2.03–5.71), $TP53_m$ (HR 0.54; CI 0.30–0.94) and $KRAS_m$ (HR 2.13; CI 1.25–3.55). The prognostic of $TP53_m$ was profoundly impacted by the co-occurrence of a $KRAS_m$ (interaction p = 0.001). Indeed, $TP53_m$ was a factor of favorable outcome in $KRAS_{wt}$ tumors (HR 0.32; CI 0.15–0.62), and conversely, a factor of poor outcome in $KRAS_m$ (HR 2.56; CI 0.88–7.23). This interaction was also validated considering disease-free survival (interaction p = 0.02) and cancer-specific survival (interaction p = 0.003). Median OS was 2.14, 4.66, 6.59 and 10.60 years for $TP53_m$-$KRAS_m$, $TP53_{wt}$-$KRAS_m$, $TP53_{wt}$-$KRAS_{wt}$ and $TP53_m$-$KRAS_{wt}$, respectively (log-rank p = 0.0005).
Conclusions: In our series, concurrent *KRAS* and *TP53* mutations conferred a very poor prognostic in patients with resected non-squamous NSCLC. Dedicated targeted therapies are urgently needed to treat this subgroup of patients.
No conflict of interest.

3455 POSTER

High throughput parallel amplicon sequencing of common driver mutations from FFPE lung cancer samples in molecular pathological routine diagnostics for a regional health care provider network

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Background: Treatment paradigms for non-small-cell lung cancer (NSCLC) have shifted from one based only on histology to one that incorporates molecular subtypes. The list of therapeutically targetable lesions is rapidly increasing including mutations in genes such as *EGFR*, *HER2*, *KRAS*, *ALK*, *BRAF*, *PIK3CA*, *AKT1*, *ROS1*, *NRAS*, *FGFR1* and *MAP2K1*. Analysis of these potential targets is becoming a challenge in terms of work load, tissue availability as well as cost. We aimed to reduce 1) the time requirement for comprehensive molecular diagnostics, 2) the minimal amount of formalin fixed paraffin embedded (FFPE) derived input DNA, 3) while at the same time increasing the number of target regions analysed.
Material and Methods: We established a multiplex PCR to amplify up to 190 lung cancer relevant target regions from at least 50ng of FFPE derived tumor DNA. The amplicon libraries were ligated to adapters encompassing medical identifier sequences that allowed multiplexing of up to 48 patients to be sequenced on a benchtop Illumina platform (MiSeq).
Results: So far, we sequenced more than 450 samples of patients diagnosed with NSCLC. We found that the time needed to complete the mutation screening as well as the needed material was significantly reduced. Out of 260 samples of patients diagnosed with squamous-cell carcinoma we could identify six new mutations in the DDR2 gene confirmed by Sanger Sequencing for which a clinical trial at the Network Genomic Medicine Lung Cancer (NGM), a regional molecular screening network of the Center for Integrated Oncology Köln Bonn, is open for the treatment with Dasatinib.
Conclusion: We have established next generation sequencing for FFPE lung cancer samples in routine diagnostics to be able to screen 190 relevant traget regions within 10 working days.
No conflict of interest.

3456 POSTER

Does the "two week wait" target improve the waiting times for specialist review and also waiting time between first seen by lung cancer specialist and diagnosis of lung cancer?

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Background: Incidence and mortality rates for men have fallen sharply since peaking in 1974. Incidence of lung cancer has risen by 76 per cent for women between 1971 and 2000, while mortality rates are falling slightly after peaking in 1994. Lung cancer 5-year survival rates are poor and have been largely static over time. Cancer waiting time targets were introduced to monitor service performance via process improvement. The intention was to improve the outcome (survival) of the disease. The aim of the study was to assess whether the 'two week-wait' target can improve survival in patients with lung cancer.
Materials and Methods: 753 patients were diagnosed with lung cancer between January 2002 and December 2006. Data were retrospectively collected from the cancer database at Queen Elizabeth Hospital, London. Survival was compared in patients that were referred via the' two week-wait' rule (Group 1) and those not referred via this pathway (Group 2).
Results: Only 27% of patients were referred under the' two week-wait' rule and of the remainder a significant proportion came from Accident & Emergency (A&E) or referred from other specialities (221 and 188 patients respectively). Waiting time between referral and first seen by lung specialist for both groups is seen in the upper half of Table 1 and waiting time between first seen by specialist and diagnosis of lung cancer for both groups is seen in the lower half of Table 1.

Table 1.

Waiting time	Group 1, TWR patients	Group 2, Non TWR patients
Between referral and first seen by lung specialist		
Average	22 days	22 days
Median	19 days	17 days
Range	−100 to 161 days	−20 to 429 days
Between first seen by specialist and diagnosis of lung cancer		
Average	9 days	9 days
Median	10 days	5 days
Range	0 to 37 days	−26 to 480 days

Conclusions: There is no difference in the waiting times for specialist review between the two groups and both groups have similar waiting time for diagnosis once they have been examined by the lung specialist.
No conflict of interest.

3457 POSTER

Correlation of fibroblast growth factor-inducible molecule14 (Fn14) expression with mutational profile and clinical outcome in patients (pts) with non-small cell lung cancer (NSCLC)

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Background: Fn14, the cell surface receptor of tumor necrosis factor-like weak inducer of apoptosis (TWEAK), is highly expressed in NSCLC. In pre-clinical models of NSCLC, elevated Fn14 expression has been associated with increased tumor cell migration and invasion. We seek to evaluate the prognostic value of Fn14 in pts with NSCLC.
Methods: We evaluated primary tumor samples (TS) from 114 pts with NSCLC who also had primary tumor xenografts (PTX) generated in NOD-SCID mice from these samples. Expression of Fn14 in tissue microarrays created from TS as well as from corresponding PTXs was assessed by immunohistochemistry using anti-human Fn14 monoclonal mouse antibody MAKM-1.11.17-IgG(SPA) generated by Roche Professional Diagnostics (Penzberg, Germany) and H-score (intensity × percentage) was calculated. Mutational profiling was performed on DNA isolated from formalin-fixed paraffin-embedded TS, using either Sequenom OncoCarta™ v 1.0 or a lab-customized lung cancer panel. Multivariable analyses of disease free survival (DFS) and overall survival (OS) were performed based on TNM stage, histology, mutational status, and Fn14 expression in TS or PTX.
Results: Pt characteristics: Stage I/II vs III/IV = 84:30; squamous vs adenocarcinoma vs other = 52:56:6. Fn14 expression was present in 41 of 84 (49%) of TS with a median H-score of 0 (range: 0–140), and in 76 of 97 (78%) of PTX with a median H-score of 15 (range: 0–250). Sequenom analysis detected mutations in 40.2% (43/107) of samples with *K-RAS* and *EGFR* mutations being the most common (17% and 8.4% respectively). Median Fn14 H-scores were significantly higher in PTX with *K-RAS* mutation than wild-type (56.2 vs. 10, $P = 0.017$). In multivariable analyses, high PTX Fn14 expression (H score>15) was the only independent prognostic factor for DFS when controlled for mutational status, stage, and histology (HR: 2.56, 95% CI: 1.28–5.11, $P = 0.008$). Fn14 expression in TS was not prognostic of DFS or OS in multivariable models.
Conclusions: High expression of Fn14 in PTX confers poor DFS in pts with NSCLC and exhibits a stronger prognostic value than Fn14 in TS.
Conflict of interest: *Ownership: Roche. Other substantive relationships: Employment: Roche Diagnostics GmbH, Hoffmann-La Roche, Inc.*

3458 POSTER

Highly multiplexed detection of actionable mutations in surgically resected tumor specimens from Japanese patients with lung adenocarcinoma by ultra-deep targeted sequencing

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Background: Detection of tumor genetic alterations is critically needed for lung cancer clinic as well as for the development of novel molecular targeted therapeutics. This report describes the results of a broad spectrum of genetic alterations identified in Japanese patients with lung adenocarcinoma by ultra-deep targeted sequencing.
Material and Methods: Highly multiplexed amplicon sequencing was performed using genomic DNA extracted from snap-frozen surgically resected tumor specimens. TruSeq amplicon cancer panel (Illumina) was used for the detection of somatic mutations in 48 cancer related genes followed by ultra-deep sequencing (Illumina) at an average coverage of approximately 2800x. *ALK*, *ROS1* and *RET* translocations and *EGFR, MET, PIK3CA, FGFR1* and *FGFR2* amplifications were also detected by multiplex RT-PCR and quantitative PCR, respectively.
Results: The demographics of 140 consecutive patients enrolled in this prospective study at Shizuoka Cancer Center between July 2011 and November 2012 are as follows: median age 69 years (range: 43−89); male 57.9%; never smoker 34.3%; tumor stage: I 62.9%, II 20.0%, III 12.1%, IV 5.0%. *EGFR* mutation was most frequently detected (43.0%) followed by *TP53* mutation (33.8%). In addition, mutations in genes such as *KRAS* (17.6%), *PIK3CA* (14.1%), *STK11* (6.3%), *CTNNB1* (5.6%), *MLH1* (4.9%), *HER2* (2.1%), *BRAF* (1.4%), *MET* (1.4%), *PTEN* (1.4%), *SMAD4* (1.4%), *VHL* (1.4%), *ATM* (0.7%), *GNAS* (0.7%), *HRAS* (0.7%), *JAK2* (0.7%) and *PTPN11* (0.7%) were identified. Gene amplifications in *EGFR* (2.8%), *MET* (0.7%) and *PIK3CA* (0.7%) and fusion genes such as *EML4-ALK* (0.7%) and *KIF5B-RET* (0.7%) were also detected. It is noteworthy that, contrary to previous reports claiming the mutual exclusivity of genetic alterations in lung adenocarcinoma, 40.8% of patients harbored simultaneous actionable mutations in this study, suggesting the genetic complexity of lung adenocarcinoma.
Conclusions: We managed to detect a wide range of genetic alterations and identified additional actionable mutations besides popular driver mutations such as *EGFR*, *KRAS* and *EML4-ALK* mutations in Japanese lung adenocarcinoma patients. This approach may facilitate elucidation of detailed molecular characteristics of lung adenocarcinoma, thereby implementing personalized cancer medicine.
No conflict of interest.

3459 POSTER

Accelerated normofractionation in medically inoperable stage I non-small cell lung cancer yields excellent local control

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Background: The standard of care for stage I non-small cell lung cancer (NSCLC) is surgery. Due to co-morbidities some patients are medically not operable. These patients are treated with radiotherapy. The best fractionation scheme is a matter of debate. Stereotactic body radiotherapy (SBRT) was successfully introduced in the past decade but is limited to smaller tumor volumes. In this study we used a schedule of dose differentiated accelerated radiotherapy with twice daily fractions of 1.8 Gy (DART-bid).
Material and Methods: Between 07/2002 and 12/2010, 54 patients (36 male, 18 female) with 56 histologically proven tumors were treated for stage I NSCLC. The median age was 71 years (range 53−87 years). The median Karnofsky Performance Score (KPS) was 70 % (range 50–100 %). Total doses were applied based on tumor size measured by the mean of 3 perpendicular diameters: 73.8 Gy for tumors <2.5 cm, 79.2 Gy for 2.5−4.5 cm, 84.6 Gy for 4.5−6 cm, 90 Gy for tumors >6 cm. Lymph nodes were electively irradiated in 16 patients (median 45 Gy, range 45−63 Gy). Toxicity was assessed according to CTC 4.0. A CT scan was performed on each follow up visit. Local failure was defined as enlargement of the lesion compared to the previous CT.
Results: The median follow up of all patients was 28.5 months (range 2–108 months), local control (LC) at five years is 90.9% (51/56). Local failures occur within the first 16 months (median 11 months, range 8−16 months). No regional lymph node failures were observed. In 12.9% (7/54) of the patients distant metastases occurred, the period of time to metastases covered a range of 4 to 52 months. 53.7% (29/54) of the patients died for non-tumor related reasons, 18.5% (10/54) cancer specific deaths occurred, and 15 patients are still alive. In the Cox regression analysis, prognosticators for LC were tumor volume ($p = 0.035$), for DFS tumor diameter ($p = 0.014$) and duration of radiotherapy ($p = 0.029$), for overall survival KPS ($p = 0.008$). Acute esophagitis grade 1 or 2 occurred in 7 cases, which resumed completely after 3 months. No chronic toxicity > grade 1 was detected.
Conclusion: DART-bid is a feasible fractionation scheme that combines high BEDs up to 101.7 Gy ($\alpha/\beta = 10$) with shortened overall treatment time, yielding high LC without significant toxicity. LC is equal to SBRT, with lower toxicity compared to reported incidences. Especially for tumor sizes out of range for SBRT, this treatment regimen serves as radiotherapeutic alternative for Stage I NSCLC patients.
No conflict of interest.

3460 POSTER

Multicenter analysis for prognostic role of high-resolution computed tomography and positron emission tomography/computed tomography in clinical stage IA lung adenocarcinoma

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Background: Although ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) is widely and increasingly used to diagnose, stage, and therapeutically assess lung cancer, the malignancy grade of tumors assessed by Maximum standardized uptake values (maxSUV) has not been investigated in detail. This study aimed to investigate the role of PET/CT as well as high-resolution computed tomography (HR-CT) to estimate the malignant behavior and prognosis of early lung adenocarcinomas.
Methods: maxSUV from PET/CT and ground-glass opacity (GGO) ratios on HR-CT before complete resection were measured in 610 patients with clinical stage IA lung adenocarcinoma. Pathological invasiveness and survival were examined in relationship to clinical factors and radiographic findings including the maxSUV, which was adjusted to correct for inter-institutional discrepancies that confer limitations upon multicenter PET studies.
Results: On analyses of receiver operating characteristic curves, optimal cutoffs of maxSUV and GGO ratio were demonstrated to predict recurrence of 2.9 (area under the curve [AUC], 0.816) and 25% (AUC, 0.803), respectively. Significant differences in RFS ($p < 0.001$) were identified between tumors having a maxSUV of $\leqslant$2.9 (5-year RFS ratio, 95%) and >2.9 (72%), and between those with GGO ratios $\geqslant$25% (98%) and <25% (79%). Both the maxSUV and GGO ratio reflected tumor invasiveness, nodal metastasis, recurrence and patient survivals, and were significant prognostic factors not only on recurrence-free and cancer-specific survivals but also on multivariate Cox analysis (all, $p < 0.001$). We grouped the patients based on GGO ratios and maxSUV of $\geqslant$25% and $\leqslant$2.9 (n = 319; Group 1), $\geqslant$25% and >2.9 or <25% and $\leqslant$2.9 (n = 152; Group 2), and <25% and >2.9 (n = 139; Group 3), respectively. The Recurrence-free survival ($p < 0.001$) also significantly differed among the groups (5-year DFS rates in Groups 1, 2 and 3: 99%, 88% and 70%, respectively).
Conclusions: The combination of maxSUV and GGO ratio is a better predictor of malignant tumor grade than either alone in clinical stage IA lung adenocarcinoma and should be considered before choosing therapeutic strategies.
No conflict of interest.

Poster Session (Sun, 29 Sep)
Lung Cancer − Metastatic

3461 POSTER

The research for the identification of the most effective and highly accepted clinical guidelines for the cancer treatment: RIGHT3 PROJECT

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Background: Clinical oncology societies develop and regularly update evidence-based guidelines in order to improve the quality of care of patients with cancer and reduce variability in cancer care. In 2004 AIOM (Italian Association of Medical Oncology) created the RIGHT (Research for the Identification of the most effective and hIGHly accepted clinical guidelines for cancer Treatment) program, successfully applied to colorectal and breast cancer guidelines. The third step of the RIGHT3 program, aims to evaluate the concordance between AIOM 2009 lung cancer guidelines and clinical practice in Italian lung cancer centers.
Materials and Methods: RIGHT3 is a retrospective observational study conducted in a sample of 53 Italian centers for lung cancer care representative of 230 AIOM centers. Site sampling from AIOM database was stratified by presence vs absence of Thoracic Surgery Unit and geographic distribution (North; Center, South). In each stratum sampled site number was proportional to the total number of AIOM sites. 14 indicators were identified to verify the concordance between 2009 AIOM lung cancer guidelines and clinical practice about staging and treatment (surgery, chemotherapy and radiotherapy). Patients with NSCLC diagnosis who had their first visit at the site during 2010 and followed-up for at least 6 months were included in 3 groups defined according to staging: I−II−IIIA, IIIB and IV.
Results: Among the 708 enrolled, 225 I−II−IIIA stage, 156 IIIB stage and 299 IV stage patients were eligible for analyses. Results showed that cyto-histological diagnosis was available for 95% of I−II−IIIA stage patients, 87% for stage IIIB and IV. PET was performed in 64% of I−II−IIIA patients and in 46% of IIIB ones. 88% of I−II stage patients underwent lobectomy and 56% of II−III stage patients undergoing complete surgery were treated with adjuvant chemotherapy.
As regards stage IV patients, 33% of them had a molecular analyses; platinum-based first-line treatment was prescribed to 87% of them, 70% underwent second-line treatment and 94% of older-than-70 y patients were treated with chemotherapy.
Conclusions: RIGHT3 study showed that guidelines adherence is high for stage IV patients and PET is not frequently used for diagnosing. Guidelines adherence monitoring and subsequent update represent crucial activity in order to provide useful instruments for better plan health care interventions.
No conflict of interest.

3462 POSTER

Encouraging outcome of patients with oligometastatic NSCLC through intrathoracic radical approach

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Background: Patients with Stage-IV NSCLC are usually subjected to palliative chemotherapy (CTX) and/or radiotherapy (RT). However, more radical treatment approaches are arising, trying to eliminate all tumor manifestations with a radical approach in case of oligometastatic disease. There is prospective data, indicating for a fraction of almost 20% long- term survivors after this regime, underlining the necessity to rethink the current treatment standards (De Ruysscher, 2012). We report supporting data from a retrospective, single-center study of radical treatment of stage-IV NSCLC.
Materials and Methods: 1029 NSCLC patients UICC stage IV were screened, who were discussed in the local Comprehensive Cancer Center and treated between 2008 and 2012. Selection criteria were <5 distant metastases and a radical treatment approach towards all tumor manifestations (surgery, RT and CTX + combinations). Patients were followed using clinical reports, imaging data and external reports. Statistical analysis was performed with SPSS 21.
Results: 16 patients (69% men, 31% women) were identified with a median age of 62 (52−75) years at diagnosis. Median Karnofsky performance index was 90 (70–100) %. Local UICC stadium (ignoring metastases) was: stage I: 20%, II: 20%, IIIA: 27% IIIB: 33%. Staging PET/CT was available in all cases. Sites of metastasis were brain (37%), lung (19%), distant lymph nodes (19%), adrenal glands (7%), and other (19%). Bioptic confirmation showed 56% adeno- and 44% squamous cell carcinomas. Loco-regional thoracic surgery was part of the interdisciplinary treatment in 62% of the cases. All patients received RT, of which 38% were combined chemoradiotherapies of intrathoracic disease. One patient was treated with stereotactic radiation therapy. Other irradiation sites included brain (42%), intrathoracic (53%) and bone (5%). No metastases were treated surgically. 53% of all patients received CTX during their course with mainly platin-based regimens. Median overall survival was 38 months with 1-/2- year rates of 79% and 56%, while median disease- free survival was 10 months with 1-/2- year rates of 41%, 33%, respectively.
Conclusions: This study confirms that radical treatment of NSCLC stage-IV disease can lead to long- term survival. The data show the importance of interdisciplinary cooperation of surgeons, oncologists and radiation oncologists along with selection of appropriate patients. To further improve the outcome of metastasized disease, more prospective data is needed.
No conflict of interest.

3463 POSTER

Adrenalectomy for adrenal metastases in low-tumor-burden metastatic lung cancer: Results of a single institution experience

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Background: Adrenal gland is a common site of metastasis in lung cancer. Adrenal metastasis (AM) can occur at the time of diagnosis (synchronous AM) or later (metachronous AM). When an AM appears as an isolated site of dissemination it is considered a good-prognosis metastatic disease. Some other times, AM occurs in the presence of other sites of metastasis. Nevertheless, few data are available about the prognosis and the optimal management of these patients and about which is the role of adrenalectomy in this situation.
Methods: Retrospective analysis of the historical series of adrenalectomies in patients treated of lung cancer at our institution.
Results: From April 2002 to April 2011, 30 patients (27m/3f) were diagnosed of AM of lung cancer (16 non-squamous, 8 squamous, 6 small-cell; 21 metachronous AM, 9 synchronous AM). We analysed 19 pts with single AM and 11 pts with AM plus other metastatic sites (8 pts with brain dissemination and 3 pts other sites). All of them were treated with adrenalectomy (26 laparoscopic, 4 open surgery). Median age was 55 years old (range: 42−71). Median size of the AM was 35 mm (range: 12–140). R0 was achieved in 26 pts (87%). Adjuvant teatment was administrated in 13 pts. There were no severe complications of surgery in any patient. All the patients had received radical treatment for the primary tumour and for other metatatic sites (8 patients brain metastases, 3 patients other sites) before adrenalectomy. Median overall survival (OS) and disease-free survival from adrenalectomy for the entire group were 44 (95% CI: 10−78) and 15 (95% CI: 7.6–22.3) months respectively. We found an statistical trend ($p = 0.087$) of better OS from adrenalectomy for patients with non-squamous histology compared with squamous histology: 57 (95% CI: 38.4–75.6) and 21 (18.3–23.8) months respectively. The percentage of alive patients at 2 and 5 years was 59.1% and 36% respectively. No significant differences were observed between matachronous and synchronous AM neither between single AM vs AM plus other sites.
Conclusions: These results add new data about the prognosis of patients with adrenal metastases into the context of low-tumor-burden metastatic lung cancer. Adrenalectomy is a tolerable procedure which plays a role in the management of these patients.
No conflict of interest.

3464 POSTER

Impact of epidermal growth factor receptor mutation status for post recurrence survival of patients with non-small cell lung cancer

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Background: The survival characteristics and prognosis of patients with recurrent non-small cell lung cancer (NSCLC) after surgical resection have not been well demonstrated. The aim of this study is to identify the prognostic factors associated with the post-recurrence survival after surgical resection of NSCLC, and to examine the best therapeutic strategy for this disease from the view point of the epidermal growth factor receptor (EGFR) status and EGFR tyrosine kinase inhibitors (EGFR-TKIs) therapy.
Patients and Methods: From 2000 through 2011, 1237 consecutive patients with NSCLC underwent pulmonary resection at National Kyushu Cancer Center. Of those, 280 patients experienced a postoperative recurrence before the end of 2012. We retrospectively reviewed these cases and analyzed the post-recurrence survival and predictors of this survival.
Results: Postoperative recurrence developed in 183 males (65%) and 97 females (35%). The mean age of the patients was 66 years. Adenocarcinoma accounted for 68% (n = 189) of the recurrences, followed by squamous cell carcinoma (n = 51, 18%) and other histological types (n = 40, 14%). The EGFR mutation status was examined in 183 cases (65%), and 83 patients (30%) were positive for an EGFR mutation. The median post-recurrence survival time and the five-year survival rate of all cases were 25 months and 20.8%, respectively. As initial treatment for the recurrence, chemotherapy was administered to 152 patients (54%), chemoradiotherapy to 62 (22%), radiotherapy to 32 (12%) and surgical resection was performed in 15 (5%) cases. There have been no significant survival differences based on the initial treatment strategies. A multivariate analysis identified that the Eastern Cooperative Oncology Group (ECOG) performance status (PS), presence of brain metastases, number of recurrent sites and EGFR mutation status were independent prognostic factors for the post-recurrence survival. In all cases, the median post-recurrence survival time according to the use of EGFR-TKIs therapy were as follows: 49 months for EGFR mutation-positive patients treated with EGFR-TKIs therapy, 20 months for EGFR wild or unknown cases treated with EGFR-TKIs and 17 months for those not treated with EGFR-TKIs therapy ($p < 0.01$). With regard to the adenocarcinoma patients, the median post-recurrence survival time according to the EGFR-TKIs therapy were 49 months, 23 months, and 20 months, respectively ($p < 0.01$).
Conclusion: Patients with recurrent NSCLC with an EGFR mutation positive status received some benefit from EGFR-TKIs therapy. It is essential for recurrent NSCLC patients to be examined for their EGFR mutation status, especially those with adenocarcinoma. The therapeutic strategy for recurrent NSCLC should be considered after evaluating the EGFR mutation status.
No conflict of interest.

3465 POSTER

Assessing the role of chemotherapy for solitary fibrous tumors of the pleura in a routine practice setting

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Background: Solitary Fibrous Tumors of the Pleura (SFTP) refer as to a heterogeneous group of mesenchymal malignancies with various anatomic and histologic features. Upfront surgical resection is the standard approach, but the outcome of patients is unpredictable. Recurrences may be aggressive and difficult to treat.
The most widely accepted staging system has been proposed by De Perrot et al., and is based on the anatomy of the tumor implantation (sessile/pedunculated), and the presence of histologic signs of aggressiveness, including cellularity with crowding and overlapping of nuclei, cellular pleomorphism, high mitotic count, necrosis, or stromal/vascular invasion. Given the rarity of the tumor, limited evidence is available about the role and the modalities of perioperative and definite chemotherapy for SFTP.
Material and Methods: Multicenter retrospective study of patients (pts) with histologically-proven SFTP with complete follow-up from surgical diagnostic to tumor recurrence and death.
Results: 68 pts (28 males/40 females) were included. Median age at diagnosis was 62 year-old. Tumor stage according to the De Perrot system was 0/I for 29 pts, II for 23 pts, III for 7 pts, and IV for 4 pts. Adjuvant chemotherapy was given to 7 patients, mostly with stage III/IV SFTP, consisting of doxorubicin-based regimen. Recurrence rate and median time-to-progression (TTP) after surgery were 3%, 52%, 71%, and 75% ($p<0.001$), and 107, 70, 29, 11 months ($p = 0.006$) for stage 0/I, II, III, and IV tumors, respectively. Besides tumor stage, predictors of shorter TTP were incomplete resection ($p<0.001$) and a higher number of histologic signs of malignancy ($p = 0.009$). At time of tumor recurrence, 12 pts received chemotherapy. Highest disease control rates were observed with trabectedine (7/9 pts; Disease Control Rate (DCR): 78%; median TTP: 3.4 months), and gemcitabine-dacarbazine combination (2/3 pts, DCR: 66%; median TTP: 1.9 months). Median overall survival of the whole cohort was 56 months.
Conclusion: This study 1) confirms the prognostic value of the De Perrot staging system, 2) indicates a high recurrence rate in patients with stage II tumors, for which perioperative chemotherapy may be considered, and 3) suggests an interest for trabectedine in the setting of recurrent tumors. Besides clinical data, further molecular characterization, including recently identified specific gene fusions, may help to better predict the outcome of patients with SFTP.
No conflict of interest.

3466 POSTER

Impact of doxycycline (doxy) prophylaxis on dermatologic toxicity from dacomitinib (D) for NSCLC, by CTCAE and patient (pt)-reported outcomes (PRO) measures in a placebo-controlled trial

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Background: D, an irreversible small molecule inhibitor of human epidermal growth factor receptor (HER) 1, 2 and 4 tyrosine kinases, has shown potential efficacy in NSCLC and is currently in Phase (P) 3 trials. This study (ARCHER 1042: NCT01465802) explores prophylactic interventions to minimize the impact of common adverse events (AEs) associated with EGFR targeted therapy, including select dermatologic AEs of interest (SDAEI; pruritus, dermatitis acneiform, skin exfoliation, exfoliative rash, paronychia, nail disorders, skin fissures, skin lacerations, skin infection, skin ulcers, rash, dry skin, nail discoloration).
Methods: In Cohort 1 of this P2 clinical trial, 104 pts with measurable or non-measurable advanced NSCLC, at least 1 prior chemotherapy, ECOG Performance Status (PS) 0−2, are planned to be randomized (pt blinded) to (a) D 45 mg daily (QD) plus placebo (D+p) or (b) D 45 mg QD plus doxy 100 mg twice daily (BID) x 4 wks (D+d). Primary endpoints include the incidence of all-grade (G) and G⩾2 SDAEI and PRO (Skindex-16 scores) in the first 8 wks. Secondary endpoints include safety and tolerability, concomitant medication use and relative dose intensity of D.
Results: Reported results are for the first 8 wks of treatment. As of 15 Mar 2013, 37 pts were randomized to Cohort 1 D+p and D+d, 30 of whom (median age 65.5 years, 50% male, 70% adenocarcinoma) were evaluable and with data through Day 56 (15 in each arm). All-causality rates for G and G⩾2 SDAEI were 100.0% and 46.7% for D+p vs. 66.7% and 26.7% for D+d. Average compliance with PRO over 8 wks was 97.4% for D+d and 97.0% for D+p. Comparing PRO mean change from baseline scores over the first 8 wks, D+p exceeded the minimum clinically important difference (MCID) of 10 points worse for the PRO Total Score 4/7 visits (v); Symptom subscale 3/7 v; Emotion subscale 5/7 v; and Functioning subscale 2/7 v, whereas D+d exceeded the MCID for only Symptom subscale at 1/7 v. There was no difference in the overall AE profiles between the 2 groups.
Conclusions: This study uses a novel comprehensive approach to assessing the impact of AEs from both provider and pt assessment. Preliminary data suggest prophylactic doxy at onset of D therapy was well tolerated, with a reduced incidence of SDAEI ($p = 0.05$) and better PRO scores compared with reactive treatment. The study is ongoing, with further results available at presentation.
Conflict of interest: *Ownership: Stephen Sonis − Biomodels, LLC,Inform Genomics, Tenera Diana Gernhardt, Tao Wang, Jim Doherty and Joseph O'Connell − stock ownership with Pfizer Inc. Advisory board: Dorothy Keefe − Merck, Helsinn Stephen Sonis − Pfizer Inc, Galera, Actogenix, Alder, Soligenix, Polymedix, Novartis, Synedgen, Reata. Board of directors: Dorothy Keefe − MASCC. Corporate-sponsored research: Mario Lacouture − Berg Steven Grunberg − Pfizer Inc Dorothy Keefe − Entera, Helsinn Stephen Sonis − Helsinn Aminah Jatoi − Pfizer Inc. Other substantive relationships: Mario Lacouture − has received honoraria from Pfizer Inc, Roche, Wyeth, Novocure, Merck, Novartis, Amgen, Bayer, Boehringer-Ingelheim, BMS, Genentech, Genzyme, GSK, ImClone, Lilly, Onyx, OSI Stephen Sonis − consultant for Clinical Assistance Programs, Piramal, TheraVida Diana Gernhardt, Tao Wang, Jim Doherty and Joseph O'Connell − employed by Pfizer Inc*

3467 POSTER

EGFR mutation and management of advanced non-small cell lung cancer (NSCLC) adenocarcinoma in Germany and France

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Background: EGFR mutations (M+) predict response to EGFR tyrosine kinase inhibitors (TKI) in NSCLC. The AstraZeneca-sponsored non-interventional studies REASON (Germany, NCT00997230) and MUTACT (France, NCT01167972) aimed to investigate associations between clinicopathological characteristics and EGFR M+ in NSCLC, and record real-world management and outcomes in M+ patients. We present a subgroup analysis of the stage IV adenocarcinoma patients in these studies.
Material and Methods: For this post-hoc analysis, patients ⩾18 years old with stage IV adenocarcinoma and a planned EGFR mutation test were eligible. Baseline demographic and first-line treatment decision data were collected. Associations between patient characteristics and M+ status were evaluated in logistic regression models adjusted for study (REASON vs MUTACT). Heterogeneity tests were performed to assess differences between the effect of characteristics on M+ status between the studies.
Results: 3403 patients were identified (2409 from REASON, 994 from MUTACT; 57% male; 98% Caucasian; 75% current or former smoker; median age 65 years [range 26−93]). M+ frequency was 14% in REASON and 23% in MUTACT, a difference that could be explained at least in part by the inclusion of more non-smoking women in MUTACT. The only characteristic that showed a significantly stronger univariate association with M+ status in MUTACT vs REASON was smoking status (heterogeneity $p = 0.01$). In a multivariate model, M+ status was more frequent in women (odds ratio [OR] 1.9; 95% CI 1.5−2.3; $p < 0.0001$), ex- or non-smokers (OR 1.8; 1.3−2.4; $p = 0.007$ and OR 6.3; 4.7−8.4; $p < 0.0001$), patients with performance status (PS) 0 (0 vs 2: OR 1.6; 1.1−2.3; 0 vs 3: OR 2.2; 1.1−4.1; $p = 0.02$), and patients with brain (OR 1.3; 1.0−1.7; $p = 0.02$) or bone (OR 1.3; 1.1−1.7; $p = 0.01$) metastases. Overall, 74% of patients received first-line treatment; 53% of patients with M+ NSCLC received EGFR-TKI; 60% of patients with M- NSCLC received platin-based agents and 34% received pemetrexed.
Conclusions: Despite the limitations inherent to real-world evidence studies and differences between the studies, this analysis brings important information on EGFR M+ incidence in NSCLC and its predictive factors in a large cohort of Western European patients with stage IV adenocarcinoma.
Conflict of interest: *Advisory board: MD: AstraZeneca. Corporate-sponsored research: MD: AstraZeneca. WE: Eli Lilly. JCS: Roche. PS: AstraZeneca, Novartis, Roche. MT: Eli Lilly. Other substantive relationships: MD: honoraria (AstraZeneca). EW: consultant/honoraria (Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Hexal, Merck, Merck-Serono, Novartis, Pfizer, Roche, Teva). CL: honoraria (AstraZeneca). JCS: consultant/honoraria (AstraZeneca, Boehringer Ingelheim, Roche). PS: consultant/expert testimony (AstraZeneca, Novartis, Pfizer, Roche). MT: consultant/honoraria (AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novartis, Pfizer, Roche). WS: consultant/honoraria (Amgen, AstraZeneca, Eli Lilly, Merck, Roche). If accepted for presentation, PJS may receive reimbursement of expenses from AstraZeneca.*

3468 POSTER

Open label phase II study to establish the efficacy of intravenous loading doses of Ibandronate 6 mg in patients with lung cancer and skeletal metastases experiencing moderate to severe bone pain: NVALT 9 (NTR1602)

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Background: Pain due to bone metastases is a frequent problem in non-small cell lung cancer (NSCLC). Loading doses of ibandronate, a potent biphosphonate, rapidly relieve bone metastases related pain in breast and prostate cancer patients (pts).
Material and Methods: In this open label multi-center phase II study pts with NSCLC and painful bone metastases with patient-reported mean 'worst pain score' over the last 7 days on brief pain inventory (BPI) $\geqslant$5 were included. Pts had to be treated with at least a NSAID or a weak opioid based on the WHO analgesic ladder step 2. Pts were treated with 6 mg ibandronate i.v on day 1, 2 and 3. Main efficacy endpoint was bone pain response, defined as 25% decrease in mean pain score over a 3-day period (day 5−7) compared to pain score at baseline as determined by the 'worst pain' scale of the BPI, with no more than a 25% increase in mean analgesic consumption during the same 3-day period. Secondary endpoints were mean 'worst pain' scale of the BPI over time (first 7-days), interference scales of the BPI, analgesic consumption, WHO performance score and QOL (EORTC QLQ-C30).
The study was designed according to Simon's Optimal 2-stage design with 90% power to declare the treatment active when the pain response rate is 80% or more. If in the first 19 pts 12 or less successes are observed the study will be stopped, otherwise 34 additional pts will be included. The treatment will be declared to have sufficient activity if >38 pain responders are observed.
Results: Between 12/2007 and 11/2010 20 pts were enrolled in the study, 2 pts did not start treatment. Patient characteristics: 12 males and 6 females, mean age 58 years. The mean pain score over the last 7 days was 5 in 4 pts, 6 in 2 pts, 7 in 5 pts, 8 in 4 pts, 9 in 2 pts and 10 in 1 pts. All pts completed the 3- day treatment. No related adverse events were reported. In 4 out of 18 pts (22%) >25% decrease of mean pain score over day 5−7 was observed. No change in QoL was observed between baseline and day 7. According to the stopping rule, further enrollment was stopped.
Conclusion: Only 4 out of the 18 pts responded with a rapid reduction of pain to a loading dose ibandronate. In accordance with the Simon 2-stage procedure the trial was stopped at the interim analysis due to insufficient pain relieve of ibrandronate in NSCLC pts with bone metastases.
Conflict of interest: *Advisory board: Roche*

3469 POSTER

Clinical features and outcome differences in patients with thymoma and thymic carcinoma

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Background: Thymic epithelial tumours (TETs), consisting of thymoma and thymic carcinoma (TC), are rare cancers with specific morphological clinical features. The clinical characteristics and outcomes of TETs have not been well investigated because of their rarity.
Methods: The study was a retrospective review of 187 Japanese patients with TETs from 1976 to 2012 at our institution. The clinical features studied included clinical demographics, histology, staging, treatment interventions, and overall survival (OS). Differences in survival were assessed using Kaplan–Meier analysis and uni- and multivariate Cox proportional hazards regression analyses.
Results: The study included 51 patients with stage I, 37 with stage II, 22 with stage III, and 76 with stage IVa/IVb according to the Masaoka-Koga Staging System. On histology, 5 patients had type A, 33 had type AB, 19 had type B1, 39 had type B2, and 15 had type B3; 68 patients with TC included 12 with neuroendocrine carcinomas according to the 2004 WHO classification. Eight patients had either other histological types or missing data. Paraneoplastic syndrome was seen in 26 patients only in the thymoma group (23.4%). Most of the patients who were symptomatic at presentation had myasthenia gravis or TC. Secondary cancers were seen in 25 patients (13.3%). The median OS was 235.2 (95% CI, 137.3-not reached) months for thymoma and 32.4 (95% CI, 23.7–52.2) months ($p < 0.0001$) for TC of all stages. Furthermore, overall survival rates at 5 and 10 years were 85.4% and 33.8%, respectively, for thymoma and 71.5% and 2.3%, respectively, for TC. Immunological complications or secondary cancers in the thymoma group were not always associated with a poor prognosis ($p = 0.24$). OS compared between thymoma and TC in each stage group showed a significant difference for stage IVa. The stage and whether the tumour was thymoma or TC were significant determinants of survival on multivariate analysis.
Conclusions: The role of treatment should be further investigated for thymoma and TC separately because of differences in clinical demographics.
No conflict of interest.

3470 POSTER

Erlotinib in previously treated NSCLC − a critical appraisal based on multicenter post-marketing analysis

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Background: Erlotinib is a potent inhibitor of the EGFR (epidermal growth factor receptor) tyrosin-kinase activity and its efficacy has been demonstrated for the treatment of NSCLC in large randomized trials. The registration study BR.21 (N Engl J Med 2005;353:123−32) showed to prolong significantly OS and PFS in Erlotinib arm. The median age of the patients in this study was 61.4 years.
We have conducted a prospective observational study, using institutional data collected through onco-AIFA, a web-based national Italian registry of new oncology drugs.
The aim of our study was to assess median OS and PFS in clinical practice in comparison to outcome values obtained from the registration study.
Materials and Methods: Ten Italian oncology centers (Meldola − 222 pts, Padova − 159, Parma − 145, Pescara − 82, L'Aquila − 64, San Donà di Piave − 61, Cosenza − 42, Bolzano − 38, Trieste − 36, Bassano del Grappa −11) collected data from the registry to establish the real clinical impact of the drug. The observation period was October 2006 − November 2012. Every patient was checked for the length of the treatment and outcomes. For the efficacy/effectiveness comparison assessment we used the RCT outcome measures: OS, PFS with Kaplan–Meier estimates. EGFR wasn't a mandatory status for drug administration.
Results: A total of 860 patients treated with Erlotinib were reviewed (median age = 66.8 years, M= 61%).
Median PFS and OS were 2.4 (95% CI: 2.3−2.6) and 5.3 (95% CI: 4.7−6.3) months respectively compared to Erlotinib arm of the BR.21 study with PFS 2.2 months and OS 6.7 months. We recorded 26 (3%) suspensions of the treatment for toxicity. The median duration of treatment was 2.3 months (range 0.5–49.2) and 1-year survival rate was 33%. Moreover, there was a statistically significant difference in OS between males and females (5.0 *vs* 6.4 months respectively, $P < 0.001$).
Conclusions: The post-marketing studies in real life practice are needed in order to verify effectiveness and safety in general population and test the validity of the randomized trials. Moreover, the post-progression survival assessment may be crucial to determine the real clinical impact of a drug in combination with other treatments as it is usually missed in the approval RCTs.
Our results do not differ particularly from the study BR.21 and the slight difference in OS noticed by us can be explained by the fact that in our study the median age was higher than in the pivotal trial (66.8 *vs* 61.4 years).
No conflict of interest.

3471 POSTER

Results of the MARS study on the management of antiangiogenics' renovascular safety in lung cancer

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Background: Anti-VEGF drugs (AVD) are widely used in cancer patients (pts). Hypertension (HTN) and proteinuria (Pu) are class-side-effects of AVD, related to the inhibition of the VEGF pathway. The MARS study has been conducted to assess the renovascular tolerance of these drugs in the clinical setting.
Methods: This multicentric, prospective, observational study evaluated the renovascular safety of AVD in pts naive from any AVD, conducted in 7 centres in France, from 2009 to 2012, with a follow-up (f/u) of 1 year. Data collected included: gender, age, serum creatinine (SCr), diabetes, HTN, hematuria (Hu) and dipstick Pu, at baseline and at each visit.
Results: 1124 pts were included. 104 pts had lung cancer (LC) and all but 3 received bevacizumab (1st line: 57.4%; median durations of treatment: 11.4 months). Median age at inclusion was 56 years (28−80). Visceral, bone and cerebral metastasis frequencies were 71.3, 45.5 and 13.9%, respectively. Diabetes and HTN prevalences were 8.9 and 23.8%, respectively. Baseline renal assessment retrieved: Pu 16.0%, Hu 3.0%, mean aMDRD 97.4 ml/min/1.73m^2 and 7 pts with aMDRD<60. The incidence of *de novo* Pu and HTN during f/u was 72.1 and 22.1% (Table). 88.9% of pts with Pu at inclusion improved or remained stable. Among pts with *de novo* Pu, 40.9% afterwards improved/normalized. No Grade 3/4 Pu has been reported (at inclusion or during f/u). Renal function decreased with a mean aMDRD of 90.6 at the end of f/u. 12.3% had grade 2−3 SCr increase (no grade 4). No thrombotic micro-angiopathy (TMA) was reported.
Conclusion: These results on the renovascular safety of bevacizumab in LC patients showed that 1) TMA is rare, 2) Pu develops in 72.1% of the pts, (no Grade 3/4), 3) 22.1% developed HTN. Furthermore, in case of a renovascular effect, investigators followed the recommendations from the French Society of Nephrology (Halimi JM. Nephrol Ther 2008) and no treatment withdrawal for unmanageable renovascular toxicity occurred.
Conflict of interest: *Other substantive relationships: Merck, Amgen, Novartis, PharmaMar, Sanofi, Roche.*

Table: Renovascular effects in LC patients

Renovascular effects	Prevalence at inclusion	Incidence during f/u
Pu*	n = 81	n = 61
All G	16.0%	72.1%
G1	14.8%	59.0%
G2	1.2%	13.1%
G3−4	0.0%	0.0%
HTN	n = 101	n = 77
	23.8%	22.1%
Hu	n = 68	n = 52
All Hu	3.0%	7.7%
Traces/+	1.5%	7.7%
++	0.0%	0.0%
+++	1.5%	0.0%
SCr increase*	−	n = 81
All G		74.0%
G1		61.7%
G2		11.1%
G3−4		1.2%

*NCI-CTC v4; G: Grade; Number of patients may vary due to missing data.

3472 POSTER

Treatment decisions for elderly patients with advanced NSCLC in Italian clinical practice

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Background: In 2004, Italian Association of Medical Oncology (AIOM) created the RIGHT (Research for the identification of the most effective and highly accepted clinical guidelines for cancer treatment) program. The third step of the program, RIGHT3, aimed to evaluate the concordance between AIOM lung cancer guidelines and clinical practice in Italy. Description of treatment decisions for elderly patients with advanced non-small-cell lung cancer (NSCLC) was among the indicators. According to 2009 AIOM guidelines, single-agent chemotherapy with a third-generation agent was a reasonable choice for elderly patients with advanced NSCLC, whilst evidence about use of platinum-based treatment in the elderly population was judged potentially affected by selection bias and not conclusive.
Materials and Methods: RIGHT3 was a retrospective observational study conducted in a sample of 53 Italian lung cancer centers, representative of 230 AIOM centers. Proportion of elderly patients with stage IV disease receiving chemotherapy was among the 14 indicators evaluated. Patients with NSCLC diagnosis who had their first visit at the oncology center during 2010 and followed-up for at least 6 months were included.
Results: Overall, 306 pts with stage IV NSLSC were enrolled, and 299 were evaluable. Of these, 90 (30.1%) were older than 70. In the elderly subgroup, 81 pts (90.0%) were treated with first-line chemotherapy. In detail, a single-agent treatment was administered in 28 (34.6%) of cases, and a combination chemotherapy in the other 53 cases (65.4%). Among pts receiving platinum-containing doublets, carboplatin was more frequently used than cisplatin: carbo–gemcitabine (16 pts), carbo–pemetrexed (12 pts), cisplatin–pemetrexed (8 pts), cisplatin–gemcitabine (7 pts), carbo–vinorelbine (4 pts) were the 5 most frequently used regimens. Thirty pts (33%) received a second-line chemotherapy: single-agent in 23 cases, combination chemotherapy in 7 cases.
Conclusions: First-line platinum-based combination chemotherapy was commonly used in elderly patients with advanced NSCLC in 2010 by the Italian Lung cancer centers involved. First-line single-agent treatment, recommended by AIOM 2009 guidelines as the treatment choice with highest level of evidence, was used only in a minority of patients.
No conflict of interest.

3473 POSTER

Insights into the management of bone metastases in patients with lung cancer: A comprehensive European survey

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Background: Bone metastases commonly occur in patients with solid tumours including lung cancer. Associated skeletal-related events (SREs; pathologic fracture, radiation or surgery to bone and spinal cord compression), hypercalcaemia and pain can substantially reduce quality of life. Bone-targeted agents (BTAs) may be used to prevent or delay these skeletal complications. We investigated how BTAs are used to treat European patients.
Materials and Methods: Prospective, observational chart audit in France, Germany, Italy, Spain and the United Kingdom. In total, 881 participating physicians completed brief questionnaires on patients with bone metastases examined during the observation period and detailed questionnaires for further patients meeting specific criteria. Patient cases were weighted according to the probability of prospective inclusion in the study. We report data on the subset of patients with lung cancer.
Results: Brief questionnaires were completed for 1646 patients with lung cancer and bone metastases. Detailed questionnaires were completed for a further 1139 patients. Only 56% of patients with lung cancer and bone metastases were receiving bisphosphonates (the only BTAs available at that time), 13% had been previously treated, 8% had treatment planned and 23% were expected never to receive BTAs. The most common reasons cited for not treating with a BTA were short life expectancy (63%), poor risk/benefit profile for the patient (37%) and renal impairment (25%). However, 26% of patients who were never expected to receive bisphosphonates

had a life expectancy of at least 1 year at time of bone metastases diagnosis, and around 74% of these patients were judged by their treating physician to be at moderate to high risk of experiencing an SRE. The main reasons for delaying bisphosphonate treatment were inappropriate patient profile (50%) or bone metastases responding to initial anti-tumour therapies (48%); safety concerns and bone metastasis characteristics each led to treatment delay in 26% of patients.

Conclusions: A substantial percentage of patients with bone metastases secondary to lung cancer do not receive treatment with a BTA, despite the impact that SREs can have on their quality of life. As the life expectancy of lung cancer patients increases with better treatment, there is a need for further awareness of these SREs and increased use of the most appropriate BTAs.

Conflict of interest: *Ownership: PS, IH, SS − own Amgen shares. Advisory board: PW − Amgen. Corporate-sponsored research: PW, AF − Amgen. Other substantive relationships: PS, IH, SS − employed by Amgen*

3474 POSTER

25-OH-vitamin D (vD) serum levels and malignant pleural mesothelioma (MPM) in a highly asbestos-polluted area in Piedmomt, Italy: A case-control study

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Background: Low serum vD levels are a known risk factor for several diseases, including many types of human cancer. Furthermore in vitro and in vivo studies have demonstrated vD anti-tumor effects. The aim of this study is to identify a potential association between vD serum levels and MPM in a case-control study in the highly asbestos polluted area of Casale Monferrato, in Italy.

Material and Methods: Ninety-one subjects diagnosed with MPM since June 2002 to June 2006 constituted the case group. Two controls per patient (196), matched for age and gender, were randomly selected from the local population. A standard questionnaire was administered to collect information about demographics, life-style, occupational history and asbestos exposure. Serum samples were collected and stored at −20ºC until vD measurements were performed with a chemiolumiscence immunoassay (LIAISON, DiaSorin, Minnesota, USA). After evaluation of factors influencing vD in controls, the association of vD levels with case/control status was assessed, adjusting for the detected variables. Unconditional multivariate logistic regression analysis was mainly used but exploratory analyses using multivariate linear regression (GLM) were also conducted. ORs and 95% CIs were calculated for unit increase of the logarithm of vD and for quartiles of the distribution.

Results: Factors associated with vD variations in controls were age, gender and season, no data were available on nutrition. Median vD concentrations (ng/ml) in cases and controls were 11.50 (IQR: 7.75–19.50) and 20.85 (13.60–28.55), respectively. In both groups vD distribution was skewed and therefore analyses were conducted after logarithm transformation. In GLM multivariate analyses caseness was associated to a lower level of ln(vD) ($p < 0.0001$). In logistic regression analyses adjusted by age, gender, season and occupational exposure, the OR for a unit increase of ln(OR) was 0.298 (95% CI: 0.171–0.521), showing a statistically significant protective effect of vD.

Conclusion: In this series low vD levels strongly associate with MPM case status. Further investigations are ongoing to elucidate whether this striking difference between cases and controls could be involved in the pathogenesis of MPM as it is in other cancers.

Conflict of interest: *Other substantive relationships: Bonelli F is a Diasorin Employee*

3475 POSTER

First-line gefitinib in Caucasian patients (pts) with epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC): Results from a multinational, prospective, open-label, single-arm Phase IV study

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Background: Study NCT01203917 (sponsor: AstraZeneca) assessed efficacy and safety/tolerability of first-line gefitinib in Caucasian pts with *EGFR* mutation-positive NSCLC.

Materials and Methods: Pts: Caucasian, ⩾18 yrs, PS 0−2, histologically confirmed Stage IIIA/B/IV *EGFR* mutation-positive NSCLC eligible for 1st-line treatment. Treatment: gefitinib 250 mg/day until disease progression (assessed 6-weekly by RECIST 1.1). Primary endpoint: objective response rate (ORR; investigator assessment; full analysis set [FAS]). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), safety/tolerability. Pre-planned exploratory objectives included the analysis of *EGFR* mutations in duplicate plasma samples (I and II; plasma I data presented).

Results: Of 1060 screened pts with NSCLC, 106 whose tumours harboured activating, sensitising *EGFR* mutations were enrolled (Sep 2010-Feb 2012; FAS). Demographics (FAS): female 71%; adenocarcinoma 97%; never smoker 64%. At data cut off (Aug 2012), ORR was 70% (95% confidence interval [CI] 61−78), DCR 91% (95% CI 84−95), median PFS 9.7 months (95% CI 9−11) and median OS 19 months (95% CI 17-not calculable; 27% maturity). Most common adverse events (AEs; any grade): rash (45%), diarrhoea (31%). Serious AEs (SAEs): 19%. AEs CTC grade 3/4: 15%. SAEs considered related to gefitinib by investigator: 1.9% (2 pts). Of 1033 pts with tumour samples, 859 had known *EGFR* mutation status (118 positive; mutation frequency 14%). Of 106 patients with *EGFR* mutation-positive tumours enrolled, 66% had exon 19 deletions and 31% L858R point mutations. Of 903 pts with baseline plasma I samples, 784 had known *EGFR* mutation status (82 positive; mutation frequency 11%; 68% exon 19 deletions, 31% L858R point mutations). Comparison of *EGFR* M status in matched tumour and plasma I samples and concordance between matched tumour vs plasma I is shown in the table.

Table: *EGFR* mutation status in tumour and plasma I samples (pts evaluable for both)

Tumour	Plasma, n		
	Positive	Negative	Total
Positive	69	36	105
Negative	1	546	547
Total	70	582	652
	n	%	**95% CI**
Concordance	652	94	92−96
Sensitivity	105	66	56−75
Specificity	547	100	99–100
Positive Predictive Value	70	99	92–100
Negative Predictive Value	582	94	92−96

Conclusions: First-line gefitinib was effective and well tolerated in Caucasian pts with *EGFR* mutation-positive NSCLC, consistent with the previous studies in Asian pts. Plasma samples could be considered for mutation analysis if tumour tissue is unavailable.

Conflict of interest: *Advisory board: AstraZeneca: J-Y Douillard: Participation in Advisory Boards and meeting symposia. Corporate-sponsored research: AstraZeneca: J-Y Douillard: Compensated contribution as PI for protocol revision before submission, Steering Committee. Other substantive relationships: AstraZeneca: R. McCormack, A. Webster, T. Milenkova: Employees of AstraZeneca and hold shares in AstraZeneca*

3476 POSTER

Crizotinib safety profile in elderly and non-elderly patients (pts) with advanced ALK+ non-small cell lung cancer (NSCLC)

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Background: Crizotinib is an oral tyrosine kinase inhibitor that targets ALK and has been approved in several countries for treatment of advanced *ALK+* NSCLC. The availability of data from a large number of pts from three ongoing crizotinib studies (Pfizer) allowed us to assess the safety profile of crizotinib in elderly pts (⩾65 y) versus that in non-elderly adult pts (<65 y). PROFILE 1001 (P1001; NCT00585195) is a single-arm study with a treatment-naive or previously treated *ALK+* NSCLC cohort. PROFILE 1005 (P1005; NCT00932451) is a large global single-arm phase II study in pts with previously treated *ALK+* NSCLC. PROFILE 1007 (P1007; NCT00923893) is a global randomized phase III study comparing crizotinib with standard chemotherapy as second-line therapy for advanced *ALK+* NSCLC. Previously reported ORRs with crizotinib in the three studies were 60−65%, and median values for PFS were 7.7−9.7 months.
Materials and Methods: Pts in all three studies received crizotinib at a starting dose of 250 mg BID and were followed for AEs from the first day of study treatment until ⩾28 days after the last dose of study drug.
Results: Pts who received at least one dose of crizotinib were included in this analysis (n = 1255; P1001, 149; P1005, 934; P1007, 172). Among crizotinib-treated pts, 1056 (84%) were aged <65 and 199 (16%) ⩾65 y. The overall frequency of treatment-related (TR) AEs in crizotinib-treated pts was comparable between pts aged <65 and ⩾65 y (93% and 97%). In the two age groups, respectively, the most common TRAEs were nausea (49%, 50%), diarrhea (44%, 45%), visual impairment (43%, 37%), and vomiting (41%, 43%). No TRAEs were reported at frequencies that differed by ⩾10 percentage points between the groups. Only the frequency of visual impairment was ⩾5 percentage points higher in pts aged <65 than ⩾65 y. Peripheral edema, decreased appetite, and edema were reported at frequencies ⩾5 percentage points higher in pts aged ⩾65 than <65 y. TRSAEs were reported in 79/1056 pts aged <65 y (7%) and 30/199 pts ⩾65 y (15%). Among pts aged <65 y, TRSAEs reported in >2 pts were renal cysts (n = 9), increased ALT (n = 6), pneumonitis (n = 6), dyspnea (n = 4), and febrile neutropenia, diarrhea, pneumonia, and ILD (n = 3 each). Among pts aged ⩾65 y, only pneumonitis (n = 4) was reported in >2 pts.
Conclusions: The safety profiles of crizotinib in pts aged <65 and ⩾65 y were similar in terms of types and frequencies of TRAEs. TRSAEs were reported at relatively low frequencies in both age groups.
Conflict of interest: *Ownership: Keith Wilner, Patrick Schnell and Anna Polli − stock ownership: Pfizer. Advisory board: Dong-Wan Kim − Pfizer Benjamin Besse − Pfizer. Corporate-sponsored research: Fiona Blackhall − Pfizer Benjamin Besse − Pfizer. Other substantive relationships: Fiona Blackhall − honoraria: Pfizer Alice Shaw − consulting: Pfizer, Novartis, Ariad, Chugai, Daiichi-sankyo Pasi J*nne − consulting: Boehringer-Ingelheim, Roche, Genentech, Abbott, AstraZeneca, Pfizer, Sanofi, Chugai other: LabCorp Keith Wilner, Patrick Schnell and Anna Polli − employment: Pfizer*

3477 POSTER

Treatment strategies after failure to reversible tyrosine kinase inhibitors (rTKI) in EGFR mutant (mut) non-small cell lung cancer (NSCLC) patients (p): A retrospective analysis of 41 Spanish patients

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Background: Different therapeutic approaches have been used in the clinical setting in NSCLC p harbouring *EGFR* mutations progressing to rTKI, although the standard of care in this situation is still not well established.
Methods: A multinstitutional database from four different centers in Spain was review to identify *EGFR* mut p with acquired resistance to rTKI in order to evaluate the therapeutic strategies after rTKI failure and the effect on the post-progression survival (PPS) of these treatments.
Results: 41 p with acquired resistance to rTKI were identified: 63% female; median (m) age 62 ±11 yrs; 95% Caucasian; del19 76%, never or light former smokers 100%; 90.2% adenocarcinomas; 51 % received TKI as first line therapy; 85% were initial stage IV. mPFS for the rTKI was 8.4 months (mo) and mOS was 29.7 mo for the entire population. P were treated with a median of 2 therapeutic strategies after the rTKI failure. 6 therapeutic strategies have been identified. As immediate approach, 16 p were switched to chemotherapy (CT) with a mPPS of 3 mo. 9 p were switched to an irreversible TKI obtaining a mPPS of 3.9 mo. rTKI plus other drug was maintained in 11 p: rTKI plus CT in 9 p with a mPPS of 4 mo and rTKI plus other drug different to CT in 2 with a mPPS of 2 mo. Despite the progression, rTKI was maintained in 2 p considered slow progressors and local therapy, in addition to the rTKI, was administered in 3 p with oligometastatic progressive disease obtaining a mPPS of 1.4 and 36 mo, respectively. 8 p were treated sequentially with ⩾5 strategies. These p attained a mOS of 27.7 mo.
Conclusions: The combination of different strategies when treating *EGFR* mut p after rTKI failure may impact the survival especially when p are candidates to receive some of this treatments sequentially. These strategies may reflect different subsets of *EGFR* mut disease.
No conflict of interest.

3478 POSTER

Individualized dose adjustments facilitate continuous treatment with afatinib, allowing patients (pts) with advanced NSCLC previously treated with chemotherapy and erlotinib or gefitinib to maintain clinical benefit

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Background: Gastrointestinal adverse events (AEs) − in particular, diarrhoea − are characteristic of epidermal growth factor receptor (EGFR)-inhibiting agents and guidance on their effective management can facilitate continuous treatment, allowing pts to obtain maximum therapeutic benefits. Afatinib (A) is an oral, irreversible, ErbB Family Blocker that blocks signalling from EGFR (ErbB1), human epidermal growth factor receptor 2 (HER2; ErbB2) and ErbB4. In LUX-Lung 4, A was effective in third- or fourth-line NSCLC Japanese pts with acquired resistance to erlotinib/gefitinib (median progression-free survival [PFS] of 4.4 months based on central independent review at the primary endpoint analysis [data cut-off 14 Feb 2011]). Here, in a subsequent exploratory analysis, we show that appropriate dose interruptions facilitate continuous A treatment.
Methods: 62 pts received A, which was given until progression or intolerable AEs. The A starting dose of 50 mg could be reduced by 10 mg increments to 40 mg or 30 mg daily.

Table: Japanese pts with PFS ⩾180 days (independent review; data cut-off 14 Feb 2011)

Pt*	Days on A treatment			Total treatment duration	PFS
	50 mg	40 mg	30 mg	(days)	(days)
1	98	370	−	462	423
2	38	48	273	357	197
3	140	16	−	155	183
4	303	−	−	303	192
5	28	156	127	309	252
6	20	10	199	227	195
7	32	50	403	483	421
8	23	51	125	197	232
9	38	148	−	185	184
10	15	27	117	157	181
11	8	341	−	348	191

*6/11 pts dose reduced due to diarrhoea.

Results: Median/mean duration of A treatment was 3.9/4.6 months (data cut-off 14 Feb 2011); the updated mean duration of A treatment was 4.9 months, with a maximum treatment of 25 months (data cut-off 9 Feb 2012). Diarrhoea was the most common AE that led to A dose reduction in 26 pts;

16 pts had grade 3 diarrhoea, and only 2 pts discontinued A due to grade 3 diarrhoea. Dose reduction allowed pts to continue A treatment to prevent disease progression (Table). Eleven pts had durable disease stability for ⩾180 days, two of whom for >400 days (data cut-off 9 Feb 2012) − 759 and 753 days, respectively, based on investigator assessment. One pt remains on A treatment (3.4 years as of 7 Apr 2013). Additional response and safety data will be presented.
Conclusions: In LUX-Lung 4, individualized A dose adjustments allowed pts to remain on treatment for as long as they had clinical benefit.
Conflict of interest: *Other substantive relationships: Akira Inoue has held compensated consultant or advisory roles for Boehringer Ingelheim, and honoraria for AstraZeneca, Chugai, Eli Lilly. Toyoaki Hida has received research funding from Boehringer Ingelheim. Ryuichi Ebisawa is employed by Nippon Boehringer Ingelheim Co., Ltd, Japan.Mehdi Shahidi is employed by Boehringer Ingelheim, Bracknell, United Kingdom. Nobuyuki Yamamoto has held uncompensated consultant or advisory roles for Boehringer Ingelheim, and honoraria for Boehringer Ingelheim. Nobuyuki Katakami, Shinji Atagi, Koichi Goto, Takeshi Horai and Yoko Seki have nothing to disclose.*

3479 POSTER

Identification of a clinical biomarker for 2nd line combination with nintedanib in adenocarcinoma non-small cell lung cancer (NSCLC) patients in two phase III trials

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Background: Nintedanib, a triple angiokinase inhibitor, is in advanced development with two pivotal 2nd line NSCLC trials. LUME-Lung 1 (LL1) randomised 1314 patients (all histologies) to nintedanib + docetaxel or placebo + docetaxel, met its primary endpoint of PFS and demonstrated significant OS improvement in adenocarcinoma patients. LUME-Lung 2 (LL2) randomised non-squamous patients to nintedanib + pemetrexed or placebo + pemetrexed, with PFS by central review as the primary endpoint. Based on DMC futility analysis of investigator-assessed PFS, enrolment in LL2 was halted after randomising 713/1300 planned patients. Ongoing patients were unblinded and follow-up was continued per the amended protocol. ITT analysis showed a significant improvement in PFS by central independent review. Analyses to identify a clinical biomarker characterising patients benefitting from nintedanib combination treatment were performed.
Methods: Stepwise selection, using Cox proportional hazards modeling and a recursive partitioning tree, identified baseline variables prognostic for PFS in the LL2 placebo arm. Treatment by covariate interaction tests and HR by treatment interaction plots showed factors predictive of improved PFS in the LL2 nintedanib arm. These methods were applied to the LL2 DMC dataset to develop a hypothesis that was tested internally on final LL2 central PFS data and confirmed using LL2 OS data. External validation of the biomarker was performed on PFS (primary endpoint), interim OS, and final OS data from adenocarcinoma LL1 patients.
Results: Time since start of 1st line was the only prognostic, predictive clinical biomarker for 2nd line nintedanib combination in adenocarcinoma NSCLC patients. These patients progress rapidly after 1st line therapy. Interaction tests and HR 95% CIs led to selection of a 9 month cut-off since the start of 1st line to define the target population (T<9 mo). Benefit in T<9 mo patients (nintedanib vs placebo) was seen in LL2 (mPFS: 4.0 vs 2.8 months, HR 0.73, CI: 0.56–0.96, p = 0.0224; OS: HR 0.84, CI: 0.62–1.14) and confirmed in LL1 (mPFS: 3.6 vs 1.5 months, HR 0.63, CI: 0.48–0.83, p = 0.0008; interim OS: HR 0.79, CI: 0.55–1.14). Validation with final LL1 OS data show mOS: 10.9 vs 7.9 months, HR 0.75, CI: 0.60–0.92, p = 0.0073).
Conclusions: T<9 mo was validated in two independent NSCLC trials as a predictive clinical biomarker of nintedanib benefit for the adenocarcinoma patients most refractory to platinum-based 1st line therapy.
Conflict of interest: *Advisory board: Reck M: Lilly, Hoffmann-La Roche, Pfizer, AstraZeneca. Corporate-sponsored research: Hanna N: Eli Lilly, AstraZeneca. Other substantive relationships: Kaiser R, Gann C, Gomb P, Gaschler-Markefski are all employees of Boehringer Ingelheim Pharma GmbH KG, Germany. Barrueco JR: Employee of Boehringer Ingelheim Pharmaceuticals Inc, USA*

3480 POSTER

Tyrosine kinase inhibitors (TKI) treatment of non-small cell lung cancer (NSCLC) patients (p) based on EGFR mutations (m) status in serum only

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Background: Treatment of EGFR mutated NSCLC p with EGFR TKIs in phase III trials has shown improved efficacy to standard chemotherapy. However, it can be difficult to obtain sufficient tumor tissue for analysis of EGFR m status in a large proportion of p. Nevertheless, so far, no data exists for NSCLC p treated according to EGFR m status in serum alone.
Methods: We reviewed our database to identify EGFR mutated p, excluding those for whom status was available in both serum and tissue. We analyzed p treated with an EGFR TKI for whom EGFR m status was known in serum only (status in tissue unknown due to insufficient material). At the same time, we reviewed p in whom EGFR m status in tissue was available over the same period in order to compare clinical characteristics and efficacy parameters: PFS, ORR and overall survival (OS). EGFR m analysis was performed in cell free circulating DNA (cfDNA)isolated from serum and plasma using the QIAmp DNA blood mini kit.
Results: 9 p with EGFR m detected in serum and 33 p with EGFR m in tissue were included. In EGFR mutated p in serum, median age 63; male 55.6%; non-smokers 33.3%; former smokers 44.4%; ECOG PS 0−1 66.7%; adenocarcinoma 77.8%; deletion19 33.3%, L858R 66.7%; EGFR TKI treatment in 1st line 44.4%; 2nd or 3rd line 55.6%. ORR: complete response (CR) 22.2%; partial response (PR) 22.2%; stable disease (SD) 22.2%; progressive disease (PD) 11.1%. 2p had poor PS and died prior to evaluation. mPFS 4.7 months (mo). mOS 18 mo. In p with EGFR m in tissue, median age 61; male 36.4%; non-smokers 75.8%; former smokers 24.2%; adenocarcinoma 87.9%; deletion19 75.8%; L858R 24.2%; 1st line 54.5%; 2nd or 3rd line 45.5%. ORR: CR 15.2%; PR 57.6%; SD 12.1%; PD 15.2%. mPFS 8.9 mo. mOS 32.7 mo. The multivariate analysis for OS considering EGFR m in serum differed according to PS (PS 0−1 16.6 mo vs PS >2 5.2 mo).
Conclusions: Obtaining sufficient tissue from NSCLC p for analysis of EGFR m status and other molecular alterations can be difficult. Determination of EGFR m in serum alone is feasible, yields similar results to mutation status in tissue, and could permit us to take treatment decisions.
No conflict of interest.

3481 POSTER

Phase II study of combination therapy with S-1 and irinotecan in EGFR-mutated non-small cell lung cancer (NSCLC) resistant to both platinum-based chemotherapy and EGFR-TKI: NJLCG0804

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Background: From the results of recent trials it was considered that both EGFR-TKI and platinum doublet are important for prolonging survival of patients with EGFR mutated NSCLC. However, if both treatments fail, there is no established treatment in NSCLC with EGFR mutation. Some reports showed high sensitivity of TKI-resistant cell lines to 5-FU and a synergistic effect between S-1 (a novel oral fluorouracil derivative) and irinotecan. We therefore conducted a phase II trial to evaluate the efficacy and safety of a combination of S-1 and irinotecan in EGFR-mutated NSCLC that was resistant to both platinum-based chemotherapy and EGFR-TKI.
Methods: Eligible patients had advanced or recurrent NSCLC with an EGFR activating mutation, disease progression (PD) during or after second − or third − line EGFR-TKI therapy, and experience with one or two lines of chemotherapy, including a platinum doublet prior to EGFR-TKI therapy. All patients received S-1 (80 mg/m^2, day 1 to 14) orally and irinotecan (70 mg/m^2, day 1 and 15) intravenously every 3 weeks. The primary endpoint was disease control rate (DCR) at 8 weeks after enrollment. The estimated accrual was 23 patients to confirm a DCR of 60% as a desirable target level and a DCR of 30 % as uninteresting with alpha = 0.05 and beta = 0.10.
Results: From February 2009 to April 2012, 25 patients were enrolled from 6 institutions. The patients comprised 5 males and 20 females with a

median age of 62 years (range, 53 to 78 years). ECOG performance status was PS 0 in 4 patients and PS1 in 21 patients. The histological subtypes were: adenocarcinoma 23 patients (92%), squamous cell carcinoma 1 patient, adenosquamous carcinoma 1 patient. EGFR activating mutations were, exon 19 deletion in 17 patients and exon 21 point mutation termed L858R in 8 patients. The current line of treatment in this study was the 3rd in 22 patients and the 4th in 3 patients. The median cycles of treatment was 4 (range 1−12). The objective responses were CR 0, PR 13, SD 8, and PD 4, giving a DCR at 8 weeks of 84.0% (95% CI, 63.9–95.5%). The overall response rate was 52.0% (95% CI, 31.3–72.2%). The median PFS was 5.0 months, whereas the median overall survival was 17.1 months. There was no significant difference in efficacy between the two types of EGFR mutations. Major grade 3 or worse toxicities included neutropenia (52%), anemia (20%), febrile neutropenia (16%), diarrhea (16%), thrombocytopenia (4%), and pulmonary thromboembolism (4%). No treatment-related death was observed.
Conclusions: This combination therapy with S-1 and irinotecan in EGFR-mutated NSCLC that was resistant to both platinum-based chemotherapy and EGFR-TKI showed promising efficacy with manageable toxicities. Further evaluation of this regimen in comparison with other cytotoxic agents or with irreversible EGFR-TKI is warranted.
No conflict of interest.

3482 POSTER

Phase II study of the 1st line chemotherapy consisting of bevacizumab, docetaxel and carboplatin for patients with non-squamous non-small cell lung cancer: TCOG1001

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Background: Although carboplatin is slightly inferior to cisplatin in terms of survival, addition of bevacizumab to carboplatin may overcome this disadvantage. ECOG4599 and some preclinical studies suggested a possible advantage of bevacizumab combined with taxanes. The aim of this study was to explore efficacy and safety of combination chemotherapy consisting of bevacizumab, docetaxel and carboplatin in the 1st line chemotherapy for non-sq NSCLC.
Patients and Methods: Pts who are untreatable with thoracic radiotherapy, with stage IIIB/IV non-sq NSCLC, age ranging from 20 to 74 years, PS 0 or 1, adequate organ functions, measurable lesions, and written IC were eligible. Combination chemotherapy consisting of bevacizumab (15 mg/kg), docetaxel (60 mg/m^2) and carboplatin (AUC=6) on day 1 was administered every 3 weeks up to 6 cycles (induction phase). Unless PD, it was followed by bevacizumab until PD (maintenance phase). The primary endpoint was median PFS to prove its superiority to the previous standard combination chemotherapy consisting of docetaxel and cisplatin with its historical median PFS of 4.6 months. With α=0.05 and β=0.20, calculated minimum sample size was 37, and the final determined sample size was 40. It was registered to the clinical trial registration system with the ID of UMIN000004524.
Results: Among 40 pts enrolled, 39 pts were analyzed because one retracted IC before starting the therapy. They included women in 31%, pts with PS of 0 in 67%, stage IV in 92%, EGFR mutations in 13% and unknown EGFR status in 8%. The median age was 62 years. The induction phase was delivered for 4 cycles in median (range: 1−6), and 21 pts (54%) received maintenance phase with median 4 cycles (range: 2−24). Frequent toxicities $\geqslant$ grade 3 during the induction phase in completely analyzed pts (n = 32) included anemia (9.4%), neutropenia (50.0%), thrombocytopenia (9.4%), febrile neutropenia (25.0%) and hypertension (37.5%). Other toxicities $\geqslant$ grade 3 were cholecystitis, increased ALP, hyperpotassemia, proteinuria, diarrhea, appetite loss, nausea, constipation, infection, stomatitis, and cancer pain in 3.1%, respectively. Interim external reviews of 35 pts revealed ORR of 74% (26/35) and median PFS of 6.4 months (95% CI: 4.8−9.9).
Conclusions: The primary endpoint was met because the lower end of the 95% CI exceeded the threshold of 4.6 months. This combination chemotherapy seems promising in terms of safety and effectiveness, warranting phase III studies.
No conflict of interest.

3483 POSTER

EGFR-TKI re-challenge with erlotinib after gefitinib for central nervous system metastases of EGFR mutated NSCLC

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Background: The re-challenge efficacy of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) in non-small cell lung cancer (NSCLC) harboring *EGFR* mutations has recently been reported, however there is little data for central nervous system (CNS) metastases.
Methods: We retrospectively screened 46 NSCLC patients with CNS metastases who had already experienced progressive disease (PD) following first EGFR-TKI (gefitinib), and were administered second EGFR-TKI (erlotinib). Among them, we compared the re-challenge efficacy of erlotinib in CNS lesions, between patients whose CNS metastases emerged after gefitinib administration (CNS relapse group; n = 16) and those who had CNS metastases before gefitinib administration (original CNS group; n = 30).
Results: The median CNS progression-free survival (PFS) and overall survival (OS) after initiation of erlotinib were 8.8 months (95% CI: 5.4–12.4) and 18.8 months (95% CI: 12.4–24.0), respectively. CNS relapse group showed better tumor response (response rate: 73.3 vs. 50.0%, $p = 0.192$) and significantly prolonged CNS-PFS (12.4 months [95% CI: 5.4–12.4] vs. 5.5 months [95% CI: 12.4–24.0], $p = 0.019$) compared to original CNS group. There was no significant difference in OS between CNS relapse group at 14.9 months (95% CI, 8.0–29.7) and original CNS group at 19.9 months (95% CI, 6.2–29.6, $p = 0.503$). We observed a significant discrepancy in tumor response between CNS metastases and primary lesions (response rate: 58.1% vs. 6.5%, $p<0.001$). Additionally, PD rate inside CNS was lesser during erlotinib administration in both groups, compared to gefitinib administration (31.0% vs. 76.2%, $p<0.001$).
Conclusion: EGFR-TKI re-challenge with erlotinib is more effective for CNS metastases compared with primary lesions, and corresponds with lesser frequency of PD inside CNS compared with gefitinib. Having CNS metastasis before initial EGFR-TKI administration was a negative predictive factor for re-challenge efficacy of EGFR-TKI inside CNS.
No conflict of interest.

3484 POSTER

Weekly and every 2 weeks cetuximab maintenance therapy after platinum-based chemotherapy plus cetuximab as first-line treatment for non-small cell lung cancer (NSCLC): Randomized, non-comparative, phase IIIb NEXT trial

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Background: The phase III FLEX trial showed that the addition of cetuximab to cisplatin and vinorelbine chemotherapy (CT) followed by weekly cetuximab maintenance therapy significantly improved survival compared with CT alone in the first-line treatment of EGFR-expressing advanced NSCLC. The multinational, parallel-group phase IIIb NEXT trial (NCT00820755; sponsor, Merck KGaA) investigated in a community practice setting the efficacy and safety of weekly and every 2 weeks cetuximab maintenance therapy in patients with advanced NSCLC.
Material and Methods: Eligible patients with stage IIIB with pleural effusion or stage IV (UICC staging, 6th edition) NSCLC received 4−6 cycles of first-line platinum-based CT + cetuximab. At the end of combination therapy, patients free of disease progression were randomized to cetuximab maintenance therapy, weekly (250 mg/m^2) or every 2 weeks (500 mg/m^2), stratified for tumor histology and response status. The primary endpoint was overall survival (OS), from trial inclusion to death. Secondary endpoints included time to treatment failure (TTF) and response. A planned 1200 patients were to be enrolled to allow for an estimated 480 to be randomized.
Results: Enrollment was stopped prematurely when cetuximab did not gain regulatory approval in this setting. The intention to treat (ITT) population comprised 583 patients, recruited from 136 centers in 28 countries. After completion of the combination therapy phase, 311/583 (53%) patients without progression (ITT maintenance population) were randomized to maintenance therapy; 157 to every 2 weeks cetuximab and 154 to weekly cetuximab. Baseline characteristics were balanced between these two groups and exposure to cetuximab in the maintenance therapy phase was

similar. The 1-year OS rate was 62.8% (95% CI: 54.7–70.0) for every 2 weeks cetuximab and 64.4% (95% CI: 56.2–71.4) for weekly cetuximab. Median OS from inclusion was 16.1 (95% CI 13.6–18.2) and 15.5 (95% CI 13.2–19.7) months, respectively. Median TTF from inclusion was 5.8 (95% CI: 5.6−6.6) and 6.6 (95% CI: 6.1−6.9) months, respectively. Safety profiles in both the combination therapy and the maintenance phase were manageable and in line with expectations.
Conclusions: In patients with advanced NSCLC who were progression-free after 4−6 cycles of first-line CT + cetuximab, weekly and every 2 weeks cetuximab maintenance therapy were associated with similar survival outcomes.
Conflict of interest: *Ownership: Merck KGaA (BS, employment RE, employment and stock ownership). Advisory board: Merck KGaA (UG)*

3485 POSTER

Natural history of malignant bone disease in non-small cell lung cancer: Final results of a multicenter bone metastasis survey

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Background: Bone metastases represent an increasing clinical problem in advanced Non-Small Cell Lung Cancer (NSCLC) as disease-related survival improves. This is a multicenter, retrospective survey aimed to explore the impact of bone involvement in this severe, life-threatening disease.
Patients and Methods: Data on clinicopathology, skeletal outcomes, skeletal-related events (SREs), and bone-directed therapies for 591 deceased NSCLC patients (50.8% aged >66 years) with evidence of bone metastasis were statistically analyzed.
Results: ECOG performance status at diagnosis of NSCLC was 0 in 40.1% of patients, 1 in 44.7% and 2 in 12.2%. The most frequent stage at diagnosis was IV (79.5%). Adenocarcinoma was the commonest histotype (66.2%) and EGFR status was unknown in 70.4%. Chemotherapy was the preferred I line treatment in 79%. Bone metastases evident at diagnosis in 57.5% of patients. In the remaining cases median time to bone metastases was 9 months. Patients ECOG performance status when bone metastases were detected was 1 in 51.1% and 2 in 19.6%. In our sample multiple bone metastases were detected in 78.5% of patients and 73.3% were osteolitic. Axial skeleton was interested in 72.6% of cases, pelvic bones in 47.5% and limb bones in 32.3%. Bone metastases related pain was reported by 78% of patients. Median Verbal Numerical Rating Scale (VNRS) for pain was 4 and it measured >4 in 44.3% of cases. Bisphosphonates was administered in 54% of patients, before the first SRE in 26.7% and after in 73.3%; zoledronic acid was mainly used (49.2%). First SRE occurs after 12 months in patients treated with zoledronic acid and after 2 months in those who did not receive. Osteonecrosis of the jaw was reported in only 4.6% of cases. Median number of SREs/patient was one, less than half of the patients (42.3%) experienced at least one SRE, 16.9% experienced at least two SREs, and only 2% experienced at least three SREs. The most common SRE was radiotherapy (69.4%), bone fracture occurred in 16.3%, spinal cord compression in 5%, the need of surgery in 4.8% and hypercalcemia in 4.4% of cases. Median time to first SRE was 2 months. Median survival after bone metastases diagnosis was 8 months and after first SRE was 7 months.
Conclusions: This is the largest study ever presented in literature on natural history of bone metastases in non small-cell lung cancer. These preliminary data suggest that bone metastases are a relevant clinical event in the natural history of patients affected by NSCLC. Final results will be available next ESMO meeting.
No conflict of interest.

3486 POSTER

A pilot phase II trial of cabazitaxel in patients with metastatic NSCLC progressing after docetaxel-based treatment: Preliminary results

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Purpose: Cabazitaxel, a microtubule inhibitor, is a semi-synthetic derivative of a natural taxoid that has been shown to be active in docetaxel-resistant prostate cancer. We investigated its activity in patients with metastatic NSCLC progressing under or after docetaxel-based regimens.
Material and Methods: Eligible patients had stage IV NSCLC; measurable disease; ECOG performance status 0−2; up to 2 prior chemotherapy regimens for the treatment of metastatic disease from which one containing docetaxel. Treatment consisted of cabazitaxel (25 mg/m^2 iv, every 21 days) until disease progression. G-CSF was administered to the physician's discretion. The primary endpoint was the objective response rate with a planned sample size of 40 eligible patients. A 2-stage design was applied with an interim analysis after enrolment of the first 25 patients (min 2 objectives responses).
Results: At the completion of the first stage (n = 25 patients) 30% had squamous cell carcinoma, 52% adenocarcinoma and 18% a low differentiated NSCLC. Three patients received one and 22 patients two prior regimens. Among the 21 evaluable patients, 4 (19%) patients showed partial response, 8 (38%) stable disease [Disease Control Rate=57%] and 9 (43%) progressive disease. The most common adverse events were anemia (54%); lymphopenia (38%); fatigue (35%). Grade 3/4 adverse events were neutropenia: 2/2; lymphopenia: 6/0; anemia: 1/0; thrombocytopenia: 0/1; diarrhea: 1/0; fatigue: 1/0. There was no treatment-related death. The estimated median PFS is 2.8 months. Treatment compliance was 94% as 1 patient withdrew due to toxicity (fatigue). 5 cycles delayed (6.2%), 3 due to toxicity and 2 for other reasons. Hematologic toxicity was the reason for dose reduction in 3 patients.
Conclusions: These preliminary results further support that cabazitaxel is active in docetaxel-resistant tumors. Its efficacy in pre-treated patients with NSCLC implies the necessity to explore its role in the treatment algorithm either in the first or second-line setting.
No conflict of interest.

3487 POSTER

Activity of gefitinib and erlotinib in pretreated EGFR wild-type NSCLC patients: A pooled analysis of 11 randomised trials

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Background: The tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib (E) appear to be especially effective in non-small cell lung cancer (NSCLC) patients with activating epidermal growth factor receptor (EGFR) gene mutations. The role of TKIs in EGFR *wild*- type disease is still not well established. We have performed a pooled analysis to evaluate the activity of G and E in pretreated EGFR *wild*- type advanced NSCLC patients.
Material and Methods: PubMed, EMBASE, Web of Science and The Cochrane Library were systematically searched to identify published publications. Studies conducted in advanced NSCLC patients treated with G or E as $\geqslant$ second line therapy, and reporting objective response rate (RR), progression-free survival (PFS), time-to-progression (TTP) and overall survival (OS) of EGFR *wild*-type patients were included in analysis. Data on RRs were pooled by using Comprehensive Meta-Analysis software with a random-effects model. Data on outcome were summarised descriptively as median weighted PFS/TTP and OS.
Results: A total of 12 randomised controlled trials (6 phase III and 6 phase II of which 4 in second line and 8 further lines setting) were analysed for a total of 1801 patients. Five studies included G arms, 6 E arms and one compared E and G directly. Nine were studies in Caucasian population and 3 included Asiatic patients only. The reported overall weighted median PFS/TTP, median OS and pooled objective RR were 1.84 months, 6.4 months and 10.5%. In n = 4 second line trials, (n = 747 patients) median weighted PFS/TTP and OS were 3.1 and 7.6 months. In trials with Caucasian patients only, median weighted PFS/TTP and OS were similar to the overall population (1.84 and 6.4 months respectively). In Asiatic studies, median weighted PFS was 2.8 months while OS was not reported.
Conclusions: In this pooled analysis, the RR and OS outcome with G and E in a population of pretreated, and Caucasian patients also, with EGFR

wild-type NSCLC is in a range of what expected in > second line setting for NSCLC. In particular in the second line, outcome with EGFR TKIs has been nearly identical to that observed with standard docetaxel and pemetrexed chemotherapy.
No conflict of interest.

3488 POSTER

The use of epidermal growth factor receptor tyrosine kinase inhibitors in treatment of advanced EGFR wild-type non-small cell lung cancer: A meta-analysis

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Background: The epidermal growth factor receptor (EGFR) oral tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib, improve progression-free survival (PFS) compared to chemotherapy in the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) with activating EGFR mutation. Previous trials of TKIs in unselected patients suggest that they may have some activity in EGFR wild-type (WT) patients, but the magnitude of benefit is unclear. We conducted a meta-analysis to determine the outcomes of EGFR WT patients with advanced NSCLC treated with gefitinib or erlotinib.
Methods: MEDLINE was searched for phase 2 and 3 clinical trials of gefitinib or erlotinib in advanced NSCLC published between January 2000 and May 2012. Trials using TKI as treatment or control arm or as maintenance therapy were included. In addition, studies must have tested for EGFR mutation by polymerase chain reaction and analyzed EGFR WT patients. Random effects meta-analysis using the DerSimonian and Laird method was performed to pool survival estimates (hazard ratios (HR), risk ratios) and objective response rate (ORR). Placebo- and chemotherapy-controlled phase 3 trials were also evaluated separately in a subgroup analysis.
Results: Six randomized controlled trials (RCTs) with a total of 1,180 EGFR WT patients (709 on TKI, 471 on control with placebo or chemotherapy) were available for meta-analysis. Pooled overall survival (OS) from 5 RCTs was not significantly different for patients in the TKI arm compared to control arm (HR 1.00; 95% CI 0.86 to 1.16). Subgroup analysis according to type of control showed that TKI offered no OS benefit compared to either placebo (HR 0.92, 95% CI 0.63–1.35) or chemotherapy (HR 1.02, 95% CI 0.86 to 1.22) (interaction p = 0.63). Likewise, pooled PFS was similar between TKI and control in 4 RCTs (HR 1.35; 95% CI 0.79 to 2.31). However, the use of TKI significantly increased PFS compared to placebo (HR 0.78, 95% CI 0.63–0.97), but not chemotherapy (HR 1.64, 95% CI 0.96 to 2.79) (interaction p = 0.01). The rate of patients in the control arm who subsequently received TKI upon progression ranged from 3% to 52%. ORR estimated from 51 studies (1,872 EGFR WT patients) was 8.4% (95% CI 6.0–10.8), and was similar for gefitinib and erlotinib. Sensitivity analyses removing studies with estimated effect sizes did not affect these findings.
Conclusions: In this meta-analysis, gefitinib and erlotinib significantly increase PFS compared to best supportive care for advanced NSCLC with EGFR WT status. The lack of OS gain may be explained by significant crossover in these trials. TKIs may have a potential role in the management of EGFR WT patients who are not candidates for chemotherapy in the first-line setting.
No conflict of interest.

3489 POSTER

Metronomic oral vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer: Preliminary results of a phase II trial (move trial)

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Background: Metronomic oral vinorelbine could be a safe option for elderly patient with advanced non small cell lung cancer (NSCLC). Metronomic administration of chemotherapy leads to a cytostatic action shifting treatment target from cancer cell to tumor angiogenesis.
Materials and Methods: 32 chemotherapy naive elderly (⩾70 yrs) PS 0−2 patients with stage IIIB-IV NSCLC were prospectively recruited. Median age was 79 yrs (M/F 27/5) with predominantly squamous histology. PS distribution was 0−1(12)/2(20) with a median of 3.5 serious co-morbid illnesses. Study treatment consisted of oral vinorelbine 50 mg three times weekly (Monday-Wednesday-Friday). Primary endpoints were overall response rate (ORR), clinical benefit (CB) and safety. As per protocol we present the second interim analysis results.
Results: Patients received a median of 6 (range 3−20) cycles. ORR was 12.5% with 3 partial and 1 complete responses; 16/32 experienced stable disease lasting more than 12 weeks leading to an overall CB of 62.5%. Median time to progression was 6 (range 3−18) and median overall survival 8.5 (range 4−23) months. Treatment was well tolerated with rare G3/4 toxicity (two episodes of G3 diarrhoea, one of not-febrile G3 neutropenia and one G3 fatigue). Regardless of severity main toxicities observed were anemia in 40%, fatigue in 38%, diarrhoea 14%, nausea in 10% and vomiting in 7% of patients.
Conclusions: Metronomic oral vinorelbine is safe in elderly patients with advanced NSCLC with an interesting activity mainly consisting in long-term disease stabilization. Study accrual will continue to a total of 43 pts.
No conflict of interest.

3490 POSTER

Treatment-free interval (TFI) after first-line therapy and disease control rate (DCR) during second-line therapy as potential predictors of overall survival (OS) in relapsed malignant pleural mesothelioma (MPM)

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Background: Both TFI (the time elapsing from completion of 1st-line to initiation of 2nd-line) and DCR (the nonprogression rate at 1st tumor evaluation) have been found to predict OS in some tumor types.
Methods: We assessed the associations of TFI after 1st-line and DCR during 2nd-line with OS by means of an individual patient pooled analysis of MPM patients (pts) who had failed a pemetrexed-based regimen. Dataset consisted of 261 pts receiving a 2nd-line therapy with single-agent NGR-hTNF (n = 50; phase 2 trial) or single-agent chemotherapy (gemcitabine, vinorelbine or doxorubicin) plus NGR-hTNF/placebo (n = 211; phase 3 trial). In both trials, tumor response was assessed every 6 weeks using MPM-modified RECIST criteria. OS was computed from start of 2nd-line, and median follow-up was 10.2 months (95% CI, 8.8–11.6). By applying a ROC analysis, the cutpoint for estimating TFI in relation to OS was set at 6 months (AUC=0.59; 0.53–0.65). In multivariate analyses, hazard ratios (HR) for OS were derived from Cox models with covariates for baseline factors (age, sex, PS and histology).
Results: After 1st-line therapy, 60 pts (23%) had partial response (PR), 135 (52%) stable disease (SD), for an overall DCR of 75%, and 66 (25%) early PD. Median TFI was 4.4 months (95% CI, 3.8−5.0), with 97 pts (37%) experiencing a TFI >6 months. A TFI >6 months (vs ⩽6) was correlated with improved OS in univariate (HR = 0.59; 0.42–0.84; p = 0.003) and multivariate models (HR = 0.60; 0.43–0.85; p = 0.004). After 2nd-line therapy, 9 pts (3%) had PR, 130 (50%) SD, for an overall DCR of 53%, and 122 (47%) early PD. Among pts responding to 1st-line, one third (23/60, 38%) progressed early during 2nd-line, while among pts progressing early during 1st-line, half (32/66, 48%) experienced disease control during 2nd-line. In a landmark analysis set at the 6-week time point, DCR (vs PD) was significantly associated with OS improvement (HR = 0.43; 0.30–0.60; p < 0.0001), which persisted after adjusting for baseline variables (HR = 0.37; 0.26–0.57; p < 0.0001).
Conclusions: With smaller HRs, an early-look measure such as 6-week DCR shows some advantage over TFI in predicting subsequent OS in relapsed MPM. In 2nd-line trials, TFI as stratification factor and DCR as surrogate endpoint may be considered.
No conflict of interest.

3491 POSTER

Long-term treatment with erlotinib in patients with advanced non-small cell lung cancer (NSCLC): Interim analysis at 1-year follow-up (the TERRA Study)

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Background: Patients (pts) with advanced NSCLC may experience long-term benefits with erlotinib, whatever the line of treatment No prospective data on a cohort of long term responder pts to erlotinib are currently

available. We present the results of a non-interventional prospective study after 1 year follow-up. Main disease and pts characteristics were presented earlier.

Patients and Methods: Stage IV pts with advanced NSCLC after platinum based chemotherapy treated for at least 9 months with erlotinib and followed for 24 months were included prospectively. The main endpoint was median PFS. Other endpoints included: pts demographics and disease characteristics, previous treatments and erlotinib therapy, objective response rate, overall survival, long-term safety, compliance and quality of life. PFS is presented.

Results: A total of 217 pts were included in 76 French sites, 213 were analyzed. Pts characteristics were: median age 67 [36−93] years; non-Asian 96.2%; ECOG performance status (PS) 0/1/2/3, 40.2/54.4/3.9/1.5 (%); men 42.3%; current/former/never smokers 5.7/44.8/40.1 (%); adenocarcinoma, 82.4%; stage IV/IIIB, 83.4/16.6 (%). Among 62 pts tested, 56.5% presented activating epidermal growth factor receptor (EGFR) mutation. Erlotinib was administered as first/second/third line treatment in 21.6/49.8/22.5 (%) of pts. As of February 2013, median total duration of erlotinib treatment was 23.4 [9.5–73.6] months and it was definitely discontinued in 43.7% of pts, mainly for disease progression (34.7%). Median total PFS (from erlotinib initiation) was 32 months (95% CI, 27 to 43) in these responder pts. At data cutoff 20.2% of pts had died (mainly disease progression). Most pts (86.8%) were identified as 'high adherers' on the Morisky Medication Adherence questionnaire. Most frequent long-term reported AEs (all grades) during the 12-month follow-up were diarrhea (12.4%), dry skin (6.9%), asthenia (6.5%), rash (5.5%). Most frequent long-term grade 3/4 AEs during the 12-month follow-up were rash (1.4%), folliculitis (0.9%) and dyspnea (0.9%). Grade 3 dry skin occurred in 1.8% pts, Grade 1/2 perionyxis in 4.1% pts.

Conclusion: At 12 months follow-up, interim results of the TERRA cohort study show that patients with advanced NSCLC treated with erlotinib, all treatment lines, can achieve extended PFS results, and most interestingly in patients with or without activated EGFR mutation. Long-term grade 3−4 adverse events were limited and mainly cutaneous.

Conflict of interest: *Ownership: None. Advisory board: Roche (Chouaid, Moro-Sibilot, Souquet, Vergnenègre, Fournel), GSK (Chouaid), Lilly (Chouaid, Moro-Sibilot, Souquet, Milleron, Vergnenègre, Fournel), Amgen (Chouaid, Moro-Sibilot, Souquet), Boeringher (Chouaid, Moro-Sibilot, Souquet), AstraZeneca (Moro-Sibilot, Souquet, Milleron, Vergnenègre, Fournel, Locher), Pierre Fabre (Souquet), Novartis (Souquet), Pfizer (Milleron, Fournel). Board of directors: none. Corporate-sponsored research: Roche (Souquet, Milleron, Vergnenègre, Fournel, Locher), Lilly (Souquet, Milleron, Vergnenègre, Fournel, Locher), Boeringher (Souquet, Milleron, Vergnenègre, Fournel, Locher), Novartis (Souquet), Pfizer (Souquet, Milleron, Fournel, Locher), Daichi (Souquet), Ziopharm (Souquet), Astex (Souquet), BMS (Souquet, Milleron), Sanofi (Milleron, Fournel, Locher), Merck (Milleron, Fournel), Chugai (Vergnenègre, Locher), AstraZeneca (Fournel, Locher), Amgen (Fournel), GSK (Locher), Pierre Fabre (Locher). Other substantive relationships: Roche (Milleron, Fournel, Mouysset), Lilly (Milleron, Fournel), Pfizer (Milleron, Fournel), Chugai (Milleron), AstraZeneca (Fournel), Boeringher (Fournel), Amgen (Fournel)*

3492 POSTER

Phase II study of bevacizumab in combination with carboplatin plus paclitaxel as first-line chemotherapy for non-squamous non-small cell lung cancer with malignant pleural effusion

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Background: Vascular endothelial growth factor (VEGF) is involved in non-small cell lung cancer (NSCLC) with malignant pleural effusion (MPE), but little is known regarding the efficacy of bevacizumab (Bev) with carboplatin-paclitaxel (CP) to treat NSCLC with MPE. Therefore, we prospectively evaluated the efficacy and safety of Bev and CP in non-squamous NSCLC patients with MPE.

Methods: Twenty-three chemotherapy-naive non-squamous NSCLC patients with MPE were enrolled. Pleurodesis before chemotherapy was not performed. In the first cycle, patients received only CP to prevent Bev-induced wound healing delay after chest drainage. Subsequently, they received 2−6 cycles of CP with Bev. Patients who completed more than 4 cycles of CP and Bev without disease progression or severe toxicities continued to receive Bev alone as maintenance therapy. The primary endpoint was overall response, although an increase in MPE was allowed in the first cycle. VEGF levels were measured in plasma and MPE at baseline and in plasma after 3 cycles of chemotherapy.

Results: The overall response rate was 60.8%; the disease control rate was 87.0%. Response was not evaluated in 1 patient because of sudden death after 1 treatment cycle. Sixteen patients received maintenance therapy, following a median of 3 cycles. The median progression-free survival and median overall survival were 7.1 months (95% CI, 5.6−9.4 months) and 11.7 months (95% CI, 7.4–16.8 months). Most patients experienced severe hematological toxicities, including ⩾grade 3 neutropenia; none experienced severe bleeding events. Pleural effusions were controlled in 21 of 23 patients (overall MPE DCR, 91.3%). Treatment was successful in 4 of 6 patients in whom the affected lung did not re-expand after tube drainage. The only 2 patients whose MPE could not be controlled demonstrated high MPE levels, and their affected lungs did not re-expand after tube drainage. Furthermore, the control rate of MPE was improved after combination with Bev (CP, 78.3%, 18/23 patients; CP with Bev, 91.3%, 21/23 patients; $P = 0.08$). The median baseline VEGF level in MPE was 1798.6 pg/mL (range, 223.4–35,633.4). Plasma VEGF levels significantly decreased after 3 chemotherapy cycles (baseline, 513.6±326.4 pg/mL, post-chemotherapy, 25.1±14.1 pg/mL, $P < 0.01$), regardless of the efficacy of CP with Bev.

Conclusion: The combination of CP with Bev was confirmed as effective and tolerable in chemotherapy-naive non-squamous NSCLC patients with MPE. To better establish this evidence for patients with MPE, further clinical trials are warranted.

No conflict of interest.

3493 POSTER

Bevacizumab (B) (10 mg/kg) in combination with cisplatin (C) and docetaxel (D) administered every 2 weeks in patients (p) with advanced non-squamous non-Small Cell Lung Cancer (nsNSCLC): GGCP047/10 study

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Background: B in combination with platinum doublets followed by continuation maintenance with B prolongs survival and delays progression in chemo-naive pts with advanced nsNSCLC. In a phase II trial C, D and B (15 mg/kg) every 3 weeks followed by B showed a promising efficacy, in terms of progression free survival (PFS) and overall survival (OS), and an acceptable toxicity profile. In addition, a biweekly schedule of D and C in p with metastatic NSCLC as a front-line CT has demonstrated effective antitumor activity with a reduction in hematologic toxicity, comparable to the results of previous studies using 3-week schedule. Taken together, these data suggest that the addition of B to C/D administered every 2 weeks could increase the efficacy and reduce the toxicity associated with the other schedules.

Material and Methods: GGCP 047−10 is a multicenter study in chemo- naive p diagnosed with advanced nsNSCLC. Eligible p also have measurable disease according to RECIST criteria; age ⩾18 years; ECOG PS ⩽1; adequate hematological, renal and liver function; life expectancy of at least 2 months and signed informed consent. P receive C (50 mg/m^2), D (50 mg/m^2), and B (10 mg/kg) every 2 weeks for up to 6 cycles, followed by B alone every 2 weeks until disease progression or unacceptable toxicity. PFS is used as the primary efficacy endpoint. Secondary endpoints include safety profile, overall response rate (ORR), disease control rate (DCR) and OS.

Results: 32 p were enrolled in the study. Median age was 60 years (range 44−72; 28.1% ⩾65 years); male/female (%): 81/19; ECOG 0/1/2 (%): 28/63/10; adenocarcinoma (%): 84. Median PFS in overall population was 6.4 months (95% CI, 4.2−8.7). Among the 22 p evaluable for response, the ORR was 63.6% and DCR was 95.4%. Most frequent grade 3/4 hematologic toxicity was neutropenia (40.6%) and grade 3/4 nonhematologic toxicities was asthenia (12.5%) followed by mucositis (6.2%) and diarrhea (3.1%). There were no grade 3/4 hemorrhagic events.

Conclusions: Treatment with B, C and D plus maintenance B every 2 weeks is effective as front-line treatment of p with advanced nsNSCLC with acceptable toxicity. These data provide further evidence that B may be used in combination with multiple standard, platinum-based doublets in this setting.

No conflict of interest.

3494 POSTER

Multicenter trial for assessing tolerability of combination therapy with cisplatin, irinotecan, and Polysaccharide-K in extensive-stage small-cell lung cancer: RNCLC-01 study

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Background: Polysaccharide-K (PSK, Krestin®) is a protein-bound polysaccharide, extracted from culturedmycelium of Coriplus versicolor, and is associated with immunostimulatory activity. Although combinationuse of PSK with chemotherapy has been shown to prolong the response period in patients with small-cell lung cancer (SCLC), the efficacy of PSK in combination chemotherapy including cisplatin has been less examined. In this study, we examined safety and efficacy of combination therapy with cisplatin, irinotecan, and PSK in extensive-stage (ED) SCLC.
Material and Methods: Eligible pts included: histologically confirmed ED-SCLC without prior chemotherapy, age under 75 years, ECOG performance status $\leqslant$1, with evaluable disease and adequate organ function. Treatment: irinotecan 60 mg/m^2 on days 1, 8, and 15 and cisplatin 60 mg/m^2 on day 1 every 4 weeks for 4 to 6 courses, and oral PSK 3,000 mg/body daily. The treatment with PSK was continued after the end of cisplatin and irinotecan administrations, and was combined as a part of second-line therapy after exacerbations.
Results: Between January 2008 and July 2010, 17 patients were enrolled, and the efficacy and prognosis were evaluated in 15 of 17 patients. Response rate was 66.6%, one year survival rate was 66.6%, and two year survival rate was 33.2%. The major toxicities were diarrhea and myelosuppression, and the common toxicity of PSK-containing combination chemotherapy was not observed.
Conclusions: The combination chemotherapy with cisplatin, irinotecan, and PSK was effective and well tolerated in ED-SCLC. Updated survival and toxicity data will be presented at the Meeting.
No conflict of interest.

3495 POSTER

Paclitaxel and irinotecan in platinum refractory or resistant patients with small cell lung cancer: Experience from the Galician Lung Cancer Group

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Background: Patients with Small Cell Lung Cancer (SCLC) whose disease progresses during or shortly after treatment with platinum, have a poor prognosis. Paclitaxel (P) and irinotecan(I) have demonstrated activity both as monotherapy as in combination regimen for this neoplasm. We present preliminary data from our experience in patients with SCLC refractory or resistant to platinum.
Material and Methods: We included patients with measurable disease that had progressed during or within six months of first-line chemotherapy based on platinum, with an Eastern Cooperative Oncology Group (ECOG) performance status <2, adequate liver, renal and bone marrow function. They were treated with (P): 75 mg/m^2 and (I): 50 mg/m^2, both drugs administered on days 1 and 8 of a 21 day cycle. Treatment was maintained until disease progression and/or unacceptable toxicity.
Results: Twenty-four patients have been treated, with a mean age of 59.5 years (43−79) and with metastases in two or more locations in 21 of them (87.5%). A median of 4 cycles of treatment was administered and eight patients (33.3%) received six or more cycles. The main reason for discontinuation of chemotherapy was disease progression, observed in 20 patients (83.3%). Partial response was documented in 16 patients (66.6%), stable disease in three (12.5%) and disease progression in five (20.8%). The median survival time was 24.9 weeks and the 1-year survival time was 22%. There have been no treatment-related deaths. The clinical and hematologic toxicities most frequently observed were grade 1 and 2: nausea (n:7; 29.2%), asthenia (n:7; 29.2%), anorexia (n:6; 25%), diarrhea (n:4; 16.6%), anemia (n:16; 66.6%) and neutropenia (n:12; 50%). There was one (4.1%) grade 4 and two (8.3%) grade 3 neutropenia. There were no cases of grade 4 clinical toxicity and there were eight (33.3%) grade 3: three of diarrhea (12.5%), two hepatic (8.3%) and three of asthenia (12.5%).
Conclusions: This (P) and (I) regimen is an effective and well tolerated option for this subgroup of poor prognosis patients with SCLC.
No conflict of interest.

3496 POSTER

Treatment with cisplatin–etoposide in the high-grade neuroendocrine tumors of the lung: Is histology important?

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Background: The optimal treatment for neuroendocrine tumors (NE) of the lung is still a matter of discussion. There is controversy regarding chemotherapy for large cell neuroendocrine carcinoma (LCNEC), in fact is not clear if the optimal treatment for LCNEC is similarly to small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC). The aim of our study is to analyze the differences in demographic characteristics and survival between SCLC and LCNEC using the same therapeutic strategy in both histological types.
Material and Methods: 33 and 24 patients with a diagnosis of LCNEC and SCLC respectively from 2005 to 2013 received cisplatin 90 mg/m^2 d1q21, etoposide 100 mg/m^2 d1q21 plus octreotide LAR 30 mg every 28 day. Other eligibility criteria were performance status 0 or 1, any stage, no previous chemotherapy and a histologically documented LNEC. The Kaplan–Meier test was used in order to evaluate the progression free survival (PFS) and overall survival (OS).
Results: In our single institution study we retrospective examined 57 patients of whom 50 (87.7%) with smoking history, median age of 64 (range 40−80), 63.2% male. Patients received a median of 6 cycles (range 3−6). For LCNEC the median progression free survival (PFS) was 12.5 months (95% Confidence Interval, CI 5.9–19.0) and the overall survival (OS) was 18.0 months (95% CI 11.3–24.7). For the SCLC the PFS was 16.2 months (95% CI 7.9–24.6) and OS was 25.8 months (95% CI 16.8–34.9).
Conclusion: In our results LCNEC tumors treated with cisplatin and etoposide plus octreotide LAR have a lower PFS (12.5 vs 16.2 months) and OS (18.0 vs 25.8 months) than SCLC.
No conflict of interest.

	PFS, months	OS, months
LCNEC	12.5 (CI 5.9–19.0)	18.0 (CI 11.3–24.7)
SCLC	16.2 (CI 7.9–24.6)	25.8 (CI 16.8–34.9)

3497 POSTER

Cisplatin in combination with etoposide for the first-line treatment of patients with large cell neuroendocrine carcinoma of the lung

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Background: Large-cell neuroendocrine carcinoma (LCNEC), 1−3% of all lung cancers, at diagnosis are generally widespread. The prognosis is poor despite an aggressive approach with extensive surgical resection for low stages and multidisciplinary approach with chemotherapy and radiotherapy for advanced stages. In literature there is no optimal treatment for patients with LCNEC. A recent retrospective review (Sun JM et al., Lung Cancer. Aug;77−2:365−70) of 45 consecutive patients with advanced LCNEC assessed that the median PFS durations were 6.1 and 4.9 months (P = 0.41), and the median OS durations were 16.5 and 9.2 months (P = 0.10) depending on whether first-line chemotherapy used regimens designed for SCLC (n = 11) or for NSCLC (n = 34). Our aim is to evaluate the effectiveness of the doublet cisplatin–etoposide plus octreotide in LCNEC as a first-line therapy.
Material and Methods: We retrospective studied 33 patients with LCNEC from 2005 to 2013 who received cisplatin 90 mg/m^2 d 1q21, etoposide 100 mg/m^2 d 1−3q21 and octreotide LAR 30 mg every 28 days. Other eligibility criteria were performance status 0 or 1, any stage, no previous chemotherapy and a histologically documented LNEC. The Kaplan–Meier

test was used in order to evaluate the progression free survival (PFS) and overall survival (OS).
Results: 28 patients (84.8%) had a smoking history, median age was 66 (range 40−80), 60.6% men, 39.4% women. Patients received a median of 6 cycles (range 3−6). The median PFS was 12.5 months (Confidence Interval, CI 5.9–19.0) and the OS was 18.0 months (95% CI 11.3–24.7) respectively.
Conclusions: Results show that patients treated with cisplatin–etoposide and octreotide LAR have a poor prognosis similar to SCLC regardless of the stage of presentation, however our results, if compared to literature, support that cisplatin–etoposide plus octreotide based regimens may be effective against LCNEC.
No conflict of interest.

3498 POSTER

Phase 1b study of capecitabine and erlotinib in advanced non-small cell lung cancer

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Background: Erlotinib (Tarceva®, T) has been shown to improve overall survival and progression-free survival in second or third line treatment of unselected non-small cell lung cancer (NSCLC) patients (pts) compared to placebo. Thymidylate synthase inhibitors are active in NSCLC. Capecitabine (X) is an oral pro-drug of 5-fluorouracil activated by thymidine phosphorylase which is present in ~30% of NSCLC. T in combination with platinum and X in combination with docetaxel have been tested in NSCLC. Combination of X and T is active and well tolerated with no grade 4 toxicities in advanced pancreatic cancer. This provides the rationale for a phase 1b open-label 2-part study of X combined with T in pts with advanced NSCLC.
Methods: In the first part of the study, pts who received prior chemotherapy with adenocarcinoma histology and a performance status of 0−2 were investigated. The primary objective was to determine the maximum tolerated dose (MTD) and safety profile. X was administered at a starting dose of 500 mg/m^2 twice daily (bd) from day 1−14 and T 100 mg once daily (od) between day 1−21, all orally on a 21-day cycle. Successive cohorts of 3−6 pts were evaluated for dose-limiting toxicities (DLTs), defined as one episode of grade 2 or more toxicity that resulted in dose interruption or reduction. Dose escalation would only commence when all pts in the cohort had completed 42 days (2 cycles) of treatment without DLTs. The MTD was the dose at which $\leqslant$1/6 DLT was observed in that cohort.
Results: 20 pts were enrolled. No DLTs was observed in the first cohort. In the second cohort, 6 pts (3 were replacements due to early progressive disease (PD) before cycle 2) were treated with X 750 mg/m^2 bd and T 100 mg od with no DLTs. In the third cohort, X 1000 mg/m^2 bd and T 100 mg od, 1 patient had DLTs (grade 2 anaemia, grade 3 atrial fibrillation, grade 3 pneumonia) and additional 3 patients were recruited. 2 pts developed DLTs (1 had grade 2 skin toxicity and grade 2 rise in creatinine, 1 received a dose reduction as per protocol due to a drop in creatinine clearance). Dose escalation was stopped and 5 pts were recruited to the previous dose level (1 was replaced due to early PD before cycle 2 and 1 was a screen failure making a total of 6 pts in this dose level) with no DLTs and the MTD was established. Preliminary efficacy data showed 7/15 (47%) attained stable disease at the end of cycle 2 but 2 of the 7 pts went on to achieve partial response (PR) (13.3%). EGFR mutation status was not known in 7 pts and the remaining 8 pts (including 1 pt with PR) had none of the common EGFR mutations in exons 18 to 21 detected.
Conclusions: The combination of X 750 mg/m^2 bd with T 100 mg od is active and generally well tolerated in advanced NSCLC. The second part of the study has started and is recruiting pts at this dose level in the first line setting.
CCR Reference: CCR3176
Acknowledgements: We acknowledge NHS funding to the NIHR Biomedical Research Centre and support from Roche.
Conflict of interest: *Advisory board: Roche*

3499 POSTER

Multi-center randomized phase II trial of pemetrexed plus oxaliplatin or pemetrexed alone as the second line treatment for stage IV non-squamous non-small cell lung cancer

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Background: Guidelines from ESMO and NCCN indicated that the pemetrexed (Pem) alone was one of the options as the second line treatment for non-squamous NSCLC. While for the patients with a good performance status (ECOG 0−1), whether or not combining with platinum still remains unclear. This multi-center phase II trial was to evaluate the effectiveness and safety of the combination of Pem and oxaliplatin (Ox) as the second line treatment for those patients.
Materials and Methods: 53 pre-treated patients with non-squamous NSCLC were randomly assigned to Pem group (Pem 500 mg/m^2 d1/21 days) or Pem-Ox group (Pem 500 mg/m^2 d1 and Ox 135 mg/m^2 d1/21 days). The primer objective was the time to progression (TTP), and the second objectives included overall survival (OS) and treatment-related toxicities. The Kaplan–Meier analysis was performed in statistical analysis. Toxicities were recorded according to the NCI CTC version 3.0.
Results: The patients aged 42−68 years (median 55 years). The median follow-up period was 34 weeks. 21 and 22 patients was assigned to Pem and Pem-Ox group, respectively. The disease control rate (DCR) were 52.4% and 59.1%, respectively. There was no significant improvement in median TTP (13 weeks) and OS (36 weeks) in Pem-Ox group, comparing to the Pem group (median TTP: 10 weeks and median OS 32 weeks) (p >0.05, respectively). The treatment-related toxicities were similar, except more grade 1−2 peripheral neuritis were observed in the combination of Pem-Ox regimen.
Conclusions: For those patients with non-squamous NSCLC, the combination of pemetrexed and oxaliplatin did not show advantage as the second line treatment in this perspective study, comparing to the pemetrexed alone. Due to the limited study sample, further investigations might be warranted.
No conflict of interest.

3500 POSTER

Biweekly docetaxel/cisplatin vs gemcitabine/cisplatin as first-line therapy for advanced non small cell lung cancer patients who are elderly or poor performance status: Randomized multicenter phase II trial

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Background: Docetaxel/Cisplatin (DP) and Gemcitabine/Cisplatin (GP) are standard treatment regimens for advanced NSCLC. In spite of potent efficacy, conventional one-day DP is regarded to have more toxicity compared with GP. There is increasing interest in a biweekly split administration of DP to reduce its toxicity. Hypothesis was that 1st-line biweekly DP is as safe as GP in elderly or poor performance status (PS) patients (pts).
Material and Methods: Chemotherapy naive pts with advanced NSCLC (IIIB/IV) who were elderly(65<) or PS (ECOG 2) were randomized to DP or GP arm by balancing for ECOG (0−1 v. 2), stage (IIIB v. IV) and age (<65 v. 65<). DP composed of docetaxel (35 mg/m^2)/cisplatin(30 mg/m^2) iv on days 1, 8 every 3 weeks. GP composed of gemcitabine (1000 mg/m^2)/cisplatin (30 mg/m^2) iv on days 1, 8 every 3 weeks. Chemotherapy lasted upto 6 cycles or until progression. Primary endpoint was safety (proportion of grade 3/4 toxicities). Planned sample size was 49 pts in each arm.
Results: From Nov. 09 to Jan. 13, a total of 97 pts were randomized (DP 50/GP 47). Adenoca was 58% in DP arm and 51% in GP while that of squamous cell ca 34% in DP and 40% in GP. Stage IIIB/IV was

33%/66% in DP and 42%/59% in GP. In DP arm, a total 228 adverse events (AEs) were reported and 27 were grade 3/4 toxicities while 211 AEs and 21 grade 3/4 toxicities in GP arm. Neutropenia was the most frequent grade 3/4 toxicity in both arm (DP 8.9%; GP 15.9%). In DP arm, grade 3/4 leukopenia(8.9%), hyponatremia(6.7%), anemia(4.4%) and anorexia (4.4%) were observed while anemia (9.1%) and hyponatremia (6.8%) in GP. In total AEs, anemia was the most common in both arms (DP:66.7%; GP:63.6%). Then, in the following order, hyponatremia (53.3%), anorexia (53.3%) and fatigue(40%) were common in DP arm while anorexia, (56.8%), fatigue(36.4%) and neutropenia(45.5%) were common in GP. Death during treatment was occurred in 1 pt in each arm. Both regimen showed similar grade 3/4 toxicities with similar profiles. Survivals seem to be favorable in GP arm compared with DP but with no statistical significance as follows. Progression-free survivals are 3.72 (DP) and 5.56 (GP) months respectively(p = 0.341). Overall survivals are 14.93 (DP) and 20.82 (GP) months respectively(p = 0.209).
Conclusions: This study showed that DP is similar with GP in terms of toxicity and efficacy in treatment of elderly or poor performance patients.
No conflict of interest.

3501 POSTER

ABCB1 polymorphisms as a predictive biomarker of neutropenia induced by amrubicin

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Background: Amrubicin is a key drug for small cell lung cancer (SCLC) but its treatment has a high incidence of severe neutropenia. The human *ABCB1* gene encodes multidrug transporter P-glycoprotein (P-gp) and its functional single nucleotide polymorphisms (SNPs) are known to influence to clinical outcome of various anticancer drugs. Amrubicin and its active metabolite, amrubicinol, are substrates for P-gp but the involvement of *ACBC1* SNPs in neutropenia induced by amrubicin has yet to be determined.
Material and Method: In 53 lung cancer patients treated by amrubicin monotherapy, grade of adverse effects and absolute neutrophil count (ANC) at nadir in first line amrubicin treatment were investigated and genotypes of two most major *ABCB1* SNPs (C3435T, G2677T/A) were analyzed by Taqman-probe method. In 18 of them, plasma concentrations of amrubicin and amrubicinol after first administration of amrubicin were measured using high-performance liquid chromatography method and their area under the plasma concentration versus time curve (AUC) values were analyzed.
Results: Patients treated with standard dose of amrubicin (N = 30, 40 mg/m^2) showed a significantly higher incidence of grade 4 neutropenia and percent decrease of ANC compared to 23 patients treated with lower dose of amrubicin (N = 23, *P* = 0.046 and 0.01). In patients treated with standard dose, patients carrying 3435CC (N = 9) showed significantly higher percent decrease of ANC compared to patients carrying 3435CT (*P* = 0.01) and 3435TT *(P*=0.04). Also, there incidence of grade 4 neutropenia was significant higher than that of patients without this genotype (*P* = 0.03). Patients carrying 2677GG (N = 6) showed a significant higher percent decrease of ANC compared to patients without G allele (*P* = 0.04). Meanwhile, in patients treated by low dose treatment of amrubicin, no significant relation between degree of neutropenia and genotypes of *ABCB1* SNPs was seen. In pharmacokinetic analysis, there was a significant positive correlation between AUC value of amrubicinol and percent decrease of ANC (r = 0.589 P = 0.01), but there was no significant correlation between AUC value of amrubicinol and genotypes of *ABCB1* SNPs.
Conclusions: These findings suggest C3435T and G2677T/A SNPs of *ABCB1* associate with amrubicin-related neutropenia and the mechanism is independent of AUC value of amrubicinol. These *ABCB1* SNPs could be a predictive biomarker for severe neutropenia induced by amrubicin.
No conflict of interest.

3502 POSTER

A combination of pemetrexed and carboplatin as first-line treatment for advanced non-squamous non-small cell lung cancer without epidermal growth factor mutation: A multicenter, phase II trial (CJLSG0906)

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Background: Epidermal growth factor receptor (EGFR) status is very important when selecting treatment for non-small cell lung cancer (NSCLC). We evaluated the efficacy and safety of combination therapy with pemetrexed and carboplatin (PC) for the treatment of patients with advanced non-squamous (non-Sq) NSCLC without EGFR mutation.
Material and Methods: In this multicenter, phase II trial, we recruited patients with non-Sq NSCLC without EGFR mutation. Eligibility criteria were stage IIIB or IV, recurrent disease after surgery, no prior chemotherapy, age 20−74 years, Eastern Cooperative Oncology Group performance status 0−1, and adequate organ function. We evaluated the efficacy and safety of pemetrexed (500 mg/m^2) and carboplatin (area under curve 6), on day 1 of a 21-day cycle for up to 3−6 cycles. The primary endpoint was the response rate (RR), and the secondary endpoints were safety and the disease control rate (DCR). Based on the Simon 2-stage design, the planned sample size of 53 patients (pts) was determined to reject the RR of 15% under the expectation of 30% with a power of 0.80 and type I error of 0.05.
Results: From March 2009 to February 2012, 54 pts were enrolled from 18 centers and 52 pts were analyzable for outcome. The median age of these pts was 65 years (range, 43−73), and the male/female ratio was 40/12. Stage III and IV were noted in 6 and 46 pts, respectively; 46, 3, and 3 pts had adenocarcinoma, large cell carcinoma, and NSCLC, respectively. The median number of cycles was 4. We noted partial response in 19 pts with a RR of 36.5% (95% confidence interval, 23.6–51.0%). Stable disease was observed in 20 pts and the DCR was 75%. Major adverse events of grade 3−4 neutropenia were noted in 19 pts (36.5%). Grade 3−4 infection was observed in 4 cases (7.7%), but grade 3 febrile neutropenia was not noted. Grade 3−4 anemia and thrombocytopenia were observed in 16 pts (30.7%, each). Grade 3−4 nausea and vomiting were seen in 3 (5.8%) and 2 (3.8%) pts, respectively. There was no treatment-related death.
Conclusions: PC was efficacious and well tolerated in pts with advanced non-Sq NSCLC without EGFR mutation. This combination could be a standard regimen option for first-line treatment for advanced non-Sq NSCLC.
Clinical trial: UMIN000003393. This study was sponsored by Central Japan Lung Study Group.
Conflict of interest: *Advisory board: H. Saka, Eli Lilly Japan, Co H. Taniguchi, Boehringer-Ingelheim and Shionogi. & Co., Ltd. Other substantive relationships: H. Saito, Eli Lilly Japan, Co.*

3503 POSTER

Tumor-related symptoms (TRS) assessment in patients (pts) with advanced non-small cell lung cancer (NSCLC) treated with gefitinib or erlotinib: Preliminary results of an observational study

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Background: Edmonton Symptoms Assessment Scale (ESAS) is a validated tool in palliative care, which evaluates physical symptoms through a numeric scale (0−10). Symptoms improvement as a predictive factor for response rate (RR) in pts with advanced NSCLC treated with tyrosine-kinase inhibitors (TKIs) has not yet been evaluated. To this purpose, we performed an observational retrospective study.
Methods: Pts with advanced NSCLC treated with gefitinib or erlotinib were eligible. Primary outcome was the association between treatment response and tumor-related symptoms (TRS) (pain, asthenia, dyspnea) improvement. ESAS was performed at day 1 and 14 of each 28-d cycle. Symptoms' scores were divided into: not clinically relevant (0−4, NCR) and clinically relevant (5−10, CR). Sample size estimation was 115 to 165 pts to be needed for the expected difference in the primary outcome. Differences between symptoms' groups were analyzed with the paired-data

McNemar-test. All the associations were estimated using the Chi-Square test. Kaplan–Meier method was used for survival calculation. Uni- and multivariate survival analysis were carried out using the Cox regression model.
Results: Here we report data about 89 consecutive pts; median age: 69 years, males 68%, ECOG PS 0−1 88%, smokers 70%, EGFR-mutated 20%. Treatment was gefitinib (21%) or erlotinib (79%). RR: RC/RP 16%, SD 20%, PD 62%, TE 2%. Median follow-up was 7 months. 63% of pts had at least one CR TRS at baseline. Among these pts, a significant reduction ($p < 0.0001$) of TRS during treatment was observed (Table). Our preliminary data show a significant association between dyspnea/asthenia and RR ($p = 0.01$). At the multivariate analysis, TRS improvement correlates with both PFS and OS. Also related with survival were PS, EGFR status (PFS) and RR (OS).
Conclusions: Our preliminary data show that TRS improvement is significantly associated with treatment response and appears to be a prognostic factor during treatment with TKIs.
No conflict of interest.

TRS	Basal score $\geqslant$5 (%)	Nadir* score (%)
Pain	53	19
Asthenia	66	30
Dyspnea	57	23

*Lower score registered per patient.

3504 POSTER

No improvement in population-based survival of stage IV NSCLC despite increased use of chemotherapy

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Background: Objective of this study was to investigate which factors were associated with the administration of chemotherapy for patients with stage IV non-small cell lung cancer (NSCLC), and their relation to population-based survival.
Materials and Methods: All patients diagnosed with NSCLC stage IV from 2001 to 2010 in the area of the Eindhoven Cancer Registry (n = 4,091) were included. Logistic and Cox regression analyses were performed to evaluate chemotherapy use and survival, respectively.
Results: Overall, 44% of the patients received chemotherapy. Higher rates were found among younger patients (multivariable odds ratio ($OR_{\leqslant 64\_vs\geqslant 75\_years}$) 1.9 (95% CI:1.6−2.2), in higher socioeconomic status ($OR_{high\_vs\_low}$ 1.7 (95% CI:1.4−2.1)), patients without comorbidity ($OR_{\geqslant 2\_vs\_0}$ 0.6 (95% CI:0.5−0.7)), patients diagnosed in more recent years ($OR_{2001-2003\_vs\_2010}$ 0.5 (95% CI:0.4−0.6)), having adenocarcinoma ($OR_{squamous\_vs\_adenocarcinoma}$ 0.8 (95% CI:0.6−1.0)), and metastasis to bone ($OR_{brain\_vs\_bone}$ 0.5 (95% CI:0.4−0.6)). Also a large hospital variation was observed, up to OR 2.2 (95% CI:1.6−2.9). Survival did not improve over time (median 19 weeks). One-year survival rates were 31% (median 35 weeks) for patients receiving chemotherapy and 8% for those not receiving chemotherapy (median 10 weeks). Prognostic factors were receipt of chemotherapy (hazard ratio (HR) 0.4 (95% CI: 0.4−0.5)), histology ($HR_{other\_vs\_adenocarcinoma}$ 1.1 (1.0−1.2)) and grade ($HR_{poor/undifferentiated\_vs\_well/moderate}$ 1.2 (1.0−1.4), $HR_{unknown\_differentiation\_vs\_well/moderate}$ 1.2 (1.0−1.4)).
Conclusion: The administration of chemotherapy was affected by year and hospital of diagnosis, as well as patient related (i.e. age, socioeconomic status, comorbidities) and tumour related factors (i.e. histology, site of metastasis). Despite increasing administration rates of chemotherapy, population-based survival rates remained low. The role of both patient and doctor preferences in the administration of chemotherapy remains to be explored. There should be more attention for identifying subgroups of patients who benefit from chemotherapy.
No conflict of interest.

3505 POSTER

Gefitinib as first line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) in patients with activating epidermal growth factor receptor (EGFR) mutations within a Western population

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Background: Tyrosine kinase inhibitors are standard of care in first line treatment of advanced NSCLC with activating EGFR mutations. Initially gefitinib (Iressa®) was the only approved drug in the UK following the IPASS study. Majority of evidence for gefitinib is based on patients of Asian origin, female sex, never or former-light smokers with less evidence in Western populations, which prompted this audit in Merseyside.
Methods: Case notes of patients who received first line Gefitinib from September 2010 to December 2012 were reviewed. Cases were identified via electronic patient records and records of Histopathology Department. CTCAE v 3.0 was used to score toxicity and response assessed according to RECIST criteria. Survival was calculated using IBM SPSS Statistics version 19.
Results: 42 patients, 45% male and 55% female, with a mean age of 74 were identified. Performance status (PS) was 0−2 in 83% and 3 in 17%. All had adenocarcinomas with 93% having stage 3/4 disease. The remainder had relapsed disease after radical treatment and 1 patient had stage 1 disease. Most common EGFR mutations were exon 19 deletions (42%) and L858R exon 21 mutations (39%). Improved survival was seen in exon 19 deletions and patients of PS1 (20 vs. 10 months respectively) but this was not statistically significant. Median progression free and overall survival was 9 and 10 months. 1 year survival was 49.4%. A median of 7 cycles (range1−24) were delivered. 34 (81%) had lesions suitable for RECIST evaluation. At first CT scan 65% had stable disease, 26% partial response, 6% complete response, and 3% progressive disease. Of the remainder, 5 died prior to initial scan, 2 had immeasurable disease and 1 failed to have a baseline scan within an acceptable timeframe.
The most common reason for discontinuing gefitinib was disease progression with 29% (12) patients having further treatment. Palliative radiotherapy was administered in 5 and chemotherapy in 6. Common toxicities experienced were rash (56%), diarrhoea (36%), nausea and vomiting (12%) and fatigue (12%). Treatment was stopped due to toxicity in 4 patients; 2 grade 3 nausea, 1 grade 3 mucositis and 1 recurrent pyrexia.
Conclusions: Patients in our local population, of primarily Caucasian origin with advanced NSCLC and activating EGFR mutations benefit from first line Gefitinib. Benefits and toxicities broadly concur with those of the IPASS study though survival is inferior. Updated data on 100 patients will be presented.
Conflict of interest: *Other substantive relationships: Professor J R Gosney works in an advisory capacity for AstraZeneca, Lilly & Co, Boehringer-Ingelhiem and Pfizer. Dr P Jain has received financial support in the past for attendance at meetings from Lilly & Co, Roche and Boehringer-Ingelheim.*

3506 POSTER

Phase I study of oral nintedanib combined with docetaxel in previously treated Japanese patients with advanced non-small cell lung cancer (NSCLC)

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Background: Nintedanib is an oral tyrosine kinase inhibitor that targets VEGFRs, PDGFRs and FGFRs, as well as RET and Flt3. This phase I, open-label, dose-escalation study (NCT00876460) was conducted primarily to determine the safety, tolerability, and maximum tolerated dose (MTD) of nintedanib combined with docetaxel in previously treated patients with advanced NSCLC.
Material and Methods: Eligible patients had advanced NSCLC of any histology after failure of first-line platinum-based chemotherapy (not containing docetaxel), an ECOG performance status of 0−1, and adequate organ function. Patients received nintedanib twice daily (bid), given continuously at a dose of 100, 150 or 200 mg bid (days 2−21), combined

with docetaxel 60 or 75 mg/m^2 (day 1) in 21-day cycles. Standard 3+3 dose escalations were performed separately in two pt cohorts with a small body surface area (<1.5m^2) (sBSA) and standard (⩾1.5m^2) BSA (stBSA), respectively. MTD was defined as the highest dose at which incidence of dose-limiting toxicities (DLTs) was ⩽33.3%. Pharmacokinetic (PK) analysis of nintedanib and docetaxel was also performed. Preliminary antitumour activity was evaluated according to RECIST v.1.0.

Results: Forty-two patients, including 17 patients with sBSA (<1.5m^2) and 25 patients with stBSA (⩾1.5m^2), were treated. The MTD of nintedanib, given in combination with 75 mg/m^2 docetaxel, was 150 mg bid in the sBSA cohort and 200 mg bid in the stBSA cohort. All DLTs were grade 3 liver enzyme elevations, which occurred in 12 patients (6 patients each in the sBSAand stBSA cohorts). These liver enzyme elevations were fully reversible and manageable with dose reduction or treatment discontinuation. The other most frequent drug-related adverse events were neutropenia (95%), leukopenia (83%), fatigue (76%), alopecia (69%), and decreased appetite (67%). PK analysis revealed no interactions between nintedanib and docetaxel. Analysis of PKs by BSA is ongoing. Among 36 assessable patients, 10 had a partial response, yielding an overall response rate of 28%.

Conclusion: Continuous daily treatment with nintedanib combined with docetaxel was manageable and showed promising signs of efficacy in previously treated Japanese patients with advanced NSCLC.

Conflict of interest: *Advisory board: Nagakawa K: Boehringer Ingelheim. Corporate-sponsored research: Seto T:Nippon Boehringer Ingelheim Co.Ltd. Other substantive relationships: Sarashina A: Employee of Nippon Boehringer Ingelheim Co Ltd Seto T: Honoraria from Nippon Boehringer Ingelheim Co Ltd Kaiser R: Employee of Boehringer Ingelheim Pharma GmbH KG*

3507 POSTER

Phase II study of bevacizumab, cisplatin and docetaxel plus maintenance bevacizumab as first line treatment for patients with advanced non-squamous non-small cell lung cancer (n-Sq NSCLC) combined with exploratory analysis of circulating endothelial cells (CEC): Thoracic Oncology Research Group(TORG)1016

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Background: Bevacizumab has been shown to amplify efficacy against n-Sq NSCLC in combination with platinum doublet, especially taxane including regimens. Docetaxel is one of best taxane composition combined with cisplatin for first line treatment for NSCLC, and known to have anti-angiogenic effect and may act synergistically with VEGF inhibiting agent. The object of this study was to assess the efficacy and safety of bevacizumab, cisplatin and docetaxel combination treatment in patients with chemonaive n-Sq NSCLC patients (Trial Registry: UMIN 000004368).

Methods: Eligible patients had advanced or recurrent n-Sq NSCLC with no prior chemotherapy. Patients having brain metastasis or history of hemoptysis were ineligible. Patients received 4 cycles of docetaxel (60 mg/m^2), cisplatin (80 mg/m^2) and bevacizumab (15 mg/kg) on day1 every 3 weeks followed by Bev alone as maintenance every 3 weeks until disease progression or unacceptable toxicity. The primary endpoint was response rate (RR) and planned sample size of this phase II study was 47 patients (Simon's two-stage minimax design). We measured circulating endothelial cells (CEC) count day1 and 8 of first cycle for exploratory analysis of efficacy and safety prediction.

Results: From Oct 2010 to Apr 2012, 47 patients (28 males/ 19 females, median age, 61 years, 39−73) were enrolled. Stage IIIB/IV/recurrent: 5/39/3, ECOG PS 0/1: 31/16. All patients were adenocarcinoma, EGFR status: mutated/wild/unknown: 13/31/3. Bevacizumab maintenance were administered in 87% (41/47) of the patients and 9 was median number of delivered course, 4 course of induction and 5 course of maintenance. Dose reduction was required in 28% (13/47) of the patients. Thirty-five partial responses and 11 stable diseases were observed among 47 patients, yielding a RR of 74.5% (95% confidence interval: 59.7–86.1%) and disease control rate of 97.9% (88.7–99.9%), respectively. The median progression free survival duration in the patients was 9.0 (7.0–11.3) months. Grade 3/4 leukopenia, neutropenia, hypertension, nausea and febrile neutropenia were observed in 60, 96, 47, 13 and 9% of the patients, respectively. Alveolar hemorrhage (Grade 5) after 4 cycle occurred in one patient.

Conclusions: Bevacizumab, cisplatin and docetaxel combination followed by bevacizumab maintenance treatment was highly effective in patients with n-Sq NSCLC, with acceptable toxicity. Exploratory analysis of CEC is ongoing and will be presented.

No conflict of interest.

3508 POSTER

TSR-011: A potent inhibitor of ALK with activity in crizotinib-resistant tumor models in phase 1−2 development for ALK+ NSCLC

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Background: Significant progress has been made in treatment of the subset of non-small cell lung cancer (NSCLC) driven by the echinoderm microtubule associated protein like 4 (EML4) anaplastic lymphoma kinase (ALK) gene and other fusions. Despite approval of crizotinib for ALK+ NSCLC there are still significant challenges. In order to address limitations of crizotinib, such as resistance mutations in ALK, TSR-011, a potent, small molecule, second generation ALK inhibitor is undergoing clinical evaluation. TSR-011 was specifically designed using X-ray structure based drug design, and hence has very high affinity for the ALK kinase domain (Kd = 0.36 nanomolar, [nM]). TSR-011 inhibits wild type, recombinant ALK kinase activity with an IC50 value of 0.7 nM and exhibits sustained potent inhibition of ALK-dependent tumor growth in mice. ALK amplification and mutations that are important drivers of NSCLC cell growth or crizotinib resistance are inhibited by TSR-011 at low nM (IC50 values of 0.1 to 2.2 nM) concentrations. The (sub)nanomolar potency and activity against clinically observed ALK mutations of make TSR-011 a promising 2nd generation ALK inhibitor.

Methods: A Phase 1−2a dose escalation and cohort expansion study sponsored by TESARO is underway to evaluate safety, tolerability, PK, and efficacy of TSR-011. Phase 1 is evaluating patients with advanced solid tumors and lymphomas of any ALK status. The maximum tolerated or recommended Phase 2 dose will be evaluated in Phase 2a in patients required to have ALK+ tumors (defined by immunohistochemistry and fluorescent in-situ hybridization) including those with NSCLC progressing on, or naive to, ALK inhibitor therapy, as well as, non-lung malignancies. This study was approved by Institutional Review Boards of all participating institutions.

Results: As of April 2013, patients have been enrolled at doses between 30 and 480 mg orally. Tumor types include ALK+ and negative NSCLC, papillary thyroid cancer and neuroendocrine tumors. Once daily dosing resulted in dose responsive pharmacokinetic parameters and human drug exposures in excess of that associated with efficacy in murine models. No DLTs or visual changes have been reported.

Conclusions: Based on tight binding to ALK, potency at inhibiting ALK enzymatic activity, activity in crizotinib resistant cellular models and early clinical data TSR-011 is a promising agent for ALK-dependent malignancies.

Conflict of interest: *Ownership: TESARO, Inc. Other substantive relationships: stock ownership, employment*

3509 POSTER

Final results of a phase II trial evaluating oral vinorelbine as maintenance treatment after first line chemotherapy with cisplatin plus oral vinorelbine for locally advanced or metastatic non-small-cell lung cancer patients

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Background: Vinorelbine (V) plus Cisplatin (CDDP) is a commonly used platinum doublet for the treatment of advanced NSCLC which has

consistent proven efficacy. Maintenance therapy has lately demonstrated significant outcome improvement; nevertheless the high cost of treatment in developing countries remains an issue. The oral form of V is a convenient and cost-effective treatment.
Material and Methods: We conducted a multi-centre phase II trial to evaluate CDDP 80 mg/m^2 D1 in combination with Oral V 60 mg/m^2 D1 & D8 at first cycle increased at 2nd cycle (in the absence of grade III–IV haematological toxicity) to 80 mg/m^2 D1 & D8. Cycles were repeated every 3 weeks for a total of 4 cycles. Patients with objective response or stable disease after 4 cycles received maintenance therapy with Oral V 80 mg/m^2 D1 & D8 every 3 weeks for a total of 4 cycles. Primary objective: progression-free survival. Secondary objectives: objective response, overall survival and safety profile.
Results: n = 39; median age (range) 63 years (42–82); PS at inclusion: 0 (64%) or 1 (36%); number of metastatic sites: 1 (23%), 2 (54%), 3 or more (20%); Histology: non-squamous 82%, squamous (18%). 38 patients were evaluable for efficacy. Objective response was observed in 18 pts (47%) with 2 pts achieving CR (5%). Stable disease was observed in 9 pts (24%). The median duration of response was 6 months (95% CI [3.6–9.2]). 16 patients (41%) received the planned Oral V maintenance treatment. The median progression free survival for the whole population and for the population receiving maintenance treatment was 4.3 (95% CI [2.5–6]) and 7.8 (95% CI [5–9.9]) months respectively while the overall survival was 8.9 (95% CI [5.7–12]) and 10.5 (95% CI [6.6–14.3]) months respectively. Treatment was well tolerated with main observed hematological toxicities being grade 3 anemia (8%) and grade 3 & 4 neutropenia (8%). Grade 3 & 4 nausea/vomiting were observed in 18% of pts and grade 3 asthenia in 5%.
Conclusion: The study results are in line with published data, and reconfirm the efficacy of CDDP + Oral V regimen as first line treatment for advanced NSCLC. Maintenance therapy with single agent Oral V is feasible and well tolerated. Maintenance treatment with V may extend efficacy of the combination regimen, oral form being convenient to the patients for a treatment prolongation.
Conflict of interest: *Other substantive relationships: Among the authors, Cynthia Mourad is an employee of Pierre Fabre Medicament*

3510 POSTER

Phase II study of amrubicin and carboplatin for previously untreated patients with extensive-disease small cell lung cancer

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Background: Amrubicin and cisplatin are active in the treatment of small cell lung cancer (SCLC), and carboplatin is an analogue of cisplatin with less nonhematological toxicity. To determine the efficacy and toxicity of amrubicin and carboplatin for previously untreated patients with extensive-disease (ED) SCLC.
Patients and Methods: Thirty-five patients fulfilling the following eligibility criteria were enrolled: chemotherapy-naive, good performance status (PS 0–1), age <76, extensive-disease, and adequate organ function. Based on the phase I study (J Thorac Oncol 4:741, 2009), the patients received amrubicin 35 mg/m^2 i.v. on days 1, 2 and 3, and carboplatin AUC 5 i.v. on day 1. Four cycles of chemotherapy were repeated every 3 weeks.
Results: Thirty-five patients were eligible and 34 patients were assessable for response, toxicity and survival. Patients' characteristics were as follows: male/female = 27/8; PS 0/1 = 4/31; median age (range) = 64 (41–75); stage IV = 35. The overall response was 81% (CR5, PR21, SD4, PD2, NE3). Grade 4 leukopenia, neutropenia, and thrombocytopenia occurred in 11%, 60%, and 11%, respectively. There were no treatment-related death and pneumonitis. Three patients experienced hypotension for amrubicin infusion reaction and two were terminated the study. The median overall survival time, and the 1-, 2- and 3-year survival rates were 15.6 months, 63%, 33% and 8%, respectively. The median progression-free survival time was 6.5 months.
Conclusion: Amrubicin and carboplatin was effective in untreated extensive-disease small cell lung cancer.
No conflict of interest.

3511 POSTER

Biweekly cisplatin and gemcitabine as first line treatment in stage IV non-small cell lung cancer

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Background: Cisplatin plus gemcitabine is an option in treatment of stage IV non-small cell lung cancer (NSCLC). Biweekly use of this regimen is effective and more tolerable in a study. We evaluated the efficacy and tolerability of this regimen as retrospective.
Material and Methods: We analyzed patients, who had taken biweekly cisplatin/gemcitabine chemotherapy as first line treatment of NSCLC. Cisplatin 50 mg/m^2 and gemcitabine 1000 mg/m^2 were given on day 1 every 14 days.
Results: 108 patients were evaluated from five centers, 93 men (86%) and 15 women (14%). The median age was 58 (25–82). Most of patients were adenocarcinomas (n = 63, 58%). All of them had $\leqslant$2 ECOG PS. Mean 7 cycles therapy were given (2–12). After every four cycles, patients were evaluated for response. Overall clinical benefit was 68% (40% partial, 28% stable response). Progression free survival was 7.1 months. There were 41 deaths(38%) and overall survival (OS) didn't calculate. Estimated OS was 14.1 months. Six patients had died owing to progression during therapy. Grade 3/4 toxicity was detected in eight (7%) patients. They were four anemias, two neutropenias, one womiting and one nephropathy. In all grades, the most toxicity was anemia (48%). Neutropenia was 21% but only one patient had febrile neutropenia. One patient had changed therapy for grade 2 nephropathy. The predominant nonhematologic side effect were nausea and womiting.
Conclusions: Biweekly administration of cisplatin and gemcitabine as first line treatment in NSCLC is effective and tolerable.
No conflict of interest.

3512 POSTER

Clinicopathological features of non-small cell lung cancer in south India and correlation with epidermal growth factor receptor [EGFR] mutational status

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Background: There is scanty information on the prevalence of mutations in the Indian region. A prevalence of 51.8% was reported from single centre in India. We performed a retrospective analysis of 154 patients with carcinoma of the lung for whom formalin fixed paraffin embedded [FFPE] tissues was available. The clinicopathological profile, EGFR mutational status, treatment given and outcomes was collected, analyzed and are described.
Methods: All patients with histopathologically confirmed NSCLC who were treated during the two year period Jan 2008-Dec 2010 and for whom formalin fixed paraffin embedded [FFPE] tissues, on which EGFR mutational analysis could be performed, were available were included in this study. This protocol was approved by the IRB of the centre.
Results: Of the 154 cases included in the study, 48 were excluded since they were either treated elsewhere or the duration of follow up was less than 3 months. FFPE tissues of the remaining 106 patients were analysed for EGFR mutations. Forty two patients (39.6%) included in the study had a mutation in one of the four exons characterized (Table 1). The commonest mutation in exon 19 was a 15 bp deletion (n = 26, del E746-A750). Patients whose EGFR mutational status was not available at presentation prior to start of treatment were started on chemotherapy, n = 46 [43.39%]. If EGFR mutational analysis was available and mutations were present patient were stated on either upfront TKI, n = 15 [14.15%] or if on chemotherapy arm were allowed to finish 6 cycles and then start with maintenance TKIs, n = 26 [24.52%]. The median progression free survival for smokers and non smokers was 10 months (95% CI, 7–12) and 9 months (95% CI, 7–10) respectively. The median progression free survival for patients with and without mutations was 9 months (95% CI, 7–10) and 11 months (95% CI, 7–14) respectively. Better progression free survival was seen in the EGFR mutation positive group who received chemotherapy followed by TKI (log rank test, p = 0.027) as compared to those who received only

TKIs. Progression free survival in chemotherapy followed by maintenance with pemetrexed was (10 months, 95% CI, 8−11).
Conclusion: Our results show relative high prevalence of mutations in EGFR at 39.6% which is higher than the published data in western world and lower than that reported by a previous report from India which found mutations in 51.8% of patients[18]. The response rate of patients with an activating EGFR mutation was 93.3%. There was observed benefit of addition of chemotherapy over TKI in EGFR mutation positive group.
No conflict of interest.

Table 1. EGFR mutation status and its correlates

Variable	Number (%) of patients				
	EGFR mutation present (N = 42, 39.6%)		EGFR mutation absent (N = 64, 60.4%)		
Exon 18 mutation present	1 (2.4%)				
Exon 19 mutation present	32 (76.2%)				
Exon 20 mutation present	2 (4.8%)				
Exon 21 mutation present	7 (16.6%)				
	Response (%)	**Progression (%)**	**Response (%)**	**Progression (%)**	**Total**
Upfront TKI	14 (93.3)	1 (6.7)	0 (0.0)	0 (0.0)	15
Palliative care	0 (0.0)	0 (0.0)	0 (0.0)	4 (100)	4
Chemo	8 (88.8)	1 (11.2)	25 (67.6)	12 (32.4)	46
Chemo- TKI	16 (88.8)	2 (11.2)	7 (62.5)	1 (37.5)	26
Chemo-maint. chemo	0 (0.0)	0 (0.0)	14 (93.3)	1 (6.7)	15

3513 POSTER

Malignant pleural mesothelioma: maintenance chemotherapy with pemetrexed

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Background: Maintenance chemotherapy with pemetrexed is not the standard treatment of choice in patients with locally advanced or metastatic epiteliomorfe malignant pleural mesothelioma (EMPM). We would assess the safety and efficacy of a treatment with pemetrexed until progression disease after 4 or 6 cycles of induction therapy with or without platin.
Methods: From July 2008 to September 2012, 21 patients (18 males and 3 females with a median age of 67 years range 58−84) with locally advanced or metastatic epiteliomorfe malignant pleural mesothelioma (EMPM) were enrolled. In all patients histology was epiteliomorfe malignant mesothelioma. Only 15 patients (71.4%) had a PS 0 whereas 6 (28.6%) had a PS 1. All patients received an induction therapy with or without platin. Each patient received an average of 5.6 cycles of induction chemotherapy. Then all patients received a maintenance chemotherapy with pemetrexed 500 mg/mq intavenously over 10 minutes every 3 weeks. Each patient received an average of 7.3 cycles of maintenance chemotherapy. All patients received folic acid and vitamin B12 supplementation to improve safety.
Results: At the time of analysis all patients were evaluable for response. Fourteen patients (66.6%) had a partial response and two of these underwent surgery and obtained a complete response. Six patients (28.5%) had a stable disease. The median overall survival was 13 months, while median progression-free survival was 11 months. Grade 2−3 of WHO haematological toxicities (anemia and neutropenia) occurred in 4 patient (19%). We also observed grade 2−3 of WHO gastrointestinal toxicities (diarrhea, nausea and vomiting) in 2 patient (9.5%). Grade 2 of lack of appetite and asthenia occurred in 3 patients (14.3%).
Conclusions: Our data show that a maintenance chemotherapy with pemetrexed in EMPM resulted in a moderate overall survival (13 months). These results indicate that patients with EMPM could benefit from a maintenance treatment with pemetrexed.
No conflict of interest.

3514 POSTER

MED12, a component of the transcriptional MEDIATOR complex, and STAT3 influence outcome to platinum-based chemotherapy in patients (p) with advanced non-small-cell lung cancer (NSCLC)

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Background: MED12 negatively regulates TGF-b receptor signaling. Loss of MED12 induces an EMT-like phenotype associated with chemotherapy resistance. IDO and IL6 activate the JAK2/STAT3 signaling pathway, which − together with NFkB (RelA) signaling − is often altered in lung cancer. BIM could influence response to chemotherapy. We have examined these components and KRAS mutations in NSCLC tumor samples and correlated results with progression-free survival (PFS).
Methods: The mRNA expression of MED12, IDO, JAK2, STAT3, RelA and BIM was examined in microdissected tumor samples from p with stage IV NSCLC. mRNA levels were assessed by RT-PCR and categorized by terciles (high vs low/intermediate). KRAS mutations were assessed by high resolution melting.
Results: A total of 55 p with performance status (PS) 0−1, treated with platinum plus either gemcitabine or pemetrexed: median age, 62 years; 27.6% females; 84.2% smokers; 66% adenocarcinoma; 16% with KRAS mutations. There was no correlation between gene expression levels and KRAS mutation status. In the multivariate analysis, including gene expression levels, histology and PS, only MED12 and STAT3 were associated with PFS (low MED12: HR = 11.6, P = 0.005; high STAT3: HR = 6.5, P = 0.01). HR for low BIM expression was 2.4 (P = 0.16). None of the markers were associated with overall survival.
Conclusions: To the best of our knowledge, this is the first time that low expression of MED12 with significantly shorter PFS in NSCLC p receiving platinum-based chemotherapy. MED12 could be a new biomarker of chemoresistance and inhibition of TGF-bR signaling can restore chemotherapy response in patients with low MED12.
No conflict of interest.

3515 POSTER

Cell-free DNA and tumour burden in advanced NSCLC

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Background: Cell-free DNA (cfDNA) is fragments of DNA circulating in the bloodstream. Under malignant conditions, the level of cfDNA increases. The biological mechanisms behind this phenomenon remain to be fully understood, but it has been argued that the level of cfDNA is merely reflecting the tumour burden. It has also been suggested that the mechanism is far more complex, including biological pathways reflecting the aggressiveness of the disease. We aimed to examine the correlation between whole-body tumour burden in terms of total metabolic tumour volume (MTV) and total lesion glycolysis (TLG) estimated by PET-CT, and the level of cfDNA.
Material and Methods: Patients with newly diagnosed, non-small cell lung cancer (NSCLC) being candidates for first line chemotherapy were enrolled into a prospective biomarker trial at the Department of Oncology, Vejle Hospital, Denmark. From a pre-treatment blood sample, plasma was extracted and the level of cfDNA determined by an in-house qPCR. The routine staging was supplemented by a PET-CT scan when indicated. PET-scans performed within a month before blood-sampling were evaluated by an experienced nuclear medicine specialist, blinded to the level of cfDNA. The tumour contours were delineated semi- automatically by using a threshold SUV of 2.5. The primary endpoint was correlation between MTV, TLG and cfDNA. Secondary endpoints were progression free survival (PFS) and overall survival (OS) according to MTV, TLG and cfDNA. Correlations were determined by the Spearman's Rank correlation method. Survival data were analysed by the Kaplan–Meier method and the Log Rank test.
Results: Fifty-three patients were included. There was no correlation between MTV and cfDNA (r = 0.1), or TLG and cfDNA (r = 0.1), while there was a high agreement between MTV and TLG (r = 0.98). There was no

correlation between MTV, TLG, cfDNA and PFS, but patients with MTV above the median, had a significantly shorter OS compared with patients below the median (p=0.02). There was no significant difference in OS according to TLG (p = 0.08). cfDNA levels above the 75th percentile were significantly correlated to a shorter OS (p = 0.02) which was confirmed in a multivariate analysis.
Conclusions: Our results indicate that cfDNA does not merely reflect tumour burden, but is a valuable tumour marker of clinical importance.
No conflict of interest.

3516 POSTER

Phase I study of peptide vaccine targeting indeolamine 2,3 dioxygenase in metastatic lung cancer patients

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Background: To investigate the targeting of indeolamine 2.3 dioxygenase (IDO) enzyme by a synthetic peptide vaccine for patients with metastatic with non small-cell lung cancer (NSCLC).
Material and Methods: In a clinical phase I study we treated 15 HLA-A2 positive patients with stage III−IV NSCLC and disease stabilization (SD) after standard chemotherapy. Patients were treated with Imiquimod ointment and vaccine (100 microg IDO5 peptide, sequence ALLEIASCL, formulated in 900 microL Montanide) subcutaneously. Primary endpoint was toxicity. Clinical benefit and immunity were assessed.
Results: No CTCAE grade 3−4 were observed. One patient developed a partial response (PR) after 1 year of vaccine treatment while long-lasting disease stabilization (SD >8.5 months) was demonstrated in another 6 patients. The median overall survival (OS) was 2.1 years. Patients demonstrated significant improved OS (P = 0.03) when compared to the untreated group of excluded HLA-A2 negative patients. IDO specific CD8+ T-cell immunity were demonstrated by IFN-gamma Elispot and Tetramer staining. Flow cytometry analyses demonstrated a significant reduction in the T-reg population (P = 0.03) and a significant increase in the NK cell population (P = 0.05) after the 6th vaccine (2.5 months) compared to pre-treatment levels. Furthermore, expression of IDO was frequently detected in tumour biopsies by immunehistochemistry staining. High performance liquid chromatography analyses of Kynurenine/Tryptophan ratio in sera suggested stabilization of IDO activity in 10/15 (67%) of patients, with long term stability observed in two clinical responding patients.
Conclusion: The vaccine is safe and well-tolerated with no grade 3/4 toxicity occurring. Long-lasting PR+SD were seen in 47% of the patients demonstrating a median OS of 2.1 years.
www.clinicaltrials.gov. ID: NCT0129348
No conflict of interest.

3517 POSTER

Antimetastatic activity of ganetespib: Preclinical studies and assessment of progressions due to new lesions in the GALAXY-1 NSCLC trial

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Background: Heat shock protein 90 (Hsp90) maintains the stability and activity of numerous signaling proteins involved in cancer metastasis. Interim results of the GALAXY-1 trial (NCT01348126) showed an improvement in overall survival in patients with non-small cell lung cancer (NSCLC) treated with an Hsp90 inhibitor, ganetespib (G), plus docetaxel (D) compared to D alone. We evaluated the antimetastatic activity of ganetespib in preclinical models, and compared radiological disease progression due to new lesion formation in the two arms of the GALAXY-1 trial.
Material and Methods: Preclinical effects of ganetespib were investigated on the: (1) migration of cancer cells via Boyden chamber assay, (2) expression of metastatic factors using protein array and gene profiling, (3) architecture of NSCLC xenografts by IHC, and (4) metastasis to the lung in tail vein and orthotopic breast cancer mouse models assessed by bioluminescence. GALAXY-1 is a Synta sponsored randomized, international open-label study of D with or without G in patients with advanced lung adenocarcinoma, one prior systemic therapy, and ECOG PS 0/1. D was given at 75 mg/m^2 on Day 1 of a three-week cycle in both arms. In the combination arm, G was given at 150 mg/m^2 on days 1 and 15. Development of new metastatic lesions was evaluated using serial computed tomography scans. Enrollment completed in November 2012.
Results: Ganetespib blocked the migration of cancer cells and induced the degradation of metastasis drivers including FAK, MET, HIF-1α, and VEGF; significantly reduced tumor angiogenesis and proliferation in NSCLC xenografts; significantly blocked (>8×, p < 0.005) the development of lung cancer metastases in a tail vein model; and significantly reduced multi-organ metastasis in an orthotopic model and blocked extramedullary hematopoiesis induced by the primary tumor. In GALAXY-1 trial patients, the population that exhibited the strongest survival improvement (diagnosis of advanced disease >6 months, N = 175), radiologic progressions due to new lesion formation were 19 (50%) vs. 5 (17%), for D vs. D+G, respectively, at time of abstract submission.
Conclusions: Ganetespib induces the degradation of key drivers of metastasis, resulting in reduced cell migration, tumor angiogenesis and new lesion formation in vivo. Preliminary data from the GALAXY-1 study support reduced frequency of progression due to new metastatic lesion formation in advanced NSCLC patients treated with ganetespib.
Conflict of interest: *Ownership: Synta Pharmaceuticals*

3518 POSTER

Role of circulating endothelial cells in the evaluation of response to chemotherapy in non-small cell lung cancer patients

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Background: The majority of NSCLC cases diagnosed in advanced stages, which make the treatment non-curative with high recurrence rate. So it is very important to define a biological marker to aid us as a predictive factor.
When the tumour volume become at 1−2 mm, it begin the stimulation of endothelial cells by a multiple growth factors to generate a new vessels, so the circulating endothelial cells (CECs) increase in the blood stream theoretically. Many methods used to discover these cells as Immunomagnetic Separation (IMS) technique, four-color channels flow cytometry and PCR. The phenotype of these cells can be defined by the positivity of CD146 and CD31 while the CD45 is negative. Increased number of CECs was found in tumours. Many studies confirmed the normalisation of CECs levels in cancer patients after the treatment. Mancuso et al. confirmed the importance of quantify these cells to evaluate the response of chemotherapy in breast cancer.
Materials and Methods: Newly diagnosed patients with non surgical stages III or IV NSCLC have been included. Blood samples have been taken before starting any treatment then after 3 cycles of chemotherapy to evaluate the number of CECs by using IMS techniques with a Nageotte slide by a fluorescent microscope equipped with camera.
Results: 143 naive patients of have recruited. Before treatment the number of CECs was more than 80 cells/ml in 121 patients [45 pts. (81–150 c/ml), 32 pts. (151–300 c/ml) and 43 pts. More than 300 cells/ml] while, just 22 patients with less than 80 cells/ml. (79) patients were valuable after 3 cycles. The difference between CECs accounts before and after treatment was calculated as relative absolute quotient (ΔaCECs) has been considered significant when it was more than 0.1. Accordance between CECs and response to treatment was found in 61 patients (77%). The account of CECs was significantly decreased in 42 patients who showed Partial Response, while 11 patients with progression disease had significant increased number of CECs and 8 patients with Stable disease with no significant changes in CECs number. On the other hand, 18 patients (23%) didn't show accordance between the treatment response and CECs levels.
Conclusions: CECs seem to be a predictive factor in evaluating response to chemotherapy in NSCLC patients. However, further studies are necessary to evaluate the role of CECs levels in the recurrence prediction.
No conflict of interest.

3519 POSTER

Prognostic impact of central nervous system (CNS) metastases associated with T790M status after acquired resistance to EGFR-TKI

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Background: Patients with *EGFR*-mutant non-small cell lung cancer (NSCLC) can prolong survival with EGFR-TKI. However, approximately

one-third of patients seem to develop CNS metastases such as brain metastases (BM) and leptomeningeal metastases (LM) after initial response to EGFR-TKI. Generally, CNS metastases are associated with poor prognosis in NSCLC, but little is known regarding prognostic impact and T790M status of CNS metastases after acquired resistance to EGFR-TKI.
Patients and Methods: We retrospectively investigated the prognostic impact of CNS metastases in 80 *EGFR*-mutant NSCLC patients whose T790M status had been confirmed. CNS collapse was defined as patient death due to uncontrolled and progressive CNS metastases. Postprogression survival (PPS) after initial EGFR-TKI failure and T790M status were compared in patients with or without CNS collapse. Additionally, PPS and T790M status in BM and LM populations were analysed.
Results: Median PPS in 50 patients without CNS collapse (23.4 months) was significantly longer than in 30 with CNS collapse (16.7 months) ($p = 0.0017$). T790M was detected in 23 (46%) of 50 patients without CNS collapse, and in 4 (13%) of 30 with CNS collapse ($p = 0.0032$). Median PPS in 47 patients without LM (25.6 months) was significantly longer than in 33 with LM (11.4 months) ($p = 0.0007$). Median PPS was 11.2 months in 47 patients without BM, and 24.4 months in 33 with BM ($p = 0.1007$). T790M status was examined in brain tumoral tissues of 5 patients with BM and cerebrospinal fluid samples of 20 with LM. T790M was detected in 4 (80%) of 5 BM, and in 1 (5%) of 20 LM ($p = 0.0019$). In 11 patients, rebiopsies were performed both on the CNS and outside the CNS. Six patients had T790M outside the CNS, without T790M in the CNS, and 5 patients exhibited no T790M, either in or outside the CNS.
Conclusions: CNS collapse was associated with poor prognosis and T790M-negative status. BM and LM appear to have distinct tumour biologies and clinical courses. More effective therapeutic strategies, including high-dose EGFR-TKI for CNS metastases may contribute to better prognosis after acquired resistance to EGFR-TKI.
No conflict of interest.

3520 POSTER

Impact of polymorphic variants on vascular endothelial growth factor gene and non-small-cell lung cancer prognosis: A prospective study in a South-European Population

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Background: Vascular endothelial growth factor (VEGF) gene regulation showed in previous studies that may contribute to lung cancer carcinogenesis. Therefore, this study was performed in order to assess the role of some VEGF variants in non-small-cell lung cancer (NSCLC) prognosis.
Patients and Methods: Prospective study from February 2010 to April 2011. Median follow up was 12 months. NSCLC patient's genotyping was performed using the Sequenom® MassARRAY platform. Kaplan–Meier curve was used to assess overall survival (OS) and progression-free-survival (PFS). Statistical significance was considered for $p < 0.05$.
Results: 144 NSCLC patients were consecutively genotyped in order to assess 11 single nucleotides polymorphisms (SNP). Male were 78.5%. Median age was 61.5 (32−89) years old. Non-squamous cell histology was 77.1% and 91.4% were stages IIIB and IV. The following SNPs showed influence in OS: rs2010963 (*VEGF* + 405 G/C), $p = 0.042$, rs3025010 (*VEGF* intron 5 C/T), $p = 0.047$; and none SNPs showed influence in PFS.
Conclusions: This is the first large study in Portugal involving NSCLC patients and assessment of 11 SNPs on chromosome 6p12. Our study suggests that variants on chromosome 6p12 are potential prognostic biomarker in advanced NSCLC. In future, genome-identified patients may improve NSCLC screening strategies and also therapeutic management.
No conflict of interest.

3521 POSTER

Metformin inhibits IL-6-induced epithelial–mesenchymal transition (EMT) and metastasis in non-small cell lung carcinoma

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Background: Metastasis is the major causes of death for non-small cell lung carcinoma (NSCLC). Epithelial–mesenchymal transition (EMT) plays an important role in tumour invasion and metastasis. However, the underlying mechanisms of EMT in NSCLC and how to inhibit this process remain to be explored.
Materials and Methods: Invasion assay, western blotting and immunofluorescence were used to determine EMT after treatment with different dose of recombinant human IL-6 (rh-IL-6) alone, or combined with metformin. IL-6, E-cadherin and vimentin mRNA expression in the tissues of NSCLC were determined by real-time PCR, and their correlations were assayed. We inoculated lung cancer cell line ectopically expressing IL-6 in nude mice to assess the effects of metformin on EMT and metastasis of NSCLC. IL-6/Stat3 signalling pathway in NSCLC cell lines treated with (rh-IL-6) alone, or combined with metformin, or in ectopically IL-6 expressing cell line were evaluated by Western blotting.
Results: We found that IL-6 could promote NSCLC cells invasion via EMT in a dose-dependent manner in vitro, which was further proved by the positively correlation between IL-6 and vimentin mRNA expression, and negatively correlation between IL-6 and E-cadherin mRNA expression in NSCLC tissues. IL-6-induced EMT in NSCLC cells could be inhibited by metformin in a dose-dependent manner in vitro, and metformin could significantly reduce the metastasis in tumour-bearing nude mice. Furthermore, we found that the blockade of STAT-3 phosphorylation might be the underlying mechanisms of metformin on IL-6-induced EMT and metastasis in NSCLC.
Conclusions: We show that enhanced IL-6 expression is a mechanism of EMT and metastasis in NSCLC. Pharmacologically, we found that metformin could inhibit IL-6 induced EMT process by blocking STAT-3 phosphorylation, suggesting the potential clinical use for metformin to reduce metastasis and reverse chemotherapy resistance.
No conflict of interest.

3522 POSTER

The prognostic role of XRCC1, ERCC1, ERCC2 and, TP53 single nucleotide polymorphisms (SNPs) in metastatic non-small cell lung cancer (NSCLC)

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Background: Identification of biomarkers that can be used for the prognostic evaluation of metastatic NSCLC patients is important. The aim of this study was to evaluate the potential prognostic value of XRCC1, ERCC1, ERCC2 and, TP53 SNPs in metastatic NSCLC patients.
Patients and Methods: In total 145 patients, who had been treated for metastatic NSCLC with platinum based chemotherapy regimens between 2000 and 2012, were included in this study. Analysis of SNPs from peripheral blood cells was performed by polymerase chain reaction. XRCC1 Arg399Gln, ERCC1 Asn118Asn, ERCC2 Lys751Gln and, TP53 Arg72Pro polymorphisms were evaluated in conjunction with clinical and pathological parameters and survival. Kaplan–Meier method and Cox regression analysis were used.
Results: The median age of patients was 60 years (range 34−79). The median progression free survival (PFS) and overall survival (OAS) was 5.1 months (95% CI, 4.3−5.8 months) and 30.9 months (95% CI, 28.2–33.6 months), respectively. In the univariate analysis for OAS performance score (HR, 5.25; 95% CI, 1.45–19.04; $p = 0.01$), ERCC1 genotype (HR, 0.26; 95% CI, 0.12–0.57; $p < 0.01$), and XRCC1 genotype (HR, 0.37; 95% CI, 0.16–0.83; $p = 0.01$) were significant parameters. In the multivariate analysis performance score (HR, 4.80; 95% CI, 1.22–18.87; $p = 0.02$), ERCC1 genotype (HR, 0.36; 95% CI, 0.14–0.92; $p = 0.03$), and XRCC1 genotype (HR, 0.37; 95% CI, 0.14–0.98; $p = 0.04$) retained their significance. The median OAS was 45.2 months (95% CI, 25.3–65.0 months) for the ERCC1 normal (CC) and heterozygote (CT) genotypes,

and 25.5 months (95% CI, 9.5–41.5 months) for the ERCC1 mutant (TT) genotype (P<0.01).
Conclusions: In addition to performance score, ERCC1 and XRCC1 genotypes independently predicted OAS in metastatic NSCLC patients. Future prospective studies are needed for the further evaluation of potential prognostic SNPs in metastatic NSCLC.
No conflict of interest.

3523 POSTER

Impact of EGFR status and treatment selection on survival of patients with stage IV non-small cell lung cancer (NSCLC) and liver metastases (LM)

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Background: LM appear in 20−30% of patients (pts) diagnosed with NSCLC. LM are considered a poor prognosis feature of NSCLC and they may also involve a more treatment-resistant condition. However, whether the clinical outcome of NSCLC pts with LM harboring molecular alterations in EGFR, KRAS and EML4-ALK genes is substantially different depending on their distinct status is still unknown.
Methods: A total of 268 consecutive stage IV NSCLC pts were included in the analysis. The tumor molecular analysis for EGFR, KRAS and EML4-ALK was available in 205 pts (76.5%), 136 pts (50.7%) and 31 pts (11.6%), respectively. An EGFR mutation was observed in 32 pts (15.6%), KRAS was mutated in 28 pts (20.6%) and an ALK gene rearrangement was observed in three pts (9.6%). We aimed to evaluate the incidence of LM in the last consecutive NSCLC pts treated in our institution and the differences in clinical outcome regarding the status of EGFR, KRAS and EML4-ALK.
Results: Most of the pts were men (71.3%). The most common histologies were adenocarcinoma (59.3%) and squamous-cell carcinoma (23.1%). Overall, 34% of the pts showed LM at any time of the disease course. Among the whole cohort, median overall survival (OS) for LM pts was 16 months vs 42 months for pts with metastases other than LM ($p < 0.001$). Among pts with LM and EGFR mutations, the one-year survival rate was 85.7% vs 54.3% for pts with LM and EGFR wild-type ($p = 0.03$). In the subgroup of pts carrying EGFR mutations and receiving tyrosine-kinase inhibitors (TKIs), the 18-month survival rate was 75% for pts showing liver involvement compared to 80% ($p = 0.44$) for those with no LM. In contrast, in the subgroup of pts with wild-type EGFR receiving standard chemotherapy, the 18-month survival rate was 32.4% for pts showing LM compared to 74.9% for those with no liver involvement ($p < 0.001$).
Conclusions: The presence of LM at any time of the disease curse negatively impacts on the clinical outcome of pts with NSCLC. However, the presence of EGFR activating mutations significantly improves the OS of pts with liver spread of NSCLC, reaching an OS similar to those pts with no LM. Pts with EGFR mutations and LM may light down the detrimental effect of LM on prognosis, when treated with EGFR TKIs.
No conflict of interest.

3524 POSTER

Biological mechanism of acquired resistance to the EGFR irreversible inhibitor BIBW-2992 in EGFR-mutant non small cell lung cancer cell line

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Background: Non-small cell lung cancer (NSCLC) accounts for over 85% of all lung cancers and about 20% of caucasian patients harbor somatic activating mutations in the tyrosine kinase (TK) domain of the epidermal growth factor receptor (*EGFR*) gene. Most of these patients initially respond to the EGFR-TK inhibitors but eventually relapse within one year for the development of acquired resistance due to a second-site mutation (T790M) in the *EGFR gene*. BIBW-2992, an irreversible *EGFR* inhibitor, has demonstrated activity in unselected patients with advanced NSCLC who have failed previous EGFR-TK inhibitor and in EGFR mutated patients. In this study, the H-1975 NSCLC cell line, harboring the T790M mutation, was used as *in vitro* model to generate BIBW-2992 resistant clones in order to investigate the molecular mechanisms of acquired resistance.
Material and Methods: A dose-escalation study was performed to establish an BIBW-2992 resistant (R) cell line. All exons of EGFR and KRAS as well as 10 known hot spots in some genes (5 involved in the EGFR signaling cascade and 5 frequently altered in NSCLC) were sequenced using Cancer panel® by Ion PGM™ Sequencer, while the EGF pathway was studied by qPCR using TaqMan® Array EGF Pathway (Life Technologies). Concomitantly, protein expression of some genes related to the EGF pathway such as EGFR, AKT and ERK (un-phosphorylated and phosphorylated) as well as MRAS and PI3KR1 were more deeply investigated by Western Blot.
Results: Although sequence analysis of R cell line did not reveal any novel mutations, gene expression profiles disclosed an increase of some members of the RAS family (MRAS, KRAS) and PIK3R1, up-regulation of SHC and down-regulation of EGF. R cells showed a higher signal of MRAS and an increase of ERK1/2 phosphorylation compared to the parental cells. This behavior also persisted in absence of EGF stimulation and in cultures maintained in afatinib-free medium for over 6 months.
Conclusions: The absence of novel mutations suggests the implication of other mechanisms implicated in BIBW-2992 resistance. In particular the marked increase of SHC3, an adaptor immediately downstream of EGFR, leads to hypothesize its involvement in the EGFR activation. Furthermore, the EGF down-modulation together with the MRAS increased expression and ERK1/2 phosphorylation, suggest that this cell line may acquire a different way to activate the EGFR pathway.
No conflict of interest.

Proffered Papers Session (Sat, 28 Sep)
Haematological Malignancies

3600 ORAL

Racial differences in risk of hematologic malignancies

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Background: There are only sparse data from multiracial population studies detailing race/ethnicity disparities in risk of hematologic malignancies (HM).
Methods: We performed a cohort study in a multiracial population of 126,293 adults that supplied baseline information at health examinations in 1978−85. The largest race/ethnic groups by self-classification were 55% White, 27% Black, and 11% Asian. We used Cox proportional hazards models with seven covariates to study risk of HM, which occurred in 1,244 persons (801 White, 310 Black, and 78 Asian). We studied all HM and major HM sub-types yielding hazard ratios (HR) 95% confidence intervals (CI), and p values.
Results: (See Table). Compared to Whites as referent HRs were similar in Blacks but significantly lower in Asians. The similar risk of Black and White persons for all HM was consistent for men, women and several other strata. However, Blacks were at lower risk for non-Hodgkin's lymphoma (HR = 0.6 [0.5−0.7], $p < 0.0001$) and at higher risk for multiple myeloma (HR = 2.1 [1.6−2.9], $p < 0.0001$); these Black/White disparities were similar for men and for women. The lower Asian vs White risk for all HM was similar for men, women, and strata of age, interval to diagnosis, smoking, and birthplace. The lower risk of Asians was also similar in Asian ethnic subgroups. The HR for Asians was <1.0 for each HM subtype, with p values <0.05 for non-Hodgkin's lymphoma, lymphocytic leukemia, and myelocytic leukemia. Among covariate relationships to risk of any HM, male sex, increased age, and higher body mass index were associated with increased risk, alcohol drinking was associated with decreased risk, and birthplace (US vs non-US) was unassociated with risk.
Conclusions: Compared to whites: (1) Blacks are at lower risk of non-Hodgkin's lymphoma and higher risk of multiple myeloma, and (2) Asians are at lower risk of all HM and of several HM subtypes.
No conflict of interest.

Comparison*	HR (95% CI)	p-value
Black/White	0.9 (0.8−1.1)	0.2
Asian/White	0.6 (0.5−0.8)	0.0002
Chinese/White	0.6 (0.4−0.9)	0.006
Filipino/White	0.5 (0.3−0.8)	0.005
Japanese/White	0.7 (0.4−1.2)	0.2
Male/Female	1.7 (1.6−1.9)	<0.0001
Age X 10 years	1.7 (1.6−1.8)	<0.0001
BMI $\geqslant$30 vs <25 kg/m^2	1.2 (1.0−1.5)	0.04
$\geqslant$3 drinks/d vs never	0.7 (0.6−0.9)	0.007
$\geqslant$1 ppd vs never	1.2 (1.0−1.5)	0.07

*Models include age, sex, race, BMI, alcohol, smoking, education.

3601 ORAL

Study of the correlation of baseline biomarkers and DNA demethylation to clinical responses in a phase 1/2, randomized study of SGI-110, a novel subcutaneous (SC) hypomethylating agent (HMA), in the treatment of relapsed/refractory (r/r) acute myeloid leukemia (AML)

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Background: SGI-110 is a novel SC HMA synthesized as a dinucleotide of decitabine (DAC) and deoxyguanosine that has longer plasma half-life and more extended DAC exposure than DAC IV infusion. The differentiated pharmacokinetic profile offers the potential of improved biological and clinical activity and safety over currently available HMAs. Little is known about the correlation between different epigenetic and other biological biomarkers with clinical response to HMA treatment.
Materials and Methods: We completed the Phase 1 dose-escalation stage of a Phase 1−2 study of SGI-110 in r/r AML (Study SGI-110−01). The association between clinical responses and several biomarkers were studied including: global DNA methylation as a surrogate marker using LINE1 assay; baseline miRNA29b involved in methylation control; functional activity of cytidine deaminase (CDA) responsible for deactivation of DAC; and levels of deoxycytidine kinase (dCK) responsible for activation of DAC.
Results: Sixty-three r/r AML patients (pts), median age 67 (29−86), ECOG PS 0/1/2 in 13/41/9 pts, median prior regimens 4 (1−9) were treated with SGI-110 doses from 3–125 mg/m^2 randomized to either QDx5 schedule (35 pts) or QWx3 (28 pts). Thirty-five (56%) had prior HMA and 26 (41%) had secondary AML. A maximum average LINE1 demethylation from baseline of −25.9% was achieved at the 60 mg/m^2 QDx5 dose level. Five complete responses (2 CR, 2CRi, 1 CRp) were achieved at doses $\geqslant$36 mg/m^2 with mean/median duration of response of 217+/114 days (range 42–534+). Two responders had received prior HMA treatment. Clinical responses correlated with post treatment LINE1 demethylation (no responses in 31 pts with demethylation <10%; 5 responses in 19 pts with $\geqslant$10% demethylation; $p < 0.01$). There was no association between baseline miRNA29b and response. CDA functional activity correlated with dose-adjusted DAC plasma exposures (correlation coefficient $p = 0.011$). The most common drug-related adverse events were local injection site reactions (21%) mostly Gr1, and myelosuppression.
Conclusions: In r/r AML pts, SGI-110 was well-tolerated and complete responses were observed in 5/19 pts (26%; 95% CI 19−51%) who achieved adequate DNA demethylation of $\geqslant$10% regardless of prior HMA treatment. CDA activity correlated with DAC exposure ($p = 0.011$). Baseline miRNA29b did not seem to influence clinical responses. The study is supported by Astex Pharmaceuticals, Inc. and Stand Up to Cancer (ID: NCT01261312).
Conflict of interest: *Corporate-sponsored research: Astex Pharmaceuticals Inc.*

3602 ORAL

Snail expression confers drug resistance to Abl kinase inhibitors and collateral sensitivity to gemcitabine in Ph-positive leukemia cells

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Background: Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of the hematopoietic stem cells depends on the Bcr-Abl fusion protein, which displays a constitutive tyrosine kinase activity. Imatinib, a selective inhibitor of Abl kinase was approved for the treatment of chronic phase CML (CP). Imatinib clinical efficacy continuously decreases with the advancement of the disease. Blast crisis (BC) CML or Ph+ ALL patients benefit from the treatment with tyrosine kinase inhibitors only temporarily or not at all. Acquired resistance in the CP is mostly due to the acquisition of point mutations within the Abl kinase domain of Bcr-Abl. In addition, drug resistance also encounter during BC which mainly mediated by Bcr-Abl independent alterations. Second generation inhibitors of Abl kinase activity such as Nilotinib and Dasatinib and recently Ponatinib reported to overcome Bcr-Abl acquired resistance. However, all Abl kinase inhibitors failed to overcome drug resistance during BC.
Methods: In an attempt to develop a model system that resemble CML blast crisis, we introduced EMT modulators, Snail and Twist1, into Ph+ leukemia cells. The characteristics, proliferation, clonigenicity, surface markers and sensitivity to relevant chemotherapeutics drugs were evaluated for Snail and Twist1 overexpressed cells in comparison to parental cells.
Results: Overexpression of Snail, but not Twist1, confers drug resistance to Abl kinase inhibitors (AKIs) up to 600 fold in reduced sensitivity of K562/Snail to Dasatinib when compared to parental cells. Moreover, AKIs fail to inhibit Bcr-Abl auto-phosphorylation as well as other down-stream regulators such as STAT5a. Interestingly, over-expression of Snail in Ph+ leukemia cells confers sensitivity to the nucleoside analog, gemcitabine.
Conclusions: Our data showed that overexpression of snail confer characteristics that resemble blast crisis including drug resistance to AKIs. Experiments are underway to elucidate the mechanisms of AKIs drug resistance and collateral sensitivity to gemcitabine.
No conflict of interest.

3603 ORAL

Whole exome massive parallel sequencing of splenic marginal zone lymphoma reveals novel somatic mutations in NOTCH2 and SMYD1 genes

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Background: Splenic marginal zone lymphoma (SMZL) is an indolent B-cell non-Hodgkin lymphoma and represents the most common primary malignancy of the spleen. Its precise molecular pathogenesis is still unknown and consecutively specific molecular markers for diagnosis or as possible departure point for causal therapies are lacking.
Material and Methods: We performed massive parallel whole exome sequencing using Agilent SureSelect Target Enrichment and SOLid4 platform (Life Technologies) on primary tissue samples of two cases of SMZL. Fresh frozen tumor tissue was extracted by microdissection and CD3 MACS-sorted tissue of the same patient was used as non-tumorous control. After alignment and global filtering using a sequence quality threshold, the generated sequence data was screened for non-synonymous base exchanges only present in the tumor sample. Identified single nucleotide polymorphisms (SNPs) were consecutively validated by Pyrosequencing and Sanger sequencing in an independent cohort. As all detected base exchanges were heterozygos, SNP-Chip microarray analysis (Affymetrix) was performed to identify corresponding major deletions and loss of heterozygosity.
Results: The whole human exome (50Mb/sample), including miRNAs and ncRNAs, was sequenced for two SMZL samples and their respective non-tumorous tissue. Overall, 223 high fidelity SNPs (non-synonymous, high qualitiy score, 20x minimum coverage) were identified. Out of these, 53 base changes have not been described as polymorphisms before. Four high quality SNPs (SNP-call >40 % in tumor tissue and <10% in corresponding non-tumor tissue) in 4 different genes (NOTCH2, SMYD1, MYD88 and SCRN2) were successfully validated. While SCRN2 has been previously described as polymorphism, it has a global minor allele frequency below 1%. MYD88 L265P has been observed in SMZL before, while NOTCH2 Q2364X and SMYD1 C279F are newly identified mutations. We used an independent cohort of 20 SMZL samples to analyze whether the identified mutations were recurrent. While MYD88 L265P missense mutation was found present in three additional samples (12.5%), the other SNPs showed no recurrence in the validation cohort.
Conclusions: Whole exome sequencing of two cases of SMZL revealed three somatic mutations. The mutations in NOTCH2 and SMYD1 were not described before, whereas the recurrent MYD88 mutation has already been described in SMZL (frequency 10−13%). The discovered NOTCH2 nonsense-mutation is located in the PEST domain, where mutations in SMZL have been described previously (20−25% of SMZL). NOTCH2 and MYD88 mutation seem to be the most common mutation detectable in SMZL, but their rather low frequency may likely not enable reliable diagnostic application.
No conflict of interest.

3604 ORAL

Involved-field three-dimensional conformal radiotherapy vs helical tomotherapy for female patients with early-stage mediastinal Hodgkin lymphoma: A dosimetric comparative study

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Background: Chemotherapy plus involved-field (IF) three-dimensional conformal radiotherapy (3D-CRT) is the standard treatment for early stage Hodgkin's lymphoma (HL). Reductions in organ at risk (OAR) doses have been shown with intensity modulation radiotherapy. Nevertheless the role of IF helical tomotherapy (HT) in female patients treated for mediastinal HL remains unclear and the present dosimetric study was performed to compare IF HT to IF 3D-CRT.
Material and Methods: Ten young female patients affected with mediastinal stage II HL and treated with IF 3D-CRT after chemotherapy were selected from our database. For each patient, 3D-CRT and HT plans were designed to deliver 30 Gy to the target volume with a complement of 6 Gy in areas suspect of not sterilization on CT-scan simulation. HT planning solutions were optimized by inverse planning with specific dose-volume constraints on target volume and OAR. Dose-volume histograms for target volume and OAR were calculated and then compared between 3D-CRT and HT by a statistical analysis (Wilcoxon's Test).
Results: Conformity index and homogeneity index were not statistically different between HT and 3D-CRT. Mean doses to the breasts were increased with HT compared to 3D-CRT (right breast: 2.83 vs 1.45, $p = 0.006$; left breast: 3.47 vs 1.55, $p = 0.005$) whereas no difference in mean doses appeared for heart, coronary arteries, lungs, thyroid and normal tissues. Maximal doses were reduced with HT for breasts (right breast: 20.83 vs. 30.85, $p = 0.004$; left breast: 25.18 vs 31.53, $p = 0.002$) and spinal cord (20.72 vs 33, $p = 0.002$). Volume exposed to doses $\geqslant$20 Gy was significantly smaller with HT whereas volume exposed to doses $\leqslant$4 Gy was smaller with 3D-CRT for right breast, left breast, lungs, heart and normal tissues. No statistically significant decrease of mean and maximum doses was recorded for origins of coronary arteries with HT when compared to 3D-CRT. Pronounced benefits of HT in terms of heart sparing were observed for patients with lymph nodes anterior to the heart.
Conclusions: Compared to 3D-CRT, HT allowed greater sparing of breasts, heart and lungs from high doses. Nevertheless, increasing low doses especially in the breasts with HT must be taken into account concerning the risk of second malignancies for young women with HL. HT may be considered when the anterior mediastinum is invaded in order to protect large volume of heart from high doses and then decrease the risk of late complications.
No conflict of interest.

3605 ORAL

Survival analysis of follicular lymphoma in a national registry with over a thousand patients: Impact by treatment groups

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Introduction: Chemotherapy regimens containing anthracyclines and rituximab in the treatment of lymphomas CD-20 positive have significantly increased the survival of these patients. The therapeutic approach 'watch and wait' should be a strategy to take greater account in asymptomatic patients with low tumor burden, especially in elderly patients and/or comorbidities.
Material and Methods: 1178 patients diagnosed with follicular lymphoma, between 1986 and 2012, and treated at the Oncology Department of 17 Spanish hospitals were reviewed. A survival analysis were made with the generalized Wilcoxon test.
Results: A total of 1178 patients were analyzed, of whom 51% were women. The mean age at diagnosis was 57.8 years. 23% of the patients received chemotherapy without rituximab (14% based on anthracycline and 9% non-anthracycline) and 69% of the patients received chemotherapy associated with rituximab (59% with anthracycline-based chemotherapy and 10% without anthracyclines). 4.1% of patients received rituximab in monotherapy. The median overall survival was 246 months (95% CI 228 months − 264 months). There are statistically significant differences between the different chemotherapy regimens used, with a longer overall survival in patients receiving anthracyclines (252.15 months vs. 172.38 months, $p < 0.001$, HR 0.54). There is also a longer overall survival in patients treated with rituximab ($p = 0.008$). The 25.8% of patients who received radiation therapy had a significantly longer overall survival ($p < 0.001$, HR 0.51). In only 2.2% of the patients observation at diagnosis was the first approach.
Conclusion: The median overall survival of patients diagnosed of follicular lymphoma is over 20 years in our series. This increase in survival is due to the use of anthracyclines, rituximab and radiotherapy.
No conflict of interest.

Poster Session (Sun, 29 Sep)
Haematological Malignancies

3606 POSTER

Prior autoimmune disease and risk of monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma: A systematic review and meta-analysis of the literature

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Background: Chronic antigenic stimulation has been postulated as a potential trigger to the onset of plasma cell disorders monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM). Several observational studies have investigated the role of antecedent autoimmune disease and risk of MGUS and MM, however findings have been largely inconsistent and hindered by the rarity and heterogeneity of the autoimmune disorders investigated. A systematic review of the literature was therefore undertaken to evaluate the strength of the evidence linking prior autoimmune disease and subsequent risk of MGUS and MM.
Materials and Methods: A broad search strategy using key terms for MGUS, MM and 50 autoimmune diseases was used to search four electronic databases (PubMed, Medline, Embase and Web of Science) from inception through November 2011. To account for the expected heterogeneity between and within the included observational studies, a random effects model was used to generate pooled risk estimates and associated 95% confidence intervals.
Results: A total of 53 studies met the inclusion criteria, of which 36 were suitably comparable to perform a meta-analysis. 'Any autoimmune disorder' was significantly associated with an increased risk of both MGUS [n = 764 patients; pooled relative risk (RR) 1.43, 95% confidence interval (CI) 1.15–1.79] and MM (n = 2,811 patients; RR 1.11, 95% CI 1.04–1.18). This risk was disease dependent with only pernicious anaemia showing an increased risk of both MGUS (RR 1.67, 95% CI 1.21–2.31) and MM (RR 1.39, 95% CI 1.10–1.75). Other autoimmune conditions including autoimmune haemolytic anaemia, ulcerative colitis, polymyositis/dermatomyositis and ankylosing spondylitis were associated with an increased risk of MGUS or MM but not both.
Conclusions: Our findings, which are based on the largest number of autoimmune disorders and MGUS/MM patients reported to date, suggest that autoimmune diseases and/or their treatment may be important in the aetiology of MGUS/MM. The strong associations observed for pernicious anaemia with both MGUS and MM suggests that anaemia, or more precisely its underlying mechanism may be related to the onset of MGUS/MM and that clinically anaemia may be an important biomarker of disease onset.
No conflict of interest.

3607 POSTER

The association of the VEGFR2 604T/C polymorphism with aggressiveness of multiple myeloma

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Background: Increased angiogenesis (AG) has been demonstrated in the bone marrow microenvironment in multiple myeloma (MM), suggesting its potential pathophysiologic role in the disease. The most important mediators of AG during tumor development are the vascular endothelial

growth factor (VEGF) and the vascular endothelial growth factor receptor 2 (VEGFR2). Both factors are encoded by polymorphic genes and, therefore, their levels or functions are variable in healthy humans. It is known that allele C of the *VEGF* 2578C/A (rs699947) and allele G of the 1154G/A (rs1570360) are related to higher concentration of serum VEGF compared to the remaining alleles. It is also established that the G allele of the *VEGFR2* 1192G/A (rs2305948) has higher binding efficiency and the allele C of the *VEGFR2* 604T/C (rs2071559) has lower transcription activity. Since the roles of these genetic polymorphisms in the risk and clinical manifestation of MM are still unknown, these were the aims of the present study.
Material and Methods: Genomic DNA from peripheral blood of 157 consecutive MM patients and 157 age and race-matched controls was analyzed by real-time polymerase chain reaction for genotyping of the above mentioned polymorphisms. The differences between groups were analyzed by the logistic regression model. Power analysis (PA) was used to verify the effect of sample size on the results obtained in the study.
Results: Similar frequencies of the *VEGF* 2578C/A, *VEGF* 1154G/A, *VEGFR2* 1192G/A, and *VEGFR2* 604T/C, isolated or combined, were seen in MM patients and controls. Individuals with the distinct genotypes of the genes were under similar risks for the disease. In contrast, excesses of the *VEGF* 2578CC+CA (86.1% *versus* 71.8%, $P = 0.02$; PA: 59.3%), *VEGF* 2578CC plus *VEGF* 1154GG (46.0% *versus* 28.6, $P = 0.03$; PA:52.4%), *VEGF* 2578CC plus *VEGFR2* 1192GG (67.7% *versus* 43.3, $P = 0.04$; PA: 52.2%), and *VEGF* 2578CC+CA plus *VEGFR2* 604TT+TC (94.2% *versus* 81.1%, $P = 0.04$; PA: 53.1%) genotypes were seen in male patients compared to female patients. Additionally, the frequency of the *VEGFR2* 604TT genotype was higher in patients with tumors of II and III Durie & Salmon stages than in those with tumors of stage I (29.1% *versus* 10.0%, $P = 0.04$; PA: 60.7%).
Conclusions: The data present, for the first time, preliminary evidence that inherited abnormalities of *VEGF* and *VEGFR2* pathways alter the distribution of MM in distinct genders and the aggressiveness of the disease.
No conflict of interest.

3608 POSTER

Multiple myeloma − toxicity studies of innovative substances

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Objective: The prognosis of patients with multiple myeloma (MM) has substantially improved during the last years- due to implementation of novel drugs into the treatment. However, MM is still incurable and novel treatment strategies are needed. Here, we tested novel substances for their anti-myeloma activities.
Methods: 0.1–100[nM] of 11 innovative compounds with unknown activity against MM and bortezomib as a reference substance were applied to the MM cell lines OPM-2, NCI, and U-266 in vitro. Apoptosis was determined by FACS using annexin V FITC/ 7AAD-staining and expressed as IC50. Different adherent cells (foreskin fibroblasts, prostatic adenocarcinoma cells − PC3, colorectal adenocarcinoma cells − HRT, human umbilical vein endothelial cells − HUVEC and breast adenocarcinoma cells − MDA) served as controls.
Results: Viability of untreated cells was >90%. 6/11 compounds with anti-myeloma effects were identified (% apoptosis, IC50).

Table: Concentrations [nM] killing 50% of cells within 24 h of incubation

Compound Nº	1	2	6	7	8	11	Bortezomib
OPM-2	6.8	35.8	2.4	6.2	3.5	40.4	11.8
NCI	5.5	68.1	5.9	1.6	5.0	14.7	5.5
U-266	5.8	31.6	5.9	0.6	4.3	4.4	5.3
Fibroblasts/PC3	>100	>100	>100	>100	>100	>100	>100
HRT	4.0	>100	7.9	4.1	9.6	>100	>100
HUVEC	3.4	26.6	2.4	0.9	3.9	3.9	3.4
MDA	3.3	7.4	4.1	1.6	6.5	9.6	7.4

IC50 was <10[nM] on 4/6 effective substances, suggesting activity similar to bortezomib. Compounds 1, 2, 6, 8 showed relatively uniform activity in all three cell lines, compound 7 and 11 were most active in U-266 cells. Fibroblasts and PC3 are resistant to all compounds, whereas- HUVECs and MDA were similar sensitive to MM cell lines. Moreover, compounds 1, 2, 6, 7, 8 and 11 showed also activity against purified myeloma cells from 3 patients.
Conclusions: We identified new compounds with potential anti-myeloma effects and putative antiangiogenic activities in vitro. Currently, a model is being established to study the antiangiogenic and anti-myeloma effect of these new compounds in vivo.
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No conflict of interest.

3609 POSTER

Expression and activity analysis of mammalian target of rapamycin (mTOR) complexes in human lymphoma cells

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Background: The PI3K/Akt/mTOR pathway plays key roles in the translation of proteins regulating cell survival, proliferation and metabolism; it can be an ideal target of cancer therapy. The mammalian target of rapamycin (mTOR) is a serine-threonine kinase; its activity and sensitivity to mTOR inhibitors (mTORI) are variable in different tumors. This aspect is poorly characterized in lymphomas. mTOR can be localized in two different complexes referred to as mTORC1 and mTORC2. Results of clinical trials with rapalogs (C1 inhibitors) suggest the importance of using new generation dual inhibitors. We examined the effects of different mTORIs and the activity of C1 and C2 complexes in several lymphoma cell lines.
Material and Methods: We investigated the activity and expression of mTOR complexes in Hodgkin (KMH2, L1236 and DEV), Burkitt (HT58, BL41) and diffuse large B-cell (BHD1) lymphoma cell lines and in human lymphoma biopsies by immunocytochemistry, immunohistochemistry (IHC) and Western-blotting (mTOR, p-mTOR, Rictor, Raptor p-p70S6K, p-S6, p-4EBP1). The amount and the activity of C1 and C2 complexes in cell lines were characterized by the Duolink® technique. Cells were treated with rapamycin, NVP-BEZ235 and PP-242 inhibitors in vitro. The biological effects (proliferation, apoptosis) were investigated by AlamarBlue® assay and flow cytometry analysis.
Results: Increased mTOR activity was observed in all lymphoma cell lines and differences were found in the amount and activity of the two complexes (C1 and C2). mTORI treatment inhibited proliferation in all cells; however, in vitro apoptosis induction was detected only in Hodgkin cell lines after long-term treatment. Dual inhibitors were more effective than rapalogs in cells with mTORC2 overexpression. Our IHC study on different human lymphomas supports that mTORC2 related high mTOR activity is a sign of potentially worse prognosis.
Conclusions: Increased mTOR activity in different lymphomas draws attention to the potential therapeutic use of mTOR inhibitors in the future. According to our results, analysis of the expression and activity of proteins related to different mTOR complexes should have great importance before clinical trials with mTORIs are initiated in lymphomas.
Supported by OTKA81624 and OTKA84262.
No conflict of interest.

3610 POSTER

Exposure to common community acquired infections associated with increased risk of multiple myeloma

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Background: The role of infectious pathogens in the development of cancer has been well documented for several sites, including a number of haematological malignancies. However, the impact of such exposures on the subsequent development of multiple myeloma (MM) is less clear.
Materials and Methods: The United States of America, Surveillance Epidemiology and End Results -Medicare dataset was utilised to investigate the impact of fourteen antecedent common community acquired infections and subsequent risk of MM. Logistic regression was used to derive odds ratios (ORs) and associated 95% confidence intervals (CI) adjusted for sex, age and calendar year of selection. The 13 month period prior to diagnosis/ selection was excluded. Crude adjustment for multiple comparisons was undertaken using Bonferonni correction.
Results: In total, 15, 318 MM cases and 200,000 population based controls were identified. An increased risk of MM (ranging from 5−39%) was observed for eight of the fourteen investigated infections. Following

Bonferonni correction, strong associations were observed for a number of respiratory tract infections including bronchitis (adjusted OR 1.14, 95% CI 1.09–1.18), influenza (OR 1.18, 95% CI 1.11–1.25), sinusitis (OR 1.15, 95% CI 1.10–1.20) pneumonia (OR 1.27, 95% CI 1.21–1.33), skin infection herpes zoster (OR 1.39, 95% CI 1.29–1.49) and urinary tract infection cystitis (OR 1.09, 95% CI 1.05–1.14). With the exception of influenza, each of the aforementioned infections remained positively associated with MM following the exclusion of more than 6 years of claims data prior to diagnosis/selection.
Conclusions: The findings may support a role for infections in the malignant transformation to MM. Alternatively, the observed associations may be a manifestation of an underlying immune disturbance which is present several years prior to MM diagnosis, and thereby part of the natural history of disease progression from late stage monoclonal gammopathy of undetermined significance (MGUS) to MM.
No conflict of interest.

3611 POSTER

Common community acquired infections and risk of lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia: A population based study

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Background: The aetiology of lymphoplasmacytic lymphoma/Waldenström's Macroglobulinemia (LPL/WM) remains largely to be elucidated. Emerging evidence supports the role for repeated antigenic stimulation in the development of LPL/WM. Owing to the rarity of LPL/WM, few population-based studies have been conducted investigating exposure to infections and subsequent risk of malignant transformation to LPL/WM.
Materials and Methods: Using the population-based United States of America, Surveillance, Epidemiology and End Results-Medicare database we investigated exposure to fourteen antecedent common community acquired infections and subsequent risk of LPL/WM in 693 LPL/WM cases and 200,000 controls. Logistic regression was used to derive odds ratios (ORs) and associated 95% confidence intervals. All analyses were adjusted for age, gender and calendar year of selection.
Results: Of the fourteen investigated infections, five were significantly associated with an increased risk (ranging from 33−56%) of LPL/WM. Strong associations were observed for respiratory tract infections, bronchitis (OR 1.56, 95% CI 1.32–1.84)), pharyngitis (OR 1.43, 95% CI 1.17–1.76), pneumonia (OR 1.42, 95% CI 1.18–1.72) and sinusitis (OR 1.33, 95% CI 1.12–1.60) and skin infection, herpes zoster (OR 1.51, 95% CI 1.12–2.04). For each of these infections, findings remained significantly elevated following the exclusion of more than six years of Medicare claims data prior to diagnosis/selection.
Conclusions: The findings suggest that exposure to infectious antigens may play a role in the development of LPL/WM. Alternatively, the observed associations may reflect an underlying immune disturbance which is present many years prior to diagnosis and thereby part of the natural history of disease progression.
No conflict of interest.

3612 POSTER

Novel molecular markers for acute myeloid leukaemia disease activity

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Background: Acute myeloid leukaemia (AML) is the most common acute leukemia affecting adults. AML is a disease with marked heterogeneity in both response to therapy and survival. Diagnostic markers used today are poor in explaining the high prevalence of relapses, thus new molecular markers for AML prognosis and minimal residual disease monitoring are needed.
Protein phosphatase 2A (PP2A) is an essential human tumor suppressor whose inhibition has been shown to be a recurrent event in multiple types of malignancies including AML. Although mutations in PP2A have been reported in human cancers, observed mutation frequency is low in general and cannot thus be enough to account for overall inhibition of PP2A in human cancers. Instead, PP2A's growth suppressor activity has shown to be inhibited in many cancers by the endogenous PP2A inhibitor proteins. Goal of this study was to investigate the role of PP2A and its inhibitory proteins in AML and to identify novel molecular markers of AML activity.
Material and Methods: Patient samples consisted of 93 patients aged 18−65 diagnosed with *de novo* or secondary AML at Turku University Central Hospital. Sample collection included diagnosis phase, two remission phase and possible relapse phase samples.
In order to characterize gene expression changes, fusion gene transcripts and splice variants that might predict disease recurrence in AML, RNAseq was conducted for selected core binding factor (CBF) subtype samples. Quantitative real time PCR was used to study prognostic role and gene expression differences of specific genes, including CIP2A, SET, EVI1, WT1, ABL, TIPRL, PME1 and ARPP19, on the whole sample collection.
Results: EVI1 and WT1 gene expression levels within the sample collection could be divided into subgroups as reposted previously for the prognostic role of these genes in AML. As a contrary to published data, CIP2A gene expression levels did not correlate with disease activity. The potential role of other PP2A inhibitory proteins and results from RNAseq are still under investigation.
Conclusions: It is expected that results of this study will reveal novel markers for disease activity and patient stratification in AML.
No conflict of interest.

3613 POSTER

Ponatinib regulates major signaling pathways in imatinib-resistant chronic myeloid leukemia cells

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Background: BCR-ABL fusion protein, responsible for developing of leukemic phenotype as a result of (9;22) translocation, is occured in more than 90% of Chronic Myeloid Leukemia (CML) cases. Third generation tyrosine kinase inhibitor ponatinib inhibits both wild type and T315I mutant ABL1 autophosphorylation. The aim of the study was to evaluate effect of ponatinib on imatinib resistant chronic myeloid leukemia cells according to the expression of genes including several signal transduction pathways such as; NF-κB, MAP/MAPK, PI3K-Akt-mTOR.
Material and Methods: An amount of 3μM imatinib resistant cells were generated by our group and named as K562/ima3 cells. Cytotoxic effect of ponatinib in K562 and K562/ima3 cell lines were assessed by WST-1 assay. Total RNA was isolated from cultured cells treated with ponatinib in IC50 doses for 48 hours and control cells. Reverse transcription procedure was performed for cDNA synthesis by using Transcriptor First Strand cDNA Synthesis Kit according to the manufacturers' instructions. For this study, custom design 96-well plates consist of 43 genes which are important in BCR-ABL signaling pathway, 2 housekeeping genes (GAPDH, ACTB), 1 Human Genomic DNA contamination, 1 Reverse Transcription Control, 1 positive PCR control was used for gene expression analysis by using LightCycler 480 real-time PCR. Cytotoxicity analyses were evaluated by GraphPad Prism v5.0 Software. ΔΔCT method was used for data analysis. Statistical analysis was performed by web based RT^2 Profiler PCR Array Data Analysis. The expressions of 43 genes playing roles in NF-κB and MAP/MAPK, PI3K-Akt-mTOR signaling pathways were studied by real time online RT-PCR.
Results: IC_{50} doses of ponatinib were calculated as 0.24 nM and 9.87 nM, in K562 and K562/ima3 cell lines, respectively. At 48th hour, expression of genes that are components of several signaling pathways necessary for leukemia were studied by real time online RT-PCR and down regulation of MAP3K7, MAPK8, IKBKB, mTOR, MAP3K2, IRF7, REL, ERN1 genes were significant in ponatinib treated K562/ima3 cells according to control cells. Fold changes of the above mentioned genes were; 7.90, 6.81, 6.48, 6.20, 6.03, 4.07, 3.72, 2.83, respectively.
Conclusion: Our data suggest that, ponatinib is an attractive target inhibiting cell proliferation via deregulating expressions of genes which are the components of BCR-ABL signaling pathway in imatinib resistant chronic myeloid cell lines.
No conflict of interest.

3614 POSTER

Recent experience of localized radiotherapy for low grade orbital lymphoma at a tertiary referral centre

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Background: Orbital lymphoma is a rare diagnosis and is usually of low-grade histology, most commonly marginal zone lymphoma. The majority present at an early stage (IE) and after biopsy and staging imaging to confirm no systemic involvement, will be treated with curative intent. Gold standard treatment for this group of patients is considered to be radiotherapy, although technique varies; a conservative dose of 30 Gy is delivered. We have previously published our data on this disease but here concentrate on low grade disease and partial orbital/ conjunctival radiotherapy.
Material and Methods: All patients diagnosed with histologically proven low grade 1E orbital lymphoma from January 2003 until December 2012 inclusive and treated with primary radiotherapy at St Bartholomew's Hospital, London were included in this review. Data on patient's demographics, radiotherapy regimes including techniques, dose fractionation and toxicity were collected. In addition follow up data including relapse details were collected retrospectively from electronic notes and radiotherapy records.
Results: 77 patients were diagnosed and treated with radiotherapy during this period and data was reviewed for all of them. 44 were female (57%) and 33 were male (43%), with a median age of 64 (range 26−89).
65 patients (84%) were treated with a 6 mega-voltage photon technique to the whole orbit, in a custom-made mask. 12 patients (16%) (whom had conjunctival only disease) were treated with a contact lens, bearing a central lead cylinder that is positioned over the cornea to screen midline ocular structures/ lens. The median dose prescribed was 30 Gy in 15 fractions over 3 weeks (range 30−34 Gy in 15−17 fractions).
The majority of patients experienced grade 1 erythema and/or conjunctivitis. In addition 3 patients experienced cataracts post radiotherapy.
At a median follow up of 3.4 years a total of 3 patients suffered a recurrence or treatment failure. 2 had developed distant disease, 1 had persistent disease in the treated orbit, and 1 had new disease in the contralateral orbit. No patients have died of disease.
Conclusions: This data suggests that patients with low grade, localized orbital lymphoma can be managed with a conservative dose of radiotherapy, demonstrating acceptable toxicity, and a high cure rate. We encountered no cases of localized relapse in the cohort of 12 conjunctival lymphoma treated with localized, lens sparing orthovoltage radiotherapy.
No conflict of interest.

3615 POSTER

Angiogenesis in chronic myeloid leukemia

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Background: Angiogenesis is associated with growth, dissemination and metastasis of tumors. Microvascular density (MVD) being one quantitative method of assessment of angiogenesis, demonstrated by immunohistological markers would give a proportional co relate of the angiogenic process in tumors. The aim of this study is to measure MVD using CD34 staining, to co-relate micro vascular densities with the grade of fibrosis, various phases of CML and type of CML (G/GM).
Materials and Methods: Bone marrow biopsy specimens of 30 CML patients and 20 non CML (controls) cases that required bone marrow biopsy were subjected to CD34 staining and H&E staining. The mean MVD in CD34 slides was assessed by selecting hot spots and MVD was measured in these fields in high power (40 x magnifications) and the mean MVD was calculated by taking the average of four hot spots per field. Grade of fibrosis and phase of CML, type(G/GM) were assessed in H&E slides. The controls were matched with respect to age and gender.
Results: Among 30 patients with CML, 21 were in Chronic phase, 5 in accelerated and 4 in blast crisis. A normal distribution was obtained for MVD of both CML cases and controls using tests for normality. Comparison of mean MVD between CML and controls by Student's t test showed a significant increase in MVD of CML cases ($P = 0.00026$). No significant difference in MVD between the three phases viz., Chronic, accelerated and Blast crisis phase ($P = 0.302$) was obtained by using One way ANOVA. Comparison of Grade of fibrosis with MVD using independent t test showed no significant difference in MVD between low (grade 1&2) and high grade (grade 3&4) ($P = 0.805$). No significant difference in MVD was obtained between G and GM types of CML using independent t test ($P = 0.381$).
Conclusion: The study shows that there is significant increase in MVD in CML cases than controls but no significant difference in MVD could be demonstrated between different phases of CML, types of CML and grades of CML. Therefore, although there is increased angiogenesis in CML patients, there is no significant difference in the angiogenetic process with respect to the phases of CML, type of CML and grade of fibrosis.
No conflict of interest.

3616 POSTER

Methylene tetrahydrofolate reductase gene polymorphism and risk of childhood acute lymphoblastic leukemia

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Background: Childhood acute lymphoblastic leukemia (ALL) is the most common malignancy affecting children, constituting about 30% of all cancers among children. It constitutes about 75% of pediatric acute leukemia with peak incidence between ages 3 and 4. Genetic factors may predispose children to develop leukemia. Recently, genetic variants of the Methylene tetrahydrofolate reductase (MTHFR) gene have been subject to increasing attention in the etiology of leukemia. Gene polymorphism at the nucleotide 677 in MTHFR gene (C677T) (Ala?Val) results in a less stable version of the enzyme. This study aimed at determination of the relationship between MTHFR gene polymorphism (C677T) and increasing susceptibility of childhood ALL among Egyptian children.
Methods: DNA was isolated from 60 pediatric ALL patients (cases) and from 40 healthy donors (controls). We detected the MTHFR C677T genotype in ALL patients and compared it with the genotype of controls by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) using *Hinf I* restriction endonuclease.
Results: T-allele carriers were significantly lower in ALL cases (43.3%) than healthy controls (55%). Reduction in ALL risk was observed for heterozygous (CT) or homozygous (TT) carriers of the MTHFR 677T allele (OR 0.7; 95% CI, 0.5−1.0; $P < 0.05$).
Conclusion: Our data suggest that the MTHFR gene variants are associated with decreased ALL rate and risk. the reduced risk associated with the MTHFR C677T polymorphisms may be the result of changed intracellular folate redistribution.
No conflict of interest.

3617 POSTER

BETTER follow-up guidelines for Hodgkin lymphoma survivors regarding late adverse treatment effects

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Background: After the introduction of modern radiotherapy and chemotherapy, Hodgkin lymphoma (HL) has become a highly curable disease. However, survivors have an increased risk of late adverse effects from treatment leading to excess morbidity and mortality and a decreased quality of life. Specific problems include second malignancies, cardiovascular and thyroid disease, fertility issues and premature menopause, neck muscle weakness, and increased risk of infections after splenectomy. The need for long-term follow-up is increasingly recognized, but uniform recommendations are lacking at present. Therefore, the Dutch BETTER consortium (**B**etter care after Hodgkin lymphoma: **E**valuation of long-**T**erm **T**reatment **E**ffects and screening **R**ecommendations) developed follow-up guidelines aimed at reduction of morbidity and mortality due to late adverse treatment effects.
Material and Methods: The BETTER follow-up guidelines were developed according to international standards. The guideline development group consisted of clinicians, methodological experts and patient representatives. Besides literature reviews, experts were consulted for best practice recommendations; consensus was sought during meetings with the national BETTER consortium.
Results: After treatment for HL, long-term screening of specific risk groups is advised for breast cancer (mammography and breast magnetic resonance imaging), cardiovascular disease (blood pressure, lipids, biomarkers, echocardiogram and electrocardiogram), thyroid disease (hormone profile) and osteoporosis after premature menopause (bone mineral density).

Recommendations are given for fertility care and family planning, therapy for neck muscle weakness, and post-splenectomy infection prophylaxis. A healthy lifestyle and awareness of possible late adverse treatment effects are advocated. In the near future guidelines will be implemented among approximately 8,500 HL survivors throughout the Netherlands and evaluated for their diagnostic value and efficacy.
Conclusions: While much literature is available regarding the incidence of late adverse effects after HL treatment, very little evidence was found regarding the diagnostic value and efficacy of various screening tests. The new BETTER guidelines are thus mainly consensus-based. Implementation and evaluation of the guidelines will lead to more evidence-based follow-up practices and hopefully to improved life expectancy and quality of life for HL survivors.
No conflict of interest.

3618 POSTER

Long-term follow-up results of first-line treatment with doxycycline in patients with previously untreated ocular adnexal marginal zone B-cell lymphoma

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Background: Since *Chlamydophila psittasi* infection has been associated with ocular adnexal marginal zone B-cell lymphoma (OAMZL), doxycycline has been used for its treatment. However, there is not enough evidence of long-term outcomes of doxycycline therapy. Therefore, this study was conducted to evaluate long-term results of doxycycline treatment as first-line therapy for OAMZL patients.
Material and Methods: Ninety patients with previously untreated and histologically confirmed OAMZL were enrolled at Seoul National University Hospital between 2004 and 2012. Each patient was treated with two cycles of doxycycline 100 mg bid for 3 weeks and re-evaluated with ophthalmologic examination and radiologic examination (CT or MRI) every 6 months. Doxycycline outcomes were evaluated in patients who were followed for more than six months after completion of therapy. Progression-free survival (PFS) was calculated from the date of start of treatment to relapse, progression, or to the last date of follow-up. All patients were alive at last follow-up.
Results: The median age at diagnosis was 48 years (range, 21−71 years) with a male-to-female ratio of 1:1.6 and all patients had ECOG performance status 0−1. The most common site of presentation was conjunctiva (82%), followed by orbit (13%), eyelid (3%), and lacrimal gland (2%). All patients, except one patient who had bone marrow involvement, had stage IE at diagnosis. Serum lactate dehydrogenase was elevated in 20% of patients and only one patient had B symptom at diagnosis. There was no serious adverse event reported after doxycycline therapy. After a median follow-up period of 40.5 months (range, 8−85 months), the median PFS was not reached and 5-year PFS was 62.2% by intent-to-treat analysis. Twenty-nine patients (32%) showed local treatment failure without systemic spread. In these patients, median time to treatment failure was 4 months (range: 1−56 months) after doxycycline treatment. Twenty patients received CVP (cyclophosphamide, vincristine, and prednisolone in combination) and nine patients received radiation as second-line therapy. All of these patients achieved complete remission to the second-line therapy without any serious complication.
Conclusions: First-line treatment with doxycycline in patients with previously untreated OAMZL is effective without serious toxicity. Patients who failed after doxycycline therapy were successfully salvaged with chemotherapy or radiotherapy without compromising the long-term treatment outcomes.
No conflict of interest.

3619 POSTER

The relationship between transfusion independence and survival outcomes in older patients with newly diagnosed acute myeloid leukaemia (AML) treated with decitabine

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Background: Further analysis of transfusion data from the DACO-016 study in patients with newly-diagnosed AML indicated that treatment with decitabine (DACOGEN) resulted in statistically significant reduction in transfusion dependence compared to treatment choice with physician's advice (TC).
Objectives: This post hoc analysis of DACO-016 explored if transfusion dependence at baseline or on-study is a prognostic factor of survival outcomes.
Methods: In Study DACO-016 485 patients ($\geqslant$65 years) with newly diagnosed AML were randomised to decitabine 20 mg/m^2 intravenous for 5 consecutive days every 4 weeks or TC (either supportive care or 20 mg/m^2 cytarabine given subcutaneously once daily for 10 consecutive days every 4 weeks). Patient baseline or on-study transfusion independence as well as survival outcomes were analysed. Log-rank tests were conducted to test the relationship between transfusion independency and survival outcomes.
Results: For platelet transfusions, the odds of a patient treated with decitabine to become transfusion independent were 1.38 as compared to TC. Within the decitabine arm, the hazard ratios (HR) of platelet transfusion independent patients versus dependent patients for overall survival (OS) and progression free survival (PFS) were 0.42 (95% CI (0.28, 0.65), p = 0.0001) and 0.50 (95% CI (0.30, 0.80), p = 0.0031) respectively. For RBC transfusion, the odds of a patient on decitabine to become transfusion independent were 1.53 as compared to TC. Within the decitabine arm, the HRs of RBC transfusion independent versus dependent patients for OS and PFS were 0.54 (95% CI (0.40, 0.74), p = 0.0001) and 0.57 (95% CI (0.40, 0.81), p = 0.0019) respectively.
Conclusions: Decitabine induced transfusion independence in older patients with AML. Transfusion independence was shown to be a strong prognostic factor for disease progression and overall survival.
Conflict of interest: *Corporate-sponsored research: Janssen*

3620 POSTER

Analysis of the transformation of follicular lymphoma in a national registry of over a thousand patients

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Introduction: The evolution of an indolent non-Hodgkin lymphoma to a more aggressive one is known as histologic transformation. Its frequency in follicular lymphoma varies between 10 and 70% depending on the series. As established risk factors at the time of diagnosis are known: stage III/IV, elevated LDH, high β2 microglobulin, low albumin, grade III, high FLIPI and absence of complete remission after initial treatment. We unknow the impact of treatment on the risk of transformation. The frequency of histologic transformation is so variable in the series due to the histological definition, the follow-up time and the frequency in which biopsies and/or autopsies are performed to document this progression. It should be suspected when there is evidence of rapid progression of lymphadenopathy, atypical infiltration of extranodal sites, onset of systemic symptoms and increased in LDH and/or hypercalcemia.
Material and Methods: 1178 patients diagnosed with follicular lymphoma, between 1986 and 2012, and treated at the Oncology Department of 17 Spanish hospitals were reviewed. An analysis of clinical and pathological variables using SPSS v19 was made.
Results: A total of 1178 patients were analyzed, of whom 51% were women. The mean age at diagnosis was 57.8 years. A 3.5% of the total of the patients underwent a transformation over the evolution of the disease. 67% of them had stage III/IV at diagnosis. A 63.6% of the transformations were to diffuse large B-cell lymphoma and 15% were at high grade follicular lymphoma. Less frequent were Burkitt-like lymphoma, Hodgkin lymphoma, mantle cell lymphoma, T-cell lymphoma and MALT lymphoma. The median time to transformation was 40 months (standard deviation of 33.24). We do not find any statistically significant differences between the treatments that patients had received prior to the transformation; it was similar in patients treated with or without rituximab, with or without anthracyclines.
Conclusion: The different chemotherapy regimens and the use of rituximab are not associated with the risk of histologic transformation of follicular lymphoma. Re-biopsy should always be done in those cases where histologic transformation is suspected.
No conflict of interest.

3621 POSTER

Treatment of mucosa-associated lymphoid tissue (MALT) lymphoma of the ocular adnexa: A retrospective single-centre analysis

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Background: Ocular lymphomas represent a heterogeneous group of different lymphomas with a rising incidence. Although several histological subtypes may occur, orbital marginal zone B-cell lymphoma (OAMZL) constitutes for the most frequent diagnosis. However, relatively little is known about clinical course, typical features and therapy. We report our experience of patients with OAMZL seen at our institution 1999–2012.
Material and Methods: This retrospective analysis was performed of all MALT lymphoma patients diagnosed and treated at a tertiary referral centre 1999–2012. Diagnosis was made according to the WHO classification. A total of 60 patients (33 female, 27 male) with OAMZL were identified at a median age of 66 years; interquartile range (IQR) 52−75. The median follow-up time was 43 months (IQR 16−92). The study had been approved by the Ethical Board of the Medical University of Vienna.
Results: The majority presented with local disease i.e. stage IE according to Ann Arbor (n = 40/60, 67%), one patient had stage IIE (2%), two patients stage IIIE (3%) and the remaining 17 (28%) stage IVE disease. Seven patients with stage IVE presented with bilateral orbital disease whereas the others showed involvement of further organs. Autoimmune disorders were present in 17 of 47 tested patients and the most frequent diagnosis was autoimmune thyroiditis (7/17).
Treatment data were available in 58 patients. Local treatment with either radiotherapy (24%, 14/58) or surgical resection (5%, 3/58) resulted in complete or partial response (CR or PR) in 82% of patients (CR n = 13, PR n = 1). One patient had stable disease (SD), one progressive disease (PD) and one was lost to follow-up. However, a total of eight patients needed consecutive further therapy. Median time-to-progression (mTTP) in this group was 41 months (IQR 24−58). The majority of patients (47%, 27/58) received systemic treatment with (immuno-)chemotherapy regimens and response rate was identical at 81% (CR n = 16, PR n = 6, SD n = 3, PD n = 1, no data n = 1). Eleven patients warranted further therapy after a mTTP of 16 months (IQR 9−31). Eight patients received antibiotics (doxycycline or clarithromycin) as initial therapy. Two patients achieved CR now ongoing for 6 and 83 months; response rate was 38% (PR n = 1, SD n = 2, PD n = 2, no data n = 1). Median TTP in this group was 15 months (IQR 2−17). Watchful waiting was the initial approach in 6/58 patients (10%), and 4 received systemic therapy after a mTTP of 32 months (IQR 21−73). The remaining two were lost to follow up.
There was no significant difference in mTTP between the treatment arms. A total of 28/58 (48%) patients progressed and were given second line therapy. None of our patients had central nervous system involvement during follow-up.
Conclusion: OAMZL patients were treated first line with radiotherapy, surgery, (immuno-)chemotherapy or antibiotics resulting in high response rates. There was no significant difference in TTP and response rates between local vs systemic therapy, but recent data have suggested a preferential toxicity profile for systemic therapy.
No conflict of interest.

3622 POSTER

Secondary tumors in patients after lymphoma treatment

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Background: Patients after treatment of non-Hodgkin lymphoma (NHL) or Hodgkin lymphoma (HL) are at risk for secondary tumors (ST). The aim of this study was to assess the rate and risk factors for ST occurring in NHL and HL patients.
Methods: In order to reveal ST cases a total of 3056 patients with NHL or LH were identified who were treated from 1976 to 2010 in the National Cancer Institute, Ukraine.
Results: Eligible cases included 53 patients with ST after initial treatment of NHL or HL. Median age of patients at the moment of ST diagnosis was 41.5 y.o. and 75.5% were females. The majority of HL patients had lymphoma stage II (55%), 42% of patients with NHL had stage III. Patients received 2−8 courses of chemotherapy (CT) (CHOP, CNOP, BHOP, COPP, COP, ABVD, BEACOPP).
24.5% patients received CT alone as initial treatment, radiation therapy (RT) alone − 9.5% patients, combined treatment − 66% patients. RT doses ranged from 30 to 46 Gy to the cervical, axillaries, mediastinal, and inguinal and retroperitoneal regions involved and extended radiation fields. The ST occurred in the region of previous RT in 65.2% of patients. The average time of occurrence was 12.0±0.5 years (1−34).
Median of survival was 140.9 months, average life duration was 147.9±1.9 months. 5-year overall survival was 83%, 10-years survival was 63% and 20-year survival was 30% from the time of lymphoma diagnosis.
The rate of ST was as follow: breast cancer in 17%, head and neck cancer − 13%, lymphoma/leukemia − 13%, gastric cancer − 11%, lung cancer − 8%, cervical cancer − 8%, uterine neoplasm − 6%, skin cancer − 6%, colorectal cancer − 4%, ovarian cancer − 4%, prostate cancer − 2%, others − 8% of cases.
According to Bhatia S., 2003 patients the most common ST in patients after treatment HL were lung cancer, gastric cancer, colorectal, thyroid and breast cancer.
According to Rueffer U., 2001 the most common ST after treatment of NHL were MDS/AML, lung cancer, gastric cancer and breast cancer.
There was a direct correlation of the ST occurrence and previous RT, $\chi^2 = 0.39$ ($p < 0.5$), gender (female), $\gamma = 0.412$ ($p < 0.05$) and there was no correlation of tumors and CT alone ($\gamma = 0.06$), age, stage of lymphoma, type of CT and number of CT cycles.
Conclusion: Breast cancer, head and neck cancer, lymphoma/leukemia and gastric cancer were the most frequent malignancy among these patients. The main risk factor for ST was RT at initial treatment and women had a higher risk compare to men.
No conflict of interest.

3623 POSTER

The avβ3/avβ5 blockage by Cilengitide® disables the osteoclast-like differentiation of malignant plasma cells in multiple myeloma

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Background: Hyperactive osteoclastogenesis in multiple myeloma (MM) is primarily promoted by marrow MM cells while the osteoerosive activity is triggered in osteoclasts (OC) by the $\alpha_v\beta_3$ integrin that, however, is also expressed by malignant plasma cells. These cells may undergo to OC-like differentiation in vitro and the inhibition of $\alpha_v\beta_3$ by small interfering RNAs impairs their OC-like erosive activity. $\alpha_v\beta_5$ is also expressed by MM cells in their adhesion to the bone matrix and interacts with $\alpha_v\beta_3$ in driving the hyperactivation of OCs. Cilengitide® (CLG) is an antagonist of $\alpha_v\beta_3/\alpha_v\beta_5$ that restrains the proliferation of high-grade glioma cells both in vitro and in vivo as well as the osteotropism of tumor cells in animal models of breast cancer. In this study we verified its effect in inhibiting the in vitro bone resorbing activity of OC-like MM cells.
Methods: Marrow plasma cells purified from seven MM patients were primarily assessed for both $\alpha_v\beta_3$ and $\alpha_v\beta_5$ expression by flow-cytometry and then cultured up to 24 hours with CLG on vitronectin coated substrates. Cell viability and adhesion were investigated by MTT assay, whereas the cytoskeleton F-actin was visualized by immunofluorescence. Both $\alpha_v\beta_3$ and $\alpha_v\beta_5$ intracellular pathways were explored by western blot (WB), particularly the phosphorylation of Erk1/2, Pyk2, paxillin as well as Akt. Calcium phosphate, as bone resembling substrate, was used to measure the effect of CLG on the bone resorption exerted by MM cells.
Results: Both $\alpha_v\beta_3$ and $\alpha_v\beta_5$ were highly expressed (>98%) by MM cells whose incubation with CLG at 25 μg/ml up to 6-hours promoted the detachment of approximately 50% of cells from the vitronectin coating, whereas the cell viability remained mostly unaffected. However, non adherent cells showed altered and irregular F-actin localization in parallel with minor phosphorylation of ERK1/2, PYK2 and paxillin as compared with untreated cells that showed a well rearranged perimembrane F-actin ring. By contrast, the Akt phosphorylation the cells underwent to significant inhibition in their osteoerosive activity as number of pits, compared to untreated cells (34±13 and 9±2/cm2; $p < 0.05$).
Conclusions: Inhibition of $\alpha_v\beta_3/\alpha_v\beta_5$ signalling by CLG appears functional in disabling the bone resorptive properties of MM cells in our in vitro experimental model. Thus, new preclinical studies are needed to explore its potential for future treatment of the myeloma bone disease.
No conflict of interest.

3624 POSTER

Report on imatinib treated CML patients: Pregnancy outcome

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Background: Now that imatinib is being used to treat thousands of chronic myeloid leukemia (CML) patients for more than 10 year it is highly probable that many patients will get pregnant during its use. Company warns against any such use. But the fact remains that there is need for planned pregnancies in indicated cases. So we selected few cases both male and female for such pregnancies by interrupting treatment and following the pregnancy closely. Their outcome was studied so that we have an idea about what best could be suggested in such instance.
Materials and Methods: From November 2002 to January 2011, 634 patients with CML in any stage of the disease were treated with imatinib at our tertiary cancer research institute. We selected 22 (12 females and 10 males) cases of pregnancies by interrupting treatment. We reported 9 accidental pregnancies and 13 planned pregnancies involving 22 patients who or their wives conceived while receiving imatinib for the treatment of CML.
Results: Among 23 pregnancies there were 3 spontaneous abortions and 4 elective abortions. In case of 8 female patients, 3 and 5 were male and female babies respectably and in case of six male patients 4 and 4 were male and female babies. Two babies were with congenital anomaly such as one Hypospandium and one Mild-Hydrocephalus (in case of unplanned pregnancies and imatinib exposure during the first trimester of organogenesis).
Conclusions: In conclusion, exposure to Imatinib during pregnancy might result in an increased risk of serious fetal abnormalities or spontaneous abortions. Women of childbearing potential should use adequate contraception while using Imatinib. We can suggest that planned pregnancy during therapy should be encouraged but imatinib therapy in unplanned pregnancy can cause spontaneous abortion or minor congenital anomaly.
No conflict of interest.

3625 POSTER

Epidemiological analysis of follicular lymphoma in Spain: Retrospective registry in 17 hospitals

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Introduction: In Spain, between 3,000 and 5,000 new cases of follicular lymphoma are diagnosed each year. It is the second most common tumor of lymphoid lineage. It represents 22−40% of non-Hodgkin lymphomas. The annual incidence is increasing in recent decades. The development of national registers helps us to understand the clinical and pathological characteristics of the patients in our area. Thus, we can develop the best treatment program for our patients, thereby improving the effectiveness of our clinical practice.
Material and Methods: 1178 patients diagnosed with follicular lymphoma, between 1986 and 2012, and treated at the Oncology Department of 17 Spanish hospitals were reviewed. An analysis of clinical and pathological variables using SPSS v19 was made.
Results: A total of 1178 patients were registered, of which 51% were women. The mean age at diagnosis was 57.8 years with an ECOG of 0−1 over 80%. In 60% of the cases, follicular lymphoma was grade I−II. Regarding prognostic factors at diagnosis, 46% of patients were over 60 years, 22% had hemoglobin <12 mg/dl, 25% an elevated LDH, 46% a stage I−II Ann Arbor, and nearly 40% of patients had more than 4 nodal areas affected. This meant a FLIPI 0−1 in 38.4%, a FLIPI 2 in 29% and $\geqslant$3 FLIPI in 31.7%. Other important features at diagnosis are the extranodal origin in 20%, the elevation of the β2 microglobulin in 32.7%, bone marrow involvement by nearly 40%, the presence of B symptoms in 19.6% of patients and Bulky involvement by 22.8%. Currently, 19.2% of the patients are alive with disease, 59.4% are alive without active macroscopic disease and 21.5% have died.
Conclusion: To our knowledge, this is the largest registry of patients diagnosed with follicular lymphoma. Such records are necessary to determine the characteristics of the patients treated in each health area.
No conflict of interest.

3626 POSTER

Spinal cord compression in multiple myeloma

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Background: Spinal cord compression occurs in 5% of all cancer patients and its prognosis is usually poor. However, the impact of cord compression on the prognosis of myeloma patients is relatively less than that of other cancers because most cases are so sensitive to radiotherapy or chemotherapy that they can be rescued by active treatment. However, there is few data regarding clinical outcomes of spinal cord compression in Korean myeloma patients. In this study, we identified clinical features of cord compression in myeloma patients as well as analyzed its treatment outcome and prognostic impact.
Methods: We reviewed the retrospective cohort of myeloma patients in the Samsung Medical Center between 2001 and 2011. We designated a case of spinal cord compression as a myeloma patient diagnosed with spinal cord compression during or after active treatment by CT or MRI scans or histologic confirmation. We gathered clinical data associated with cord compression and treatment outcomes including functional recovery and overall survival.
Results: Of 542 patients who were diagnosed with symptomatic multiple myeloma, 65 patients (12.0%) had spinal cord compression. The onset of cord compression was variable, but 40 cases were found at diagnosis (61.5%) whereas 25 cases were found during follow up (38.5%). The most common presentation was epidural mass compressing spinal cord (73.8%), and the second common was compression fracture (20.0%). Pain was the most common symptom, occurring in 47 (72.3%) patients and 27 patients (41.5%) had neurologic impairment. Thoracic spine was most common involved site (61.5%) followed by cervical spine (21.5%). The performance status was relatively poor, thus, 46.2% of patients had poor performance (ECOG $\geqslant$2) whereas only 28.0% had poor performance in patients without cord compression ($P < 0.05$). The median overall survival was 42.9 months in patients with cord compression and it was not significantly different from patients without cord compression (53.8 months, $P = 0.23$). Radiotherapy was most commonly used treatment modality ($n = 37$, 56.9%), and 10 patients (15.4%) received surgery for spinal lesion. Among patients with neurologic deficit ($n = 27$), 18 patients received radiotherapy and 6 patients received surgical decompression. The response to treatment in terms of neurologic improvement was 77.8% in radiotherapy group and 100% in surgery group.
Conclusions: The present study is the first study of description of spinal cord compression in Korean myeloma patients, and radiotherapy might be recommended as an effective treatment in terms of neurologic deficit.
No conflict of interest.

3627 POSTER

Safety and efficacy of rituximab based chemotherapy in chronic lymphocytic leukaemia patients: A single centre experience

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Background: Rituximab (anti-CD 20) has been reported to be an effective drug for the treatment of chronic lymphocytic leukaemia (CLL) with combination of fludarabine and bendamustine. Its safety and efficacy in Indian patients has not been studied. We carried out analysis of CLL patients who received two different regimen FCR (fludarabine, cyclophosphamide, and rituximab) and BR (bendamustine and rituximab) for treatment of CLL in upfront and relapsed cases at I.R.C.H, AIIMS, New Delhi, India.
Methods: The records of patients ($N = 320$) with diagnosis of CLL between January 2000 and December 2012 were collected. Rituximab was used in 64 denovo and 25 relapsed cases. Response evaluation was done as per the National Cancer Institute-Working Group guidelines, in those patients who received at least 3 cycles of chemotherapy. Toxicity was graded as per the common terminology criteria for adverse events, version 3.0. Median event-free survival was obtained using Kaplan–Meier survival analysis.
Results: Eighty nine patients (64-upfront/de novo, 25 relapsed) were included in the study and 353 cycles were administered (median: 4 cycles per patient). Fifty-five patients received FCR and 34 received BR. Thirty patients had treatment delay in FCR and 6 patients in BR subgroup due to prolonged myelosuppression. The complete (CR), partial (PR) and overall response rate (ORR) of FCR and BR was 43%, 43%, 86% and 40%, 50%, 90% respectively those treated upfront. ORR was 50% in those with relapsed disease in both subgroup. Grade 3/4 myelosuppression occurred in 65% with FCR and 20% with BR. One third patients had developed overt tuberculosis during treatment period or subsequent follow-up in patients

who received FCR. Four patients died of pneumocystis jiroveci carinii pneumonia (PCP) in FCR group. Median follow-up period was 27 months. Median event-free survival for patients treated upfront with FCR was 24 months and BR was not achieved.
Conclusions: In our patient population, response to FCR and BR is same and similar to that in the published literature but toxicity profile is different. Prolonged myelosuppression (two third of patients leads to treatment delay) and tuberculosis (one third of patients) in FCR regimen. BR is better option to treat CLL patients in our group of population where the prevalence of subclinical tuberculosis is high.
No conflict of interest.

3628 POSTER

Graft-versus-host disease (GVHD) prophylaxis with mesenchymal stem cells transplanted on thalassemia major patients: An experience from Eastern India

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Background: Mesenchymal progenitor stem cells (MSCs) have a tremendous potential to self renew and exhibit multiple lineages of cell lines and are known to by inhibiting T cell proliferation and acceleration of hematopoietic stem cell engraftment. MSCs avoid allorecognition, tend to interfere with dendritic cell and T-cell function thus creating an immunosuppressive microenvironment by secreting cytokines. Numerous clinical trials have been reported to use MSCs to prevent graft-versus-host disease (GVHD). MSC therapy offers a safe and a therapeutic method against GVSD to Thallassemia patients without without impairing graft-versus-leukemia effects. Our aim is to see the effect of MSCs in GVHD prophylaxis and result of thalassemia major patients.
Material and Method: 16 thalassemia major patients were selected and they have undergone umbilical cord blood transplants. The age group determined was in the range of 4−15 years, having a mean of 8.5. Messenchymal stem cells were derived from sibling cord blood. We used routine GVHD prophylaxis (methotraxate, cyclosporine and methlprednisolone) on 8 patients. In another 8 patients we added additional cord blood MSCs. MSCs were cultured and administered to the recipients at doses of 0.8−1.3$\times$106/kg when the blood count indicated recovery.
Result: The comparative study of 8 thalassemic patients treated with routine GVSD prophylaxis i.e. with (methotraxate, cyclosporine and methlprednisolone) and another 8 patients with we added additional cord blood MSCs has shown that 6 out of 8 (75%) thalassemia patients had developed GVHD of stage II−IV when administered with routine GVHD prophylaxis; whereas another group of 8 patients have shown 2 (25%) patient has developed grade- III, 1(12.5%) patient grade- II and 5 (67.5%) patients developed grade- I GVHD where additional MSC were used as GVHD prophylaxis.
We have also observed that there was no difference in graft rejection rate, chronic GVHD development or any infections during the transplant. No mortality or morbidity was there in both the groups. But there was a rejection rate of 20% where no MSCs were used in the group.
Conclusion: We have came to precise information that using MSCs on GVHD patients is 100% safe and in future we will look forward to manipulate MSCs to restore the normal functioning of the patients with or without drugs or steroids that cause side effects in regular transplantation. The number is very small. We intend to continue the programme more in Thalassemia transplants as well as in other allogenic transplants.
No conflict of interest.

3629 POSTER

Differences in baseline characteristics and survival rates between GCB and non-GCB diffuse large B-cell lymphoma treated with rituximab based immunochemotherapy

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Background: In recent years, the emergence of new studies and new drugs, made division of diffuse large non-B lymphoma (DLBCL) on GCB in non-GCB subtypes increasingly important. Previous studies have shown that this distinction has prognostic significance. Addition of rituximab in both subtypes improved treatment results.
Material and Methods: We retrospectively analyzed 111 patients with de novo DLBCL, treated with rituximab-based immunochemotherapy. Division of GCB and non-GCB subtypes was performed with immunohistochemistry, according to Hans's criteria. The baseline characteristics that were correlated with the subtype of DLBCL were: patient age, sex, hemoglobin, lymphocyte count, LDH level, albumin level, Ann Arbor clinical stage, IPI and R-IPI score, percent of Ki-67 expression and expression Bcl-2 and CD5. In addition, we observed differences in response to therapy, EFS and OS.
Results: Sixty-two (56.25%) patients had non-GCB subtype. Analysed groups did not differ in age of patients (median age 56 years in both groups), patient gender (males 63.26% GCB vs non-GCB 66.12%, p = 0.909), hemoglobin <100 g/l (10.2% GCB vs non -GCB 11:29%, p = 0.901), lymphocyte count <1.3 (GCB 45.83% vs non-GCB 50%, p = 0.809) albumin <35 (GCB 22.5% vs. non-GCB 38.18%, p = 0.162), LDH elevation (65.30% GCB vs non-GCB 59.67%, p = 0.682), Ann Arbor clinical stage (I 8:16% GCB vs non-GCB 9.67% p = 0.954, II 34.69% vs. 37.09%, p = 0.95, III 30.61% vs. 27.41%, p = 0.874, IV 26.53% vs. 25.8%, p = 0.896), and IPI/R-IPI score (score 71.42% 0, 1, 2 GCB vs non-GCB 68.84%, p = 0.939). Median Ki67 expression was 70% in GCB and 62.5% in the non-GCB group. Expression of Bcl-2 and CD 5 also was not different among the subtypes. Complete remission was achieved in the group of GCB in 79.16% cases, while in the non-GCB in 67.79% (p = 0.272). Patients with GCB subtype had a longer EFS (median 26 months vs. NR, 3-year EFS 67.6% vs. 47.1%, p = 0.05), and OS (median 53 vs 35 months, 3-year OS 59.6% vs. 44.9%, p = 0016).
Conclusion: Non-GCB subtype is predictor of shorter survival in patients with DLBCL treated with rituximab based immunochemotherapy.
No conflict of interest.

3630 POSTER

CD5-positive versus CD5-negative diffuse large B-cell lymphoma treated with immunochemotherapy: Is there a difference?

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Background: CD5 is recognized as a marker of poor prognosis in patients with DLBCL. Patients with CD5 + DLBCL treated with rituximab have longer time to disease progression compared to patients treated with chemotherapy alone.
Patients and Methods: We analyzed 121 patients with de novo DLBCL, treated with rituximab-based immunochemotherapy. CD5 positivity was determined by immunohistochemistry. Basic characteristics that correlated with the CD5 status were: patient age, sex, hemoglobin, lymphocyte count, LDH level, albumin level, Ann Arbor clinical stage, IPI and R-IPI score, and the level of Ki-67expression, expression of Bcl-2, and the percentage of GCB/non-GCB phenotypes within the group, based on Hans's criteria. In addition, we observed differences in response to therapy, EFS and OS.
Results: Seventeen patients (14%) in our group were diagnosed with CD5 + DLBCL. Analysed subgroups did not differ in proportion of patients older than 60 years 41.17% vs. 33.65% (p = 0.742), hemoglobin <100 g/l 5.88% vs. 17:47% (p = 0.393), lymphocyte count <1.3 43.75% vs. 44.55% (p = 0.833), albumin level <35 30.76% vs. 24.05% (p = 0.863), LDH level elevation 64.70% vs. 54.80% (p = 0.618) for CD5+ versus CD5− respectively. Groups did not differ in Ann Arbor stage (III + IV CS CD5+ 58.82% vs 52.88% CD5− p = 0.847). Although not statistically significant (p = 0.145), male sex was more frequent in CD5-negative patients (57.49% vs. 35.29%). More patients with CD5+ DLBCL were in poor prognosis group according to R-IPI score (52.94% vs. 28.15%, p = 0.035). Median level of Ki67 expression in CD5+ DLBCL was 60%, compared to 65% CD5− patients. Groups also did not differ according to the expression of Bcl-2 nor the affiliation to GCB/non-GCB phenotype. In our series, there were no differences in the percentage of complete remissions achievement (CD5+ 75% vs. CD5− 71.84%, p = 0.970), EFS (median CD5+ 35 months vs. CD5− NR, 3-year EFS 59.3% vs. 48.8%, p = 0.629) and OS (median CD5+ 44 months vs. CD5− 37 months, 3-year OS 66.12% vs. 52.6%, p = 0.869).

Conclusion: Despite the higher number of patients with poor R-IPI score in our group of patients, the EFS and OS were the same in patients with CD5+ or CD5− DLBCL.
No conflict of interest.

3631 POSTER

International Prognostic Index (IPI) is a stronger predictor of outcome in diffuse large B cell lymphoma (DLBCL) treated with rituximab (R) and CHOP (R-CHOP) compared to revised-IPI (R-IPI)

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Background: Standard IPI was developed in the non-rituximab based chemotherapy era as prognostic tool for risk stratification of aggressive NHL. The revised IPI (R-IPI) was created in the rituximab based chemotherapy era by redistributing the risk factors of IPI; it has been suggested as an alternative and better predictor in this patient population. This is a retrospective study designed to compare the prognostic value of IPI versus (R-IPI) in DLBCL patients treated by R-CHOP.
Material and Methods: The study included 198 patients treated by R-CHOP between (8–2004 till 12–2008) at King Faisal Specialist hospital, Saudi Arabia. Demographics, presentations, stage, therapy, and IPI risk scores and survivals were collected and calculated retrospectively. Data were incomplete in 13 patients. 185 patients form the basis for this report.
Results: There were 113 males/85 females with a median age of 50 year (15−89). At a median follow-up for survivors of 68 months (19–102), the event-free survivals (EFS) and overall (OS) were 55%, 64% respectively. Event free survival and overall survival for four groups according to IPI were 79%, 46%, 47%, 29% and 85%, 59%, 53%, 36% for low, low intermediate, high intermediate and high risk groups respectively. According to R-IPI the EFS and OS were 81%, 63%, 38% and 81%, 74%, 45% for very good, good and poor risk groups respectively. While all the differences were highly statistically significant for IPI, the same did not reach statistical significance for R-IPI (Table 1).

Table 1

Risk Category	OS	HR	p-value	EFS	HR	p-value
Standard International Prognostic Index						
Low (0, 1)	85%	1		79%	1	
Low Intermediate (2)	59%	2.6	0.009	46%	2.8	0.001
High Intermediate (3)	53%	3.6	<0.001	47%	3.3	<0.001
High (4, 5)	36%	5.6	<0.001	29%	5.2	<0.001
Revised International Prognostic Index						
Very Good (0)	81%	1		81%	1	
Good (1, 2)	74%	1.6	0.4	63%	2.2	0.178
Poor (3, 4, 5)	45%	4.2	0.01	38%	5.09	0.006

HR, Hazard Ratio. All percentages are rounded.

Conclusion: Standard IPI remains a valid prognostic tool even in chemo-immunotherapy era and is more robust than R-IPI in predicting prognosis in DLBCL treated with R-CHOP.
No conflict of interest.

3632 POSTER

Incidence of second cancer in patients with chronic lymphocytic leukemia: 13 years experience from single institute

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Background: Chronic lymphocytic leukemia (CLL) is most common malignancy in the west and relatively uncommon in India. Patients with CLL have a higher incidence of second malignancies (two times) than the general population. Our study aims to present the incidence and predicting factor for second cancer in patients of CLL at our institution.
Methods: We retrospective evaluated 320 patients of CLL registered at All India Institute of Medical Sciences (AIIMS), New Delhi over a period of 15 years (2000–2012). A second malignancy was defined as another malignancy at the time of diagnosis or during follow-up.
Results: There were 230 males and 90 females. The median age was 59 years (28−90 years). The common presenting features were lymphadenopathy 63%, fatigue 25%, fever 20%, hepatomegaly 40%, splenomegaly 55%. Median total leucocyte count at presentation was 47×10^9/L. Sixty percent of patients were early (Rai stage 0−10%, stage I − 16%, stage II − 34%) and 40% of cases were in advanced (stage III −20 % and stage IV − 20%) stage. Fifty percent of patients received treatment at presentation (one hundred twelve patients (70%) received chlorambucil and 40 patients (25%) received Fludarabine and eight patients received bendamustine based chemotherapy). With a median follow-up of 40 months, total of 24 cancers were identified (18 hematological and 6 solid tumors). Seventeen cases were transformed to diffuse B cell lymphoma (richter's syndrome) and rest were myelodysplastic syndrome −1, basal cell carcinoma −1, carcinoma of larynx −1, breast cancer −1, adenocarcinoma of lung −1 and locally advanced urinary bladder cancer −1 case each. According to correlation analysis, young age (<55 years, $p = 0.015$) a high expression of CD38 positivity (>30%, $p = 0.001$) and advanced Rai stage (III & IV, $p < 0.001$) were found to be independent predictors of transformation to richter's syndrome (RS). Median time to progression to RS and overall survival was 26 months and 8 months respectively.
Conclusions: The incidence of second cancer is 7.5% in our population, richter's transformation is the most common and accounts for 5% of cases. Young age, advanced stage and high expression of CD 38 predict poor outcome.
No conflict of interest.

3633 POSTER

BAFF, TACI and BCMA receptors expression and their impact on survival of patients with diffuse large B-cell lymphoma

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Background: B-cell activating factor (BAFF) is a molecule which affects the survival and maturation of B lymphocytes. BAFF binds to three receptors: B-cell activator maturation antigen (BCMA), transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), and BAFF receptor (BAFF-R). Activity of atacicept and tabalumab in multiple myeloma emphasizes the importance of these receptors in hematological malignancies.
Patients and Methods: The study presents the pilot results of 30 patients with DLBCL treated with rituximab-based immunochemotherapy. Receptors BAFF-R, TACI and BCMA were determined by immunohistochemistry using Abcam ® antibodies. We also determined expression of Bcl-2, Bcl-6, MUM-1, CD10, CD5, Ki67 receptors. We correlated the EFS and OS in relation to: age, sex, hemoglobin level, LDH elevation, lymphocyte count, expression of Ki67, Bcl-2, CD5, GCB/nonGCB phenotype (Hans method), and the expression of BAFF-R, TACI and BCMA. We expressed the results of three-year EFS and OS.
Results: BAFF-R were expressed in 22 patients (73.3%), TACI in 19 (63.3%), BCMA in 12 (40%). The median percent expression of BAFF-R was 42.5% (0−95), TACI 52.5% (0−95), BCMA 0% (0−60). Duration of EFS and OS were not significantly influenced by sex, hemoglobin, LDH level, the expression of Ki67, bcl-2, CD5. Patients with IPI score >2 had shorter EFS ($p = 0.002$) and OS ($p = 0.02$). Ann Arbor stage influenced EFS ($p = 0.013$), while had no effect on OS. Patients older than 60 years had shorter EFS ($p = 0.0026$) and OS ($p = 0.032$). Patients with baseline lymphocyte count $\leqslant 1.3$ had statistically marginal shorter EFS ($p = 0.09$) and significantly shorter OS ($p = 0.0072$). Patients with GCB subtype had longer EFS ($p = 0.05$) but GCB/nonGCB subtype had no effect on OS. Expression of BAFF-R on over 80% of cells resulted in longer EFS (100% vs. 58.8%, $p = 0.05$), and statistically marginally significance to the OS (100% vs. 63%, $p = 0.1$). Expression of BAFF-R on over 50% of cells also affects longer OS (93% vs. 53%, $p = 0.05$). TACI receptor had no effect on EFS and OS, while the expression of BCMA receptors showed also statistically marginally effect for longer EFS (84.5% vs. 56.2%, $p = 0.09$) and OS (92.1% vs. 55.9%, $p = 0.09$).
Conclusion: In addition to the standard prognostic parameters, expression of BAFF-R and BCMA receptors influence the outcome of patients with DLBCL. These results warrant further investigation.
No conflict of interest.

3634 POSTER

Causes of death of patients treated for Hodgkin's disease in young adulthood − a population based study

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Background: Survival of patients treated for Hodgkin's disease (HD) is high, but sequelae of combined treatment, chemotherapy (ChT) and radiotherapy (RT), are frequent and are important cause of morbidity. We studied causes of death in patients treated for HD at the age of 16 to 30 years.
Material and Methods: In Slovenia, 178 patients, 98 women, 89 men, were treated for HD at the age of 16 to 30 (median 24) years between 1980–1995. They have been followed for 17−32 (median 22) years.
Results: Of the 178 patients 65 died, 34 (52%) of HD. Sixteen (25%) died of late sequelae: 13 of second malignant neoplasms (SMN) 11 to 29 (median 22) years after primary diagnosis. The SMNs were: breast cancer in four, lung cancer in 2, AML, MDS, holangiocarcinoma, endometrial cancer, cancer of stomach, pancreas and head and neck cancer one each. Three patients died of cardiac cause 17 to 31 (median 30) years after primary diagnosis; one of dilative cardiomyopathy after ChT with antracycline and mediastinal RT, two of coronary artery disease after mediastinal RT. Eight patients died of other causes: brain hemorrhage, hypothermia, accident, acute pancreatitis, bronchopneumonia and suffocation (in 2). In seven patients the cause of death 1 to 6 (median 5) years after primary diagnosis is unknown, they were lost to follow-up.
Conclusions: SMN and cardiac damage are the most frequent cause of death more than 10 years after treatment for HD in young adulthood. Long-term follow-up of those patients especially in term of SMN screening and cardiac examination is evidently necessary.
No conflict of interest.

3635 POSTER

Prognostic significance of international prognostic index (IPI) individual risk factors in patients with diffuse large b cell lymphoma (DLBCL) treated with rituximab (R) and chop (R-CHOP) based chemotherapy

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Background: International Prognostic Index (IPI) was developed in the non-rituximab based chemotherapy era as predictive tool for risk stratification of aggressive non-Hodgkin's lymphoma (NHL). This model identified five prognostic factors (Table); all were individually significant for predicting survival in this population. Whether these risk factors retain their prognostic significance in Rituximab based chemotherapy era remains unclear. This retrospective analysis reviewed the ability of these individual prognostic factors to predict prognosis in DLBCL patients treated with R-CHOP based chemotherapy.
Methods: The study included 198 patients treated with R-CHOP from 8–2004 to 12–2008 at King Faisal Specialist hospital, Saudi Arabia. Demographics, presentations, stage, therapy, and IPI risk scores and survivals were collected and calculated retrospectively.

Risk factor	Value	Number	OS %	HR	LL HR	UL HR	*P*-value
Age	<60	133	68.4				
	>60	64	45.3	2.139	1.36	3.36	0.001
Performance status	0−1	146	67.8				
	⩾2	38	34.2	2.89	1.77	4.71	<0.000
Stage	I−II	75	68				
	III−IV	120	57.5	1.4	0.862	2.29	0.172
Extranodal sites	0−1	160	64.5				
	>1	31	41.9	1.95	1.15	3.32	0.014
LDH	Normal	71	71.8				
	Elevated	119	55.5	1.76	1.05	2.95	0.031

OS = overall survival; HR = Hazard Ratio; LL HR = lower limits of HR; UL HR = upper limits of HR.

Results: There were 113 males/85 females with a median age of 50 year (15−89). Median follow-up for all alive patients was 68 months (19–102), the event-free (EFS) and overall (OS) survivals were 55%, 64% respectively. Presence of any of these risk factors revealed a higher hazard of death (HR range 1.4 to 2.89). All of them except advanced stage achieved statistical significance. Lack of statistical significance (p-value=0.174) for higher stage with a HR of 1.4 is likely secondary to inadequate sample size. Details of these results are shown in Table.
Conclusion: All five IPI risk factors of IPI retain prognostic importance in R-CHOP era. Presence of any of these factors carries higher risk of death for patients treated with R-CHOP based chemotherapy. Stage III−IV failed to reach statistical significance likely due to small sample size. These risk factors remain valid prognostic indicators individually even in chemo-immunotherapy era. A larger sample is likely to validate all these risk factors in R-CHOP treated patients.
No conflict of interest.

3636 POSTER

Early stage diffuse large B-cell lymphoma treated with CHOP with or without rituximab (R): Outcome analysis according to risk stratification

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Background: Early stage DLBCL is managed either with abbreviated chemotherapy and involved field radiation (IFRT) or full course CHOP chemotherapy. After introduction of rituximab in the management of advanced DLBCL, it has been added to CHOP in management of early stage disease even when 3 cycles of chemotherapy and IFRT are used. Mabthera International Trial included a significant percentage of early stage disease and showed benefit with rituximab in early stage DLBCL, however, no prospective trial has specifically looked at addition of R to CHOP in early stage disease. We aimed to assess the outcome of early stage DLBCL with R-CHOP and compare with therapy without rituximab.
Methods: We identified a total of 168 patients with stages I & II DLBCL and collected data on international prognostic index (IPI), therapy and outcomes. The patients with 0−2 IPI factors were assigned as low risk (LR) and those with 3−4 factors were assigned as high risk (HR). Groups were analyzed to compare for survivals for treatment with CHOP vs. R-CHOP.
Results: Of 168 patients, 75 were treated with R-CHOP and 93 with CHOP alone. Data were incomplete in 19 patients. One hundred thirty eight of the 149 patients analyzed were in LR group (R-CHOP;62 and CHOP;76) while only 11 patients had HR disease (R-CHOP;5 & CHOP;6). Disease free (DFS) survival was 65% vs. 67% (p = 0.5) and overall (OS) survival was 71.3% vs. 79% ($P = 0.1$) for R-CHOP and CHOP treated groups respectively (Table). In LR group, DFS was similar in CHOP and R-CHOP treated patients, however, OS was superior in CHOP compared to R-CHOP. We explored the impact of age, disease specific death, stage I vs. II, presence or absence of hepatitis B or C, and bulky disease in order to analyze inferior survival in R-CHOP treated patients. R-CHOP treated group had significantly more patients with bulky disease: 41.3% vs. 28% in CHOP treated group ($P = 0.036$). In HR group, addition of rituximab resulted in superior DFS and OS but did not achieve significance due to small numbers.
Conclusion: Addition of rituximab to CHOP chemotherapy did not result in improved outcomes in patients with stage I & II DLBCL with 0−2 IPI risk factors. Among those with 3−4 IPI risk factors, outcomes were superior with addition of rituximab but did not attain significance due to small numbers. Lower overall survival with rituximab in low risk group may be due to adverse feature i.e. bulky disease. Further exploration is ongoing.
No conflict of interest.

	Survival (%)		*P*-value	Hazard ratio
	R-CHOP	CHOP		
Overall Survival				
Entire group	71.3	79	0.1	1.6
Low risk	73	84	0.05	1.9
High risk	40	16.7	0.19	0.4
Disease Free Survival				
Entire group	65	67	0.5	1.16
Low risk	69	72.8	0.4	1.2
High risk	40	16.7	0.3	0.5

3637 POSTER

The prognostic impact of survivin and REG1A in diffuse large B-cell lymphoma

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Background: Non-Hodgkin lymphomas (NHL) are a group of heterogeneous malignant disorders. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype and accounts for approximately 35−40% of cases. This subgroup contains different clinical entities showing different biology and clinical outcomes. Many studies have examined the prognostic and predictive value of various biological parameters in this heterogeneous entity. Several biological markers have been reported to date, some of which provide prognostic and some predictive information about the biology of these different subgroups. In this study, we studied two anti-apoptotic markers, survivin and REG 1, in DLBCL.
Material and Methods: This study included a total of 51 DLBCL.All demographic parameters, presenting symptoms, clinical and histopathological variables, treatment schemas, and responses to the given treatment were obtained from the patients' hospital records. Formalin-fixed, paraffin-embedded lymphoma tissue sections were obtained from the pathology department. The expression of survivin was evaluated according to the IRS by assessing the percentage of marked cancer cells and the staining intensity. Staining intensity was scored as 0, no staining; 1, weak; 2, moderate; and 3, intensive staining. The percentage of positive cells was rated as follows: 0, no staining; 1, less than 10% positive cells; 2, 10−50%; 3, 51−80%; and 4, greater than 80% positive cells. Scores for the percentage of positive cells and scores for expression intensities were multiplied to calculate an IRS. An IRS value of 0−6 was accepted as negative staining; a value of 7−12 was accepted as positive staining. Any case of lymphoma was considered positive for REG1A protein if more than 20% of the cancer cells were positively stained.
Results: Twenty-five (49%) patients were survivin-positive. REG1A expression was observed in 26 (51%) patients. There was no statistical difference in the five-year OS rate between survivin-negative and -positive groups or between REG1A-positive and -negative groups.
Conclusions: In our study we were unable to demonstrate the prognostic value of REG1A in DLBCL patients. Additionally, there was no association between high REG1A expression and any other patient or disease characteristics. Although the survival curves of our negative REG1A patients were better than those of positive REG1A patients, this was not statistically significant. This might be due to the small sample size and short follow-up of our lymphoma patients. Our study is the first study to evaluate the expression and prognostic impact of REG1A in DLBCL patients. Further studies with larger patient groups and longer follow-up are required to validate the expression rates and prognostic values of both survivin and specifically REG1A in DLBCL.
No conflict of interest.

3638 POSTER

Prognostic factors for overall survival in Non-Hodgkin Lymphoma: Nonlinear hazard ratio of some continuous covariates

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Background: Knowledge of prognostic factors for survival of patients with cancer is very important for the clinical management. Here we analyzed the nonlinear functional form of continuous covariates influencing the overall survival (OS) of patients with non-Hodgkin lymphoma (NHL).
Patients and Methods: We retrospectively analyzed prognostic factors (PFs) for OS in 2160 patients (pts) with NHL, treated at INEN between 1990–2002. PFs were determinate according to Cox model with P-splines.
Results: The median age was 54 years (range 14−96) and 51% were male. The majority of the pts had good performance status (73%, WHO 0−1). The Ann Arbor stage was I−II in 51%, III−IV in 49% and B symptoms were present in 38% of the pts. The hemoglobin (Hb) was low in 48%, leukocytes (WBC), lymphocytes and LDH were elevated in 17.7%, 7.7% and 60% of pts, respectively. Of all patients, 709 (32.8%) pts had died. The median survival was 61.8 months and the survival rate at 5 and 10 years was 51.2% and 41.7% respectively.
PFs identified were: age, sex, zubrod, clinical stage, Hb, leukocytes, lymphocytes and LDH. The following table shows the p-value and hazard ratio (HR). The effect of continuous covariates in the log(HR) is non-linear. The cutoff points of highest (HR >1) match the clinically defined ones, which are: age >60 yrs, Hb<12*g/dl* and LDH >240*UI/L*. Both leukocytes and lymphocytes have two higher risk breakpoints: leukocytes >3$x10^3$ and >10$x10^3$, lymphocytes <20% and >60%.
Conclusion: PFs for OS in our group of pts were similar to other reports in NHL. Age, Hb, leukocytes, and lymphocytes are relevant to OS, which showed a non-linear effect in the log(HR).
No conflict of interest.

Variables	Test of association: p-value	HR (95% CI)	Test of PH p-value
Age: non-linear	0.028	curve	0.510
Sex: male	0.009	1.23 (1.05, 1.44)	0.963
Zubrod: 2−4	<0.001	1.86 (1.57, 2.20)	0.034
Primary: nodal	0.190	0.89 (0.75, 1.06)	0.592
Clinical stage: III−IV	<0.001	1.49 (1.26, 1.76)	0.322
Symptoms: B	0.14	1.13 (0.96, 1.33)	0.610
Hb: non-linear	0.006	curve	0.959
ln(WBC): non-linear	0.038	curve	0.747
Lymphocytes: non-linear	<0.001	curve	0.031
ln(LDH): non-linear	0.089	curve	0.393

3639 POSTER

Instrumental diagnosis of bone marrow invasion by Hodgkin's disease: Is it important for therapy planning

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Purpose: In this retrospective study we try to determine how bone marrow (BM) visualisation can influence treatment decision in patients (pts) with advanced Hodgkin's disease (HD).
Material and Methods: Since 1992 in our department whole body bone marrow (BM) visualisation is a part of routine staging for pts with HD. Since that time *632 pts with advanced HD* and whole body BM survey are available for *long term (15 years) follow-up.* All visualized BM lesions were verified by biopsy or additional instrumental examinations during follow-up. All pts had histologically confirmed HD and received 4−8 cycles of MOPP-ABVD or ABVD or BEACOPP chemotherapy. In 45 pts visualised BM lesions were irradiated within 20 Gy-50 Gy (average dose 38.1 Gy). Foci of BM invasion were outside radiation fields in another 30 cases.
Results: BM invasion was revealed in 75 (11.8%) of 632 evaluated pts: 51 pts had one or two BM lesions and another 24 − multifocal BM involvement. Overall (OS) and disease free (DFS) 10 year survival in pts with BM invasion (49% and 45%) were significantly ($p = 0.026$) lower than in other 131 pts with extranodal HD (62% and 65%). In pts with only BM involvement and those with BM and other extranodal lesions OS and DFS were comparable: 50% versus 47.5% and 48.5 versus 41%. On the contrary, OS was significantly different ($p = 0.014$) in pts with 1−2 BM lesions (57%) and multifocal BM disease (26.5%).
Irradiation of BM lesions significantly improve 10 year OS ($p = 0.00005$) and DFS ($p = 0.006$) in pts with HD: from 16% to 68% and from 23% to 58.5% correspondingly. This differences are evident in subgroup of pts with 1−2 detected BM foci: 10 year OS and DFS in pts with irradiated BM lesions are 72.7% and 57.5% versus 13.5% and 25% − for pts with non-irradiated BM lesions ($p = 0.0006$ and $p = 0.054$).
Conclusion: 1. In pts with HD diagnosis and precise characterisation (extent and localisation) of BM invasion is of crucial importance for treatment planning. 2. Possible role of radiotherapy in treatment of pts with BM invasion must be evaluated in randomized trials.
No conflict of interest.

3640 POSTER

Treatment outcomes and patterns of failure in early stage unfavourable Hodgkin's Lymphoma

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Background and Purpose: To evaluate the efficacy and outcome of using 4−6 cycles of Doxorubicin, Bleomycin, Vinblastine and Dacarbazine (ABVD) chemotherapy (CTh) and involved field radiation therapy (IFRT) in the management of early stage unfavourable Hodgkin's Lymphoma.

Materials and Methods: One hundred and fifty one patients treated with 4−6 cycles of ABVD followed by IFRT were included. There were 120 (79.5%) males. The commonest histological subtype was mixed cellularity (43%). Majority had stage IIAX disease. The IFRT doses were 25.2 Gy/ 14 fractions and 34.2 Gy/ 19 fractions for adults with complete response (CR) and partial response (PR) respectively, while the doses were 19.8 Gy/ 11 fractions and 30.6 Gy/ 17 fractions respectively for children.
Results: After a median follow-up of 50 months, the 8 year progression free survival (PFS) and overall survival (OS) were 84.5% and 89.5% respectively. On univariate analysis, prognostic factors found to have significant impact on PFS were age more than 20 yrs, nodular lymphocyte predominant histology, presence of extra-nodal disease, response to primary treatment and stage. Presence of extra-nodal disease had a significant impact on OS. On multivariate analysis, nodular lymphocyte predominant histology ($p = 0.008$) and the response at 3 months after treatment ($p = 0.000$) had a significant impact on PFS while none had a statistically significant impact on OS. CTh related acute pulmonay toxicity was documented in 21.4% patients receiving 6 cycles of ABVD compared to 4.8% in those receiving 4 cycles ($p = 0.041$). Grade I and II dermatitis for patients receiving IFRT doses more than 25.2 Gy or less were 79.6% and 76% respectively, while the corresponding incidence of mucositis was 10.5% and 5.6% respectively.
Conclusion: The combination of four cycles of ABVD followed by IFRT results in optimal outcomes in terms of disease control and treatment related toxicities.
No conflict of interest.

3641 POSTER

Role of response evaluation criteria in local disease control after combined therapy of Hodgkin's lymphoma

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Purpose/Objective: Study the role of response evaluation criteria after first-line chemotherapy in the subsequent occurrence of nodal recurrence of Hodgkin's lymphoma (HL).
Materials and Methods: Four hundred thirty-nine patients with HL stage I − IV according to the Ann Arbor classification were treated with ABVD or BEACOPP or CEA/ABVD (lomustine, etoposide, adriamycine, bleomycine, vinblastine and dacarbacine) regimen chemotherapy and IFRT or EFRT or STNI radiotherapy. New, effective classification Response Evaluation Criteria in Hodgkin's lymphoma was invented in RSCRR:
– CR or PR⩾80% (adequate response);
– PR 0−79% (an inadequate response);
– Progression after first-line chemotherapy.
The estimation of Percent Response Evaluation is based on a zone with the least effect after chemotherapy. Median doses in initially involved areas were 36 Gy (0−44), in initially uninvolved areas − 0 Gy (0−44).
Results: After a median observation time of 4.1 years, according to logistic regression analysis in group 'CR or PR⩾80%' (after first-line chemotherapy) percent of nodal recurrence in initially involved areas with RT was 1.2 percent (12 of 856), in initially uninvolved areas without RT − 1.4 percent (10 of 844). Probability of nodal recurrence in initially involved areas in patients from group 'PR 0−79%' in comparison with group 'CR or PR⩾80%' was 10.2 times higher in zones with regression more than 80% (95 % CI: 11.750–50.844, $p = 0.000$), in zones with regression: 0−79% − 39.6 times higher (95 % CI: 18.348–85.380, $p = 0.000$), in initially uninvolved areas without RT − 10.2 times higher (95 % CI: 4.738–22.138, $p = 0.000$). Probability of nodal recurrence in patients with progression after first-line chemotherapy was 59.7 times higher (95 % CI: 28.898–123.408, $p = 0.000$) in comparison with 'CR or PR⩾80%' group.
Conclusions: Correct allocation of groups with 'CR or PR⩾80%' and 'PR 0−79%', after first-line chemotherapy, is extremely important for following RT planning. These approach offer wide perspectives for Hodgkin's lymphoma treatment.
No conflict of interest.

3642 POSTER

Could the association of new systemic target treatment with helical tomotherapy become the standard of treatment of solitary plasmacytoma?

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Purpose: To report the preliminary results and the tolerance profile and efficacy of the association of new systemic target treatment and Helical Tomotherapy (HT) in patients with solitary plasmacytoma. This pilot study was conducted with aim to decrease the toxicity (using HT) and improve the therapeutic results.
Patients and Methods: Five males and one woman with biologically, histologically (bone marrow biopsy) and radiological (total body bone magnetic resonance imaging (MRI) and 18 FDG PET scan) confirmed solitary plasmacytoma have been treated in our department between September 2009 and September 2011 using a concomitant HT with a systemic targeted treatment. The total dose was 40 Gy in 20 fractions. Four patients received 4 cycles concurrent lenalidomide-dexamethasone association, 1 patient was treated with concomitant bortezomib-dexamethasone and one patient was treated with bortezomib-dexamethasone and cyclophosphamide. All toxicities were described using the Common Terminology Criteria for Adverse Effects v3.0. Clinical assessment was performed weekly during RT and monthly after the end of irradiation. The evaluation MRI was realized 6 weeks and evaluation PET scan 4 months after the RT.
Results: The tolerance profile was excellent with no higher than grade 1 toxicity observed except for one patient who presented a grade 3 leucopenia related to the systemic treatment. Three patients over six underwent a partial radiological response, four had a complete TEP/FDG response and five over six patients had a complete relief of symptoms 4 months after treatment. With a median follow up of 18 months, five of six patients are controlled clinically, radiologically and biologically.
Conclusion: HT concomitant with bortezomib or lenalidomide has been used in the treatment of solitary plasmacytoma with an excellent response rate and an excellent acute tolerance profile. Longer follow-up is needed to assess the late toxicity and the rate of progression to multiple myeloma.
No conflict of interest.

3643 POSTER

Positron emission tomography guided intensity modulated radiotherapy as a fourth line treatment option for intermediate grade non-Hodgkin's lymphoma

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Background: After failure despite three lines of systemic treatments which include chemotherapy and targeted therapy, the prognosis among non-Hodgkin's lymphoma (NHL) patients is dismal. This study explores the outcomes with the use of fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) guided intensity modulated radiotherapy (IMRT) as a fourth-line treatment option among patients with intermediate grade NHL.
Material and Methods: On a retrospective review of NHL patients' hospital records (excluding stage-IV) treated in the institution from January 1 2010 to December 31 2012, a total of 26 patient records were found eligible for analysis- having been treated with IMRT to atleast 45 Gray (Gy) to the *PET-TV* (PET-treatment volume: computed by adding a 1.5 cm margin over the PET defined gross tumour volume) whilst having relapse/residual disease despite three prior lines of systemic therapies. Also, patients with a PET-TV >500cc had ben excluded from analysis. Responses were classified as per the PERCIST criteria (*Wahl RL et al, J Nucl Med 2009*). Progression free survival (PFS) and overall survival (OS) at 3 months and 6 months were noted. The computed tomography (CT) images of each patients were retrieved and *CT-TV* (CT-treatment volume, computed by adding a 1.5 cm margin over the CT defined gross tumour volume) were calculated so as to facilitate comparisons with the *PET-TV*.
Results: Complete metabolic response was achieved in 88.5% (n = 23) and partial metabolic response was achieved in 11.5% (n = 3) of patients, thus amounting to an overall response rate of 100%. The median followup was 14 months. The PFS at 3 & 6 months were 84.6% & 38.5% respectively. The OS at 3 & 6 months were 100% and 76.9% respectively. The *PET-TV* was significantly larger than the *CT-TV* in terms of mean volume (217cc vs. 126cc, $p<0.0001$; *paired samples t-test*).
Conclusions: After failure of three lines of prior systemic treatment in patients with intermediate grade non-stage-IV NHL, the use of ^{18}F-FDG-PET-guided IMRT with curative intent holds the potential to offer durable responses and meaningful survival benefits. The use of PET for target delineation ensures a more comprehensive coverage of disease foci in comparison to CT based delineation. Prospective trials to confirm these findings are justifiable.
No conflict of interest.

3644 POSTER

Nilotinib vs dasatinib in patients with newly diagnosed chronic myeloid leukaemia in chronic phase: an indirect adjusted comparison of updated 36 months follow-up of ENESTnd and DASISION trials

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Background: Prognosis for patients with Chronic Myeloid Leukaemia (CML) has evolved dramatically since the introduction of imatinib (IMT) in the market. Nilotinib (NIL) and dasatinib (DAS) are second-generation tyrosine kinase inhibitors inducing deeper molecular responses than IMT in newly diagnosed chronic-phase CML patients. Clinical trials supporting this evidence were titled ENESTnd (NIL 300 mg BID or NIL 400 mg BID or IMT 400 mg QD) and DASISION (DAS 100 mg QD or IMT 400 mg QD). In the absence of head-to-head clinical trials between NIL and DAS the present analysis performs an indirect adjusted comparison of these second-generation tyrosine kinase inhibitors using data from the recently updated 36 months follow-up of DASISION and ENESTnd trials.
Methods: Outcomes analysed were: major molecular response (MMR, $\leqslant$0.1% BCR-ABL); progression to accelerated or blastic phase (PAB); overall survival (OS); discontinuation due to adverse events (AE). The Bucher *et al*. (1999) method for indirect comparison was used to pool results from the DASISION and ENESTnd trials in order to assess NIL 300 mg BID and DAS 100 mg QD relative clinical efficacy and tolerability having IMT 400 mg QD as common comparator. Hazard ratios (HR) and odds ratios (OR) and corresponding 95% confidence intervals (95% CI) are presented for outcomes based on rates and proportions, respectively.
Results: The rate of MMR at 36 months is estimated to be significantly higher in patients CML treated with NIL compared to DAS (HR = 1.36: 95% CI [1.01; 1.85]). The odds of progression to accelerated or blastic phase with NIL is estimated to be 32% lower than in patients treated with DAS (OR=0.68: 95% CI [0.22; 2.10]). Nilotinib is estimated to reduce the risk of death from any cause by 12% relative to dasatinib (HR of OS=0. 88: IC95% [0.33; 2.31]). Discontinuation due to adverse events is also estimated to be lower with NIL treatment (OR = 0.50: 95% CI [0.21; 1.18]).
Conclusion: This indirect adjusted comparison suggests that nilotibib 300 mg BID is more efficacious and better tolerated than dasatinib 100 mg QD for the treatment of patients with newly diagnosed chronic myeloid leukemia in chronic phase.
No conflict of interest.

3645 POSTER

Low dose cytarabine with or without anthracycline in the induction treatment of elderly patients with acute myeloid leukemia

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Background: AML is disease of elderly with overall survival (OAS) less than 12 months despite improved supportive care and novel agents due to both host and disease biology that affect the ability to tolerate chemotherapy. Standard remission induction therapy achieve complete remission (CR) rates 40% in older AML adults at a price of a high treatment-related mortality that approaches 25%.
Aim: Comparing the outcome of low dose Cytarabine (LDAC) plus Doxorubicin versus LDAC in elderly AML patients.
Methods: This is a prospective randomized trial where 90 patients with de novo AML aged $\geqslant$60 years, ECOG Performance status $\leqslant$2, left ventricular ejection fraction $\geqslant$60%, adequate liver & renal function were randomized to receive induction either with LDAC 20 mg/m^2 s.c. D1−14 (arm 1) or with LDAC 20 mg/m^2 s.c. D1−14 + Doxorubicin 25 mg/m^2 i.v. D1−2 (2+14 regimen) (arm 2), Patients who achieve CR in both groups received consolidation therapy in the form of three more cycles of the induction regimen 2+14 regimen, with 45 patients in each arm, with a 1ry end point of CR, OAS and 2ry endpoints of quality of life, hospital admission for blood product transfusions. NCCN response criteria were used to define response to induction therapy, toxicity was recorded according to WHO criteria.
Results: Patients characteristics were evenly matched with higher RR 53.4% in arm 2, compared to 26.6% in arm 1 with higher CR 7 (15.6%) patients in arm 2 compared to 2 (4.4%) patients in arm 1 p = 0.027, toxic early death was 2.2% in arm 1 compared to 11% in arm 2, regarding toxicity neutropenia was higher in arm 2 with grade 3 in 66.7%, grade 4 in 33.3% compared to arm 1 where 46.7% had grade 2, 42.2% grade 3, 11.1% with grade 4. The median survival for arm 2 was 9 months, compared to 6 months in arm 1 after a follow up period of 24 months. There were significant reduction in the number of patients who were admitted to the hospital for blood transfusion 8 (17.7%) patients in arm 2 compared to 27 (60%) patients in arm 1. Significantly shorter admission duration for transfusion in favor of arm 2 P<0.001.
Conclusion: We met the 1ry end points with a higher CR and longer OS with the 2+14 arm 2 regimen compared to LDAC arm 1 with improvement in quality of life in form of reduction in hospital admission for blood transfusion.
No conflict of interest.

3646 POSTER

Effects of haematopoietic stem cell transplantation on clinical presentation of bloodstream infections in neutropenic patients with haematological malignancy

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Background: Febrile neutropenia (FN) is a serious adverse event in patients with haematological malignancy (HM). Haematopoietic stem cell transplantation (HSCT) may affect the presentation and outcomes of bloodstream infection (BSI) in neutropenic HM patients. We investigated the clinical characteristics and outcomes of BSI in these patients on the basis of their HSCT history.
Patients and Methods: We retrospectively reviewed the medical records of FN patients with positive blood cultures at the National Cancer Center Hospital from January 1, 2008 through March 31, 2012. Patients with possibly contaminated cultures were excluded and logistic regression analysis was used to identify factors associated with mortality.
Results: In total, 203 microorganisms were identified in 192 patients (acute myeloid leukaemia, 85; malignant lymphoma, 47; acute lymphocytic leukaemia, 18; and myelodysplastic syndrome, 14) including 70 post-transplant (PT) and 122 non-transplant (NT) patients. The proportion of patients aged <60 years (p <0.01) or with FN duration $\geqslant$10 days (p = 0.01) was significantly higher among PT patients than NT patients. The ratio of Gram-positive cocci to Gram-negative rods (PT, 2.5; NT, 1.5) was comparable between the groups, however, and coagulase-negative staphylococci were the leading pathogens (PT, 32%; NT, 25%) in both groups. Oral mucositis and catheter-related infections were most commonly associated with suspected bacterial entry in PT and NT patients, respectively. Thirty patients died from infections within 30 days of BSI onset with PT patients exhibiting a higher mortality rate (p = 0.10). The mortality rate was significantly higher among PT patients with acute myeloid leukaemia than their NT counterparts. Nine of 37 such PT patients died (24%) compared to three of 48 such NT patients (6%) (p = 0.03). Death-related factors identified in univariate analysis included lower Multinational Association for Supportive Care in Cancer (MASCC) scores (p <0.01), no antacid use (p = 0.02), altered mental status (p <0.01), higher serum total bilirubin (p <0.01) or creatinine (p <0.01) levels, lower serum albumin levels (p <0.01), tachycardia (p <0.01), intensive care unit stay (p <0.01), longer duration between pathogen detection and the onset of neutropenia (p = 0.04), higher European Cooperative Oncology Group performance status (p = 0.03) and steroid (p <0.01) or vasopressor use (p <0.01). Multivariate analysis identified lower MASCC scores (p <0.01; odds ratio [OR] = 1.29; 95% confidence interval [CI]: 1.12–1.49), altered mental status (p <0.01; OR = 8.06; 95% CI: 2.61–24.9) and use of vasopressors (p <0.01; OR = 1.03; 95% CI: 2.22–47.6) as independent mortality predictors.
Conclusion: The clinical presentation of BSI in FN patients with HM may be affected by HSCT history and several risk factors were identified associated with fatal outcomes. Identification of high-risk patients, suspicion of BSI in FN patients and early appropriate therapy will be required to improve mortality rates associated with these infections.
No conflict of interest.

3647 POSTER

Evaluation of safety, tolerability and efficacy of Temsirolimus in patients with relapsed or refractory mantle cell lymphoma (rel/refr MCL) in routine clinical practice

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Background: Temsirolimus (TEMS), an mTOR-inhibitor, is approved the EU for the treatment of patients (pts) with relapsed or refractory (rel/refr) MCL A pivotal study demonstrated significantly longer progression free survival with TEMS (175 mg weekly for 3 weeks followed by 75 mg weekly) in rel/refr MCL pts compared to investigator's choice therapy (4.8 mo vs 1.9 mo; P =. 0009). To evaluate safety and efficacy of TEMS in an

unselected patient population during clinical routine, a prospective non-interventional study with TEMS in rel/refr MCL pts is useful. Here we report on interim results of the study.
Methods: A German multicenter registry for rel/refr MCL pts treated with TEMS was started in Oct 2009 (NCT00700258). Objectives are evaluation of the safety profile of TEMS, tolerability and anti-tumor activity of TEMS, patients' profile and the sequence of systemic therapies.
Results: From Oct 2012 to Mar 2013, 12 active centers recruited 29 pts. Baseline characteristics are available for 29 pts: 72.4% male; median age 73.0 yrs; ECOG PS 0 or 1 in 79.3%, ECOG PS 2 in 20.7% of the pts; MIPI score: 20.7%, 27.6%, and 51.7% of the pts are classified as low, intermediate and high risk at the time of enrollment, bone marrow involvement: 44.8% of the pts. Median time between diagnosis and start oft treatment with TEMS is 3.1 yrs. The median number of prior therapies is 5 with 65.5% treated in $\geqslant 5^{th}$ line. Most common adverse events are thrombocytopenia, anemia and diarrhea. Severe adverse events (drug related) are general, metabolic, psychiatric disorders and infections, skin and renal/urinary disorders (in 2 pts each).
Efficacy analyses are available for 21 of 27 patients and show an objective response in 5 pts (1CR and 4 PR,18.5%), a clinical benefit in 13 pts (48.1%) and PD in 8 pts (29.6%). Median PFS is 4.1 months.
Conclusions: This registry was started to evaluate the safety and efficacy of TEMS in pts with rez/refr MCL in the clinical routine. Though the here included pts are more heavily pretreated, TEMS shows a predictable, manageable tolerability profile and efficacy remains comparable with phase III data.
Conflict of interest: *Advisory board: M. Dreyling, G. Hess. Corporate-sponsored research: M. Dreyling, G. Hess. Other substantive relationships: Honoraria: G. Hess, M. Dreyling. Employment or leadership position: G. Krekeler C. Herzberg, D. Kalanovic*

3648 POSTER

Multiple myeloma with light chain-induced acute renal failure − role of bortezomib-dexamethasone & cyclophosphamide-thalidomide & dexamethasone: A prospective randomized study

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Background: We prospectively compared Cyclophosphamide, Thalidomide and Dexamethasone (CTD) with Bortezomib and Dexamethasone (BD) as induction therapy for patients of Multiple Myeloma (M.M.) with light chain induced renal insufficiency (RI).
Methods: Between February 2011 and September 2012, 43 patients (median age=56 years; range 40−77 years) received either oral Cyclophosphamide 100 mg/m^2 for 7 days, Thalidomide 100 mg daily &oral dexamethasone 40 mg/wk q 4 weekly (n = 21) or Inj. Bortezomib 1.3 mg/m^2 iv and oral dexamethasone 40 mg both weekly q 4 weekly (n = 22). Patients were assessed for renal and myeloma response as per International Myeloma Working Group Criteria. Analysis was done as intention to treat.
Results: Major renal response (CR+ PR) was observed in 58.8% of patients in CTD arm & 45% in BD arm, respectively, p = 0.14. There was a trend for early renal response in BD arm. Major myeloma response was seen in 52.9% in CTD & 80% in BD arm, p = 0.44. 5 out of 11 patients became dialysis free after treatment.

Table 1. Renal & myeloma responses in study group

	CTD Arm (n = 17)	BD arm (n = 20)	p value
Renal response			0.32
CR	5 [29.4%]	5 [25%]	
PR	5 [29.4%]	2 [10%]	
MR	3 [17.6%]	8 [40%]	
Median time to renal response (days)	88 (31–153)	69 (30–125)	0.43
Myeloma response			0.11
CR	5 [29.4%]	5 [25%]	
PR	4 [23.5%]	11 [55%]	
SD	8 [47.1%]	4 [20%]	

Toxicity was not significantly different between two arms. Anemia was commonest hematological toxicity; 23% in CTD & 15% in BD. Non-hematological toxicities included- constipation (53%) in CTD and diarrhea (30%) in BD arm. On Univariate analysis − serum LDH >250 U/L (CTD Arm) was associated with inferior renal response, p = 0.009 & bone marrow plasma cells >40% was associated with inferior myeloma response, p = 0.002. Serum LDH >300U/L was associated with inferior myeloma response in BD arm, p = 0.008. A total of 11 patients died, 6 within 8 weeks of accrual. Patients with ECOG performance status $\geqslant 3$ (p < 0.008) and requirement for dialysis (p < 0.004) were at high risk for early mortality. At a median follow up of 7.5 months, 13 patients are alive in CTD and 16 in BD arm.
Conclusion: Renal and myeloma responses were comparable in CTD and BD arm in present study.
No conflict of interest.

3649 POSTER

Impact of active surveillance, chlorambucil and intensive chemo and immunotherapy on health related quality of life in patients with chronic lymphocytic leukemia in the Netherlands

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Background: In the Netherlands, each year, more than 700 patients are diagnosed with Chronic Lymphocytic Leukemia (CLL), 70% of them is older than 65 years. Survival time is highly variable (from a few months up to decades), but as response rates improve, the number of CLL patients that live long after their diagnosis is rising. This underpins health related quality of life (HRQoL) as a relevant endpoint. Few studies have investigated HRQoL in CLL patients, and most were randomized clinical trials. As a consequence, patients with early stage CLL, elderly patients and patients with comorbidities were underrepresented. The aim of the present study was therefore to assess HRQoL in a population-based setting that includes these previously underrepresented patients.
Methods: 175 patients diagnosed with CLL between 2004 and 2011 and registered in the Eindhoven Cancer Registry received a questionnaire regarding HRQoL (which included the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)). 136 of them responded (78%).
Detailed data on stage, treatment and adverse events were collected within the scope of the Population-based HAematological Registry for Observational Studies (PHAROS); an extension of the Netherlands Cancer Registry.
The outcomes were compared to an age-and sex-matched norm population. Analysis of covariance (ANCOVA) was carried out to investigate the differences in HRQoL between types of treatment and between patients on and off treatment after adjustment for sex, age and comorbidity.
Results: Patients treated for CLL reported significantly worse HRQoL than the norm population (p < 0.01 and clinically important differences (CID)), while no difference was observed between the norm population and patients under active surveillance.
We saw more and larger differences between patients treated with chlorambucil and patients under active surveillance than between patients treated with other chemo- and/or immunotherapy and those under active surveillance.
Both patients on and off treatment scored worse on all functional scales (except cognitive functioning), fatigue and sleeping problems compared to the norm population (p < 0.01 and CID). Cognitive functioning was the only scale on which patients on treatment reported statistically and clinically important worse scores than patients off treatment.
Conclusion: Since starting treatment in CLL patients has a drastic and long-lasting effect on HRQoL, it seems wise to be restrained in starting treatment, especially in asymptomatic patients, despite the recent success in prolonging survival.
No conflict of interest.

3650 POSTER

High expression of Bcl-2 predicts poor outcome in diffuse large B-cell lymphoma (DLBCL) patients (pts) treated with CHOP-based chemotherapy

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Background: We evaluated the prognostic significance of apoptosis-related proteins in DLBCL pts treated with cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) chemotherapy with or without rituximab (R).

Methods: Pretreatment tumor biopsy specimens from 111 pts (stage I: 15, II: 29, III: 34, IV: 33 pts) with DLBCL were analyzed for Bcl-2, Bcl-6, Topoisomerase-II (Topo-II), β-tubulin and p53 proteins expression by immunohistochemistry. Thirty-nine pts were treated with CHOP regimen, while 72 pts with R-CHOP.
Results: The median follow-up duration was 77 months (14–136 months) in survivors. In univariate analysis, 5-year OS of pts with high expression of Bcl-2 was significantly inferior compared to that of pts with low expression (42% vs 72%, $p = 0.0013$). In addition, high expression of Bcl-6 ($p = 0.296$), p53 ($p = 0.775$), Topo-II ($p = 0.588$) and β-tubulin ($p = 0.627$) was not associated with outcome of pts. In terms of chemotherapy regimen, high expression of Bcl-2 was associated with poor outcome in R-CHOP group ($p = 0.007$), without significant correlation in CHOP group ($p = 0.264$). In multivariate analysis, high expression of Bcl-2 was a significant independent prognostic factor of poor OS ($p = 0.023$) along with high International Prognostic Index (IPI) score ($\geqslant 3$) ($p < 0.006$) in R-CHOP group. Furthermore, in pts with low IPI score ($n = 71$), high expression of Bcl-2 correlated with poor outcome both in all pts ($p = 0.021$) and R-CHOP group ($p = 0.042$) without significant association in high IPI score pts ($p = 0.253$).
Conclusions: High expression of Bcl-2 may be a useful prognostic factor in DLBCL pts treated with R-CHOP, especially in cases of low IPI score.
No conflict of interest.

3651 POSTER

Prognostic relevance of follicular lymphoma international prognostic index (FLIPI) in Korean follicular lymphoma patients: Comparison of FLIPI and FLIPI2

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Introduction: Follicular lymphoma (FL) is one of the most common types of Non-Hodgkin's lymphoma (NHL) among mature B cell neoplasm. The incidence of FL in Korea showed increased frequency. Prognostic index with validity and reproducibility is essential to plan a treatment strategy and mange patients with FL because of its heterogeneity and diverse clinical course. Follicular Lymphoma International Prognostic Index (FLIPI) was first introduced, and FLIPI2 using easily accessible clinical data was newly developed after rituximab-era. Even if there are several studies validating the FLIPI or FLIPI2 for FL, all of the studies were performed using western populations. It is still necessary that validation of FLIPI and FLIPI2 in Korean population where the epidemiology of FL is somewhat different with that of western countries.
Method and Materials: We aimed to evaluate the validity the FLIPI and FLIPI2 on our retrospective cohort of patients with FL. From 1995 to 2012, we collected clinical data for scoring FLIPI and FLIPI2 in Samsung Medical Center, Korea. We stratified patients as three categories according to FLIPI or FLIPI2 scores: low-, intermediate-, and high-risk group. Distribution of each parameter based on risk groups was analyzed. And we searched relevant factors in respect to patients' outcome. Finally Progression-free survival (PFS) and overall survival (OS) were estimated between three groups using Kaplan–Meier curve to evaluate the role of FLIPI/FLIPI2. If there is any statistical significance between any groups, we planned to discriminate which group has statistical significance on survival among three groups.
Results: Total number of target population was 125 patients. Median follow-up duration is 5.1 year (1.3–13.9). Median age was 53 years old. Using FLIPI score, 71 patients (56.8%) were in LR group, 27 patients (21.6%) in the IR group, and 27 (21.6%) in the HR group. In terms of FLIPI 2, 36 patients (28.8%) were in LR group, 39 patients (31.2%) in the IR group, and 12 patients (9.6%) in the HR group. 38 patients were unknown due to unavailable data of 38 patients. Using FILIPI, there was significant longer PFS and OS in LR group compared to IR or HR group ($p < 0.0001$). However, neither PFS nor OS showed statistical difference between IR and HR group ($p = 0.472$ and 0.648, respectively). In terms of FLIPI 2, there were same statistical patterns as in FLIPI, LR group was shown to have longer duration of PFS and OS compared to those of IR group ($p = 0.001$ and 0.025, respectively). There was no statistical difference between IR and HR group, either ($p = 0.41$ and 0.49, respectively). Whether patients received rituximab-based chemotherapy or not was not found to be responsible for discriminating power of FLIPI/FLIPI2.
Conclusions: Based on our study, FLIPI and FLIPI 2 are likely to discriminate LR patients from higher risk populations. However, stratification of IR and HR group is shown to be somewhat ambiguous, suggesting that FLIPI/FLIPI2 has limited role of discriminating patients with or without HR in Korean populations.
No conflict of interest.

3652 POSTER

Efficacy and safety of cladribine: Subcutaneous versus intravenous administration in hairy cell leukemia

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Background: Hairy cell leukemia (HCL) is rare B-cell lymphoproliferative disorder. Its treatment has evolved from splenectomy with time to failure (TTF) of 19 months to Cladribine that increased complete remission (CR) rate to 90%, with only small percentage of patients relapsing at 30 months. Cladribine (CDA) is originally administered intravenously as continuous infusion for 7 days; Subsequently, it was administered subcutaneously. This study aims at comparing efficacy and toxicity of Subcutaneous (SC) versus Intravenous (IV) administration of CDA in treatment of HCL.
Material and Methods: This retrospective study included HCL patients presented to National Cancer Institute and Nasser Institute, Cairo, Egypt, during period 2004–2010. Included patients received CDA as 1st or 2nd line with minimum follow up of 12 months. All files were reviewed for baseline clinical & laboratory parameters, route of administration, response, adverse events and survival.
Results: This study included 49 eligible patients, 41 patients received CDA as 1st line treatment, while 8 patients as 2nd line. Eighteen patients were treated by continuous IV infusion whereas 31 patients by SC injections. Both groups were comparable regarding baseline clinical and laboratory parameters with no statistically significant difference. At median follow up period of 33.5 months, complete remission rate was 94% in IV group versus 97% in SC group ($p = 0.691$); median TTF for IV group was 52.9 months while that for SC group was not reached ($p = 0.035$). The median time to achieve CR in both arms was similar. By analyzing different factors affecting TTF using multivariate analysis, route of administration proved to be the only statistically significant factor ($P = 0.006$). Regarding adverse events, there was no difference between both groups in hematological toxicities. IV route was associated with a significant higher incidence of mucositis ($p = 0.02$) and viral infections ($p = 0.01$). Hepatotoxicity and neurotoxicity were higher in SC group but difference was not statistically significant.
Conclusions: SC administration of cladribine is an alternative route to IV in treatment of HCL with similar response rate, longer time to treatment failure and better tolerability.
No conflict of interest.

3653 POSTER

Combination immunotherapy of indolent B-Cell non-Hodgkin's lymphoma (B-NHL) with R-CHOP regimen and recombinant interleukin-2 (rIL-2) "Roncoleukin®"

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Background: rIL-2 is the potential agent capable to increase the affect of rituximab in the treatment of indolent CD 20+ B-NHL, which is conformed in a number of pre-clinical and phase 2 clinical trials. However, this issue remains under investigation. The goal of the present study is to evaluate the effect of rIL-2 on the R-CHOP regimen in the first line treatment of indolent B-NHL.
Material and Methods: 39 patients with indolent B-NHL (9 low-grade follicular NHL, 20 lymphocyte NHL, 10 mantle cell NHL) were randomized ether in the group of R-CHOP or R-CHOP in combination with rIL-2. All patients had indications for treatment. 19 patients were treated with standard R-CHOP regimen (rituximab, vincristine, doxorubicin and prednisolone) and 20 patients received R-CHOP in the combination with rIL-2. Patients received rIL-2 at a dose of 0.5 MIU s.c. twice a day during days 1 to 5 or 1 MIU s.c. once a day during days 1 to 5. The primary and point of the study was progression-free survival (PFS).
Results: R-CHOP plus rIL-2 combination therapy was safe and generally well tolerated. The median follow-up in the R-CHOP and R-CHOP plus rIL-2 groups was 33.9 (range, 0.3−73.6) and 34.7 (range, 1.0−74.0) months, respectively. In each group 10 patients experienced clinical progression. The median survival in R-CHOP group was 31.2 months and 27.0 months in R-CHOP with rIL-2. The 5-year PFS rate was 38.0% and 36.5%, respectively.
Conclusion: The combination of R-CHOP and rIL-2 in the first line treatment of indolent B-NHL does not improve PFS.
No conflict of interest.

3654 POSTER

Combination of bendamustine and rituximab as salvage therapy for patients with relapsed or refractory chronic lymphocytic leukemia: Experience of single center in Russia

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The patients with fludarabine-refractory chronic lymphocytic leukemia (CLL) have short survival and limited treatment options. Refractory CLL is characterized a high incidence of unfavorable molecular and clinical features. Moreover these patients are also severely immunosuppressed and experience a high rate of infectious complications. Bendamustine is an alkylating agent with high activity against CLL and excellent tolerability. Several limited studies have shown encouraging results have been obtained using combination of bendamustine plusrituximab (BR) in patients with refractory CLL.

The aim of this study was to evaluate safety and clinical efficacy of combination BR in patients with relapsed and/or refractory CLL.

Patients and Methods: Twenty patients (15 males, 5 females) with relapsed and/or refractory CLL were included in this study during 01–09.2012. Seventeen (85%) patients received BR: bendamustine 90 mg/m^2 i.v.on days 1 and 2 combined with rituximab 375 mg/m^2 on day 0 of the first course (cycle 1) and 500 mg/m^2 during subsequent courses (cycles2−6). The doses of bendamustine were increased from 70 mg/m^2 to 90 mg/m^2 compared with previously published studies (Fisher K., et al.J Clin Oncol., 2011). Bendamustine only was administered at a dose of 100 mg/m^{2}on days 1 and 2 every 28 days in 3 (15%) cases of known resistance to rituximab.Treatment was planned for 6 cycles. The efficacy of treatment was assessedaccording to the guidelines International Working Group criteria for CLL.

Results: Median age of patients was 63.4 years (range, 52−77). Binet stage B was diagnosed in 10 (50%) of patients, stage C − 10 (50%). In 2 (10%) cases was documented del17p. Seven (35%) have relapses, that were sensitive to the last line of therapy, and13 (65%) were refractory. A median duration of history of CLL was 6.1 years (range, 1.3 to 12.3 years). The median number of lines of previous therapies was 2 (range, 1−6). The majority of patients previously received fludarabine − 15(75%), rituximab in combination with chemotherapy − 17 (85%) and as maintenance therapy − 9 (45%). The best response to previous therapy was complete response (CR) for 5 (25%), and partial response (PR) − 8 (40%), and stable disease (SD) − 5 (25%). Two (10%) patients were refractory to all previous treatments. With median follow-up time of 5.6 months of therapy with bendamustine all patients were alive. A median number of BR cycle were 4 (range, 2−6). The treatment response was assessed for 17 patients: ⩾ PR achieved 9 (53%), and only SD − 6 (35%). None of toxic deaths were reported. The key grade 3/4 toxicities were neutropenia − 5 (25%), anemia − 3 (15%), thrombocytopenia − 3 (15%) and infection − 1 (5%). Probability of achieving ⩾ PR was higher in patients who received less 3 lines of previously therapy ($r = 0.67$; $p = 0.004$) and in the case of relapse against refractory ($r = 0.61$; $p = 0.01$).

Conclusion: Combination of bendamustine plus rituximab is effective salvage treatment for relapsed or refractory CLL afterfludarabine-containing regimens.

No conflict of interest.

3655 POSTER

Brentuximab vedotin (SGN-35) in Hodgkin's lymphoma patients with relapsed after autologous peripheral blood stem-cell transplantation

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Background: Approximately 15 to 30% of patients with Hodgkin's lymphoma (HL) do not have a long-term remission with conventional therapy. Autologous peripheral blood stem-cell transplantation (APBSCT) represents a potentially curative treatment for some patients with recurrent or progressive HL after failure of initial combination chemotherapy. Unfortunately, APBSCT is only effective in approximately 50% of such patients. Brentuximab vedotin comprises an anti-CD30 antibody conjugated by a plasma-stable linker to the potentantial microtubule agent, monomethyl auristatin. Brentuximab vedotin selectively induces apoptotic death of CD30+ cells.

Methods: We evaluated the efficacy and safety of brentuximab vedotin in patients (pts) with relapsed HL after APBSCT. Pts received brentuximab vedotin1.8 mg/kg q3 weeks (wks) as a 30 minute out patient IV infusion for upto 16 cycles. The primary endpoint was the objective response rate (ORR) and toxicity.

Results: Ten pts were enrolled; eight pts were male and median age was 26 yrs (range, 22−30 yrs). Pts had received a median of 4 (range 3−5) prior cancer-related systemic therapies excluding APBSCT. Fifty percent of pts had primary refractory disease and 80% had not responded to their most recent prior therapy. We evaluated all pts every three cycles. After 6 cycles of therapy, tumor regression occurred in 80% of patients and the overall objective response rate was 80% (n = 8), with partial remissions (PRs) in 7 pts. and complete remissions (CRs) in 1 pt. The most common treatment-related adverse events (AEs) of any grade were alopecia, abdominal pain, fatigue, insomnia and diarrhea. AEs ⩾ grade 3 occurred in ⩾60% of pts were fatigue, insomnia artralgia and diarrhea.

Conclusions: With manageable AEs, single-agent brentuximab vedotin induced objective responses in 80% of pts with relapsed HL after APBSCT. Brentuximab vedotin is effective in the early period of treatment. This agent can be considered as a method of bridge treatment prior allogeneic stem cell transplantation.

No conflict of interest.

3656 POSTER

Thyroid lymphomas − a study of 32 cases from a single centre

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Background: Extra nodal involvement in Non Hodgkin's lymphoma (NHL) can occur in around 25−30 % of cases. But thyroid as an extra nodal site is rare. Here we present our experience with this disease.

Aim: To study the presentation, treatment and survival of patients with NHL of the thyroid gland.

Materials and Methods: Thirty two patients with NHL of the thyroid was seen and treated by us at Regional Cancer Centre, Trivandrum, India during the period 2000–2009. The clinical and treatment details of these patients were analysed and survival data collected.

Results: Among 32 cases, there were 16 males and 16 females. The median age at presentation was 62 years (range 31−77 yrs). The predominant symptoms were swelling of the neck (26), stridor/ dyspnoea (16), and hoarseness (5). The median duration of symptom was 4 months. Lymph nodes of the neck was palpable in 9, and 2 had B symptoms. Bone marrow was positive in 2 cases. The Ann Arbor stage was I in 19, II in 9, III in 2, and IV in 2. The histopathology subtypes were Diffuse Large B cell in 12, MALT in 4, follicular large cell in 3, diffuse mixed in 2 and one each of marginal zone, burkitt and the subtype was not specified in 9 cases. Two patients had NHL in association with Hashimoto's thyroiditis and papillary carcinoma of thyroid. CD20 was positive in 23 cases. Twenty nine patients received treatment, 11 had surgery and chemotherapy, 7 surgery alone, 5 had chemotherapy along with radiation, 3 had chemotherapy alone and 1 radiation alone. Three patients received all 3 modalities. Chemotherapy consisted of combinations of cyclophosphamide, doxorubicin or mitoxantrone, vincristne and prednisolone. Ten patients underwent total thyroidectomy, and 6 subtotal thyroidectomy. Radiation dose ranged from 35−40 Gy. Median survival was 36 months.

Conclusions: NHL thyroid is a disease of the elderly, predominantly of diffuse large B cell subtype and needs multimodality management.

No conflict of interest.

3657 POSTER

Impact of rituximab and IPI on survival in diffuse large B cell Lymphoma (DLBCL) patient treated at tertiary cancer center of Pakistan

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Background: International prognostic index (IPI) is a tool to predict overall survival and response to treatment in DLBCL. Anti CD 20 Rituximab has a significant impact on survival in patient with DLBCL. The objective of this study is to determine the impact of rituximab and IPI on survival in patient with DLBCL treated at our institution.

Method: 93 patients with DLBCL registered from 2007 to 2010 were included and data was reviewed retrospectively. Their base line IPI score,

stage at presentation and type of chemotherapy i.e. CHOP (Group 1) and R-CHOP (groups 2) were recorded.
Results: Median age was 43 years (range 18−76), with predominantly males 58%. Stage at presentation was Stage-I 15.1%, stage-II 44.1%, stage-III 21.5% and Stage-IV 19.4%. IPI risk categorization, low risk (63.4%), low intermediate risk (24.7%), high intermediate risk (10.8%) and high risk (1.1%). Thirty-one (33%) patients were treated with CHOP chemotherapy and 62(67%) patients with R-CHOP.
Median Survival for all patients not reached. Kaplan Meir estimated overall survival (OS) at 4.5 years in both group was 56%. At 4.5 years, OS for group 1 and group 2 are 45% and 66%, respectively. The difference in OS was statistically non-significant (p = 0.4). At 4.5 years, OS for Low, Low intermediate and high intermediate risk group were 69%, 54% and 15%, respectively and it was statistically significant with p-value of 0.000.
Conclusion: Rituximab had non statistical significant impact on survival in our patients that could be due to small sample size more over most patients belong to low risk group. We merit future controlled trial to assess the effect of Rituximab in our population. However, IPI risk categorization has statistical significant impact on survival in our study.
No conflict of interest.

3658 POSTER

Clinical features and outcome of relapsed refractory aggressive peripheral T-cell lymphoma − a ten-year study from a single institute in India

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Background: Relapse or progression is a major determinant of outcome despite initial response to therapy in aggressive peripheral T-cell NHL (PTCL). We analyzed the clinical features and outcome to second-line therapy of patients with aggressive PTCL.
Methods: Medical records of patients with relapsed or refractory aggressive PTCL registered at our institute from Jan 2002 to June 2011 were retrieved and reviewed for demographics, clinical manifestations at relapse, imaging findings, treatment and outcome.
Results: The median age of the cohort of 65 patients, male/female ratio of 3.6:1, was 45 years (range: 1−86 yrs). Baseline histopathological diagnosis comprised of PTCL-NOS (n = 27), ALK +ve ALCL (n = 3), ALK-ve ALCL (n = 7), AITL (n = 4), NK/T-cell (n = 4), SPTCL (n = 2) and T-NHL-unspecified (n = 18). Complete remission to first-line therapy was achieved in 39 (60%) patients. The median duration of CR was 4.9 months (range 1.2−80 months). Twenty-nine patients (46.7%) had 'B' symptoms at progression/ relapse. Lymph node involvement was present in 41 (67.2%). Extranodal site of disease was detected in 34 (55.74%). The commonest site of extranodal disease was skin (n = 10). Liver and spleen involvement was present in 13 (20%) and 16 (24.6%). Forty (61.5%) received second-line therapy, common regimes being MINE (n = 10), ICE (n = 7) and DHAP (n = 7). Complete remission was achieved with salvage therapy in six, 12 had PR and one had stable disease. Ten patients progressed at various periods during therapy. Autologous transplant was done in five patients; four are alive without disease and one died of progression. A total of 22 patients (33.9%) died due to disease progression and 8 are alive. Ten patients were lost to follow- up. Median EFS was 9.9 months. None of the clinical factors (age, sex, 'B' symptoms, extranodal or bulky disease) or laboratory parameters (hemoglobin, albumin, LDH) were significant to predict EFS.
Conclusion: The most common diagnosis for relapse/progression was PTCL-NOS. The median duration of CR prior to relapse was 4.9 months and median EFS was 9.9 months. Complete remission rate with salvage therapy was 9%. None of the clinical or laboratory parameters could predict event free survival.
No conflict of interest.

3659 POSTER

Ifosfamide, methotrexate, and etoposide (IMVP) as a salvage therapy for transplant-ineligible aggressive non-Hodgkin lymphoma patients − long term surveillance

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Background: Conventional salvage regimens without high dose therapy (HDT) with platinum- containing regimens, are associated with poor long-term disease control and significant toxicity in relapsed aggressive lymphoma.
Long-term results of gemcitabine and oxaliplatin +/− rituximab as salvage treatment, showed continuous relapses without a clear plateau on survival curves. Results were particularly disappointing in non − Rituximab cohort (42 mts. FFS and OS, 7% and 7%) (Corazzelli G. et al., 2009).
Due to contradictory reports on the outcomes of IMVP regimen (ifosfamide, methotrexate, and etoposide), the aim of study was to evaluate retrospectively the results of long term surveillance of those patients in our institution.
Patients and Methods: Patients with refractory/relapsing aggressive B-cell lymphoma (16 diffuse large B cell and 5 follicular G III), were treated with IMVP regimen (ifosfamide 1000 mg/sqm, d 1. − 5., methotrexate 30 mg/sqm, d. 1. and 5., etoposide 100 mg/sqm, d. 1. − 3.), q 21 d., G-CSF (ESMO guidelines).
Major endpoints of the study were: response to therapy (RR) and time to progression (TTP).
Results: From April 2007 y. to January 2013 y., twenty one (21) patients were enrolled: M = 28.6%, F = 71.4%, median age 63. y. (range, 47. − 78.); clinical stages II = 23.8%, III/IV = 76.2%; previous chemotherapy lines 1= 61.9%, 2= 38.1%; PS ECOG 0 = 23.8%, 1= 61.9%, 2= 14.3%; relapse = 85.7%, refractory = 14.3%.
Overall (RR) and complete response (CRR) rates were 66.6% and 4.7%.
At 59 months, median time to progression (TTP) was 11 months (95% CI), respectively, with curve plateau forming.
76 cycles of therapy were delivered with median 3.6 cycles (range: 1−6).
Grade 3/4 toxicities were rare and manageable. One episode of granulocytopenia gr. IV, one episode of trombocytopenia gr. III (WHO), and one episode of non − hematological toxicity, mucositis gr. III (WHO), were recorded.
Conclusions: IMVP regimen is to be considered as an alternative for transplant-ineligible patients with refractory/relapsing aggressive B-cell lymphoma.
Our proposition is to 'restart' IMVP +/− Rituximab in a randomized study.
No conflict of interest.

3660 POSTER

Phenotyping TILs in situ: Automated enumeration of FOXP3+ and CD69+ T cells in follicular lymphoma

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Background: In many cancers, tumor-infiltrating lymphocytes (TILs) indicate levels of tumor immunogenicity and predict survival. In particular, increased levels of regulatory T cells (Tregs) are associated with poorer prognosis, whilst CD69+ T-cells may also be prognostic. Understanding the phenotype and pattern of TILs in situ within tumors would be advantageous. However, visual TIL assessment cannot easily determine the type of lymphocyte in situ and multimarker quantitation is difficult with standard methods. We present a multi-marker, computer-aided event-counting method for determining the phenotypes of lymphocytes in follicular lymphoma using a multispectral imaging (MSI) automated tissue segmentation and counting approach.
Material and Methods: A tissue microarray containing follicular lymphoma (FL) cores from 70 patients was chromogenically immunostained for CD3, CD69 and FOXP3, counterstained with hematoxylin, of which 40 cores were informative for both triplex staining and clinical follow-up. Each core was imaged using MSI and the individual staining of each marker separated from each other using spectral unmixing. Images were analyzed using software trained to recognize different tissue compartments based on morphology, specifically based on CD3 rich (extra-follicular) and poor (intra-follicular) areas. The FOXP3 or CD69 status of each CD3+ TIL was then determined and number Treg (FOXP3+/CD3+) and CD69+ T-cells counted in the intra- and extra-follicular areas.
Results: The intra-follicular (CD3 poor) and extra-follicular (CD3 rich) regions were accurately recognized within each core, based on abundance of CD3 cells. MSI enabled the accurate quantitation of CD3, CD69 and FOXP3 without crosstalk. The number of FOXP3+/CD3+ Tregs and CD69+ T-cells were counted in each core and used in Kaplan–Meier survival analysis, which demonstrated association of FOXP3+/CD3+ Tregs with favourable outcome in both the intra- (p = 0.0173) and extra-follicular (p = 0.0173) areas, as well as CD69+ T-cells in intra-follicular (p = 0.0175) areas; CD69+ T-cells were not prognostic in extra-follicular areas (p=4509).
Conclusions: This study demonstrates use of an automated method for counting Tregs in follicular lymphoma, showing association of FOXP3+ Tregs with good outcome. Given the generic nature of the method automated multiplexed tissue cytometry analyses are feasible for routine clinical studies and work with many multiplexed IHC staining methodologies, of importance for translational cancer studies in general.
Conflict of interest: *Other substantive relationships: PerkinElmer, Inc.*

3661 POSTER

mTOR inhibition in MDR acute myeloid leukemia

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Background: Signaling through the PI3K/PTEN/AKT/mTOR pathway is aberrantly activated in several human cancers, including Acute Myeloid Leukemia (AML) patients where it contributes to leukemic cell proliferation, survival and drug resistance. In leukemia patients treated with drugs such as anthracyclines, vinca alkaloids, chemo-resistance one of the major problems contributing to therapeutic failure, where all this drugs are modulated in their intracellular retention by a 170 kDa Phosphoglycoprotein, an mdr-1 gene product. The role of mTOR in various processes such as proliferation, growth, has been comprehensively described in many reviews, following its inhibition by rapamycin. Thus inhibition of mtor signaling in AML blasts could account for enhancing their sensitivity to cytotoxic agents. This study is to embrace the effect of Rapamycin, an allosteric mTOR inhibitor on MDR AML patients.
Materials and Methods: We selected samples of 30 MDR AML patients isolated from bone marrow or peripheral blood and cultured *in vitro*. The effects of Rapamycin and Evarolimus (EvarTOR) on fresh AML samples were analyzed by treating the cells with intermediate drug concentrations (100 nM) for 24 h,48 h, 72 h, 96 h respectively followed by cytotoxicity assay (MTT assay). The effects of the drug on proliferation of cells were analyzed also by cell counting.
Results: A marked reduction in cell viability at 96 h was detected in 25 samples treated with Rapamycin and Evarolimus. Out of the 30 analyzed samples, 16 were sensitive to Rapamycin, 19 to Evarolimus where it was observed that the leukemic cell count came down to almost 2% whereas 11 samples displayed various degree of resistance to the drug. Overall, these findings demonstrated that Rapamycin and Evarolimus have a cytotoxic activity against primary cells from AML patients with up-regulated mTOR signaling.
Conclusion: We have evaluated the *in vitro* effects of Rapamycin on AML patient samples where reduced cell viability primary cells from AML patients were observed. However, further studies of the additional effects of Rapamycin and Evarolimus will be of the supreme importance, as they could help in designing more efficient curative protocols, for the treatment of acute leukemia patients.
No conflict of interest.

3662 POSTER

Increased leukemia-specific CTL induction by dendritic cells matured with cocktails of TLR agonists

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Background: Despite consolidation chemotherapy, relapse occurs in majority of patients with acute myeloid leukemia (AML) because of the presence of minimal residual disease. Dendritic cell (DC) based immunotherapy can help to maintain patients in remission. In spite of apparent progress in DC-based immunotherapy, some differences were reported in generating potent DCs. The aim of this study was to determine the best combination of TLR agonists with the synergistic effect on maturation of human monocyte-derived DCs for immunotherapy of acute myeloid leukemia.
Methods: Here we generated DCs by culturing isolated peripheral blood monocyte in the presence of GM-CSF and IL-4 for 5 days. Then, immature DCs were cultured in the presence of different TLR ligand cocktails for an additional day. The morphology, expression of key surface molecules and allostimulatory activity were assayed on DCs. Moreover, the ability of DCs in induction of CTLs specific for Leukemia blasts was determined.
Results: Our results revealed that among 10 different TLR agonists and their combinations, cocktails containing R848 (a ligand for TLR7/8) could efficiently produce DCs with increased expression of costimulatory molecules such as CD83, CD86, HLA-DR and CCR7. Such potent DCs also showed great capacity to stimulate allogeneic T cells. Finally, enhanced killing of leukemia blasts was observed by CTLs induced in the presence of regarding DCs.
Conclusions: In conclusion, combination of TLR agonists containing R848 could be considered as an appropriate maturation cocktail for DC production and its potential use for immunotherapy of AML patients.
No conflict of interest.

Proffered Papers Session (Sat, 28 Sep)
Melanoma and Skin Cancer

3700 ORAL

Ultrasound (US) − guided fine needle aspiration cytology (FNAC) of the sentinel node (SN) in 1000 consecutive melanoma patients

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Background: The surgical Sentinel Node (SN) procedure is currently considered standard of care worldwide for the staging of AJCC stage I/II melanoma patients (pts). It remains unclear if SN followed by early completion lymph node dissection (CLND) in case of metastasis can lead to a survival benefit. Unlike other types of cancer, US-guided-FNAC has not been proven to be effective in melanoma. We use the Berlin Morphology criteria for US-FNAC, a low threshold for the performing of a FNAC and overnight cytology reports. Now we report sensitivity (sens), specificity (spec), positive (PPV) and Negative (NPV) predictive values from our expanded experience from our prospective database.
Methods: Between 2001 and 2013 over 1500 stage I/II consecutive melanoma patients have undergone US-FNAC prior to SN. We report on the first 1000 consecutive pts. All patients underwent lymphoscintigraphy prior to US-FNAC. Peripheral Perfusion (PP), Loss of Central Echoes (LCE), Balloon Shaped (BS) are the Berlin Morphology Criteria, which were registered. FNAC was performed in case of presence of any (one or all) of these factors. SN tumor burden was measured according to the Rotterdam Criteria. All patients underwent SN or LND in case of positive FNAC. All patients with neg FNAC underwent a SN.
Results: Mean/median Breslow thickness was 2.58/1.57 mm (0.2−44 mm). Mean/median follow-up was 56/53 months (1–132). Ulceration was present in 24%. SN positivity rate was 20.8% (208/1000). Sens was 51%. Spec, PPV and NPV were 99%, 99% and 89%. Sensitivity was highest for T4 tumors (76%) and in ulcerated melanomas (63%). PP, LCE, BS had sens of 69%, 24%, 24%. Sens of US-FNAC increased with increasing SN tumor burden (17% in <0.1 mm to 61% in >1 mm). PP was an early sign of metastasis (58% in <0.1 mm mets). Threshold for positive FNAC was 0.3 mm in maximum diameter. 5-yr survival correlated to US-FNAC status (95% in neg, 59% in pos). Survival of patients with PP was 89% vs. 57% in BS vs. 96% in negative patients (P = 0.001).
Conclusions: US-FNAC according to the Berlin Morphology criteria can correctly identify half of the positive SNs. PP is an early sign of metastasis, BS is a late sign. US-FNAC can significantly reduce the amount of unnecessary surgical SN procedures. US-FNAC sensitivity correlated with increasing T-stage, increasing SN tumor burden and ulceration. US-FNAC can accurately predict survival. A multi-observer validation study is necessary to confirm our results.
No conflict of interest.

3701 ORAL

The prognostic significance of sentinel node tumour burden in melanoma patients: A European-Australian multicenter study

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Prognosis of patients with sentinel node (SN) positive melanoma is heterogeneous. Patient characteristics, primary tumour and SN parameters, and models for risk stratification of SN-positive patients have been assessed in numerous studies with respect to prediction of non-SN (NSN) status and survival. The aim of the current study was to evaluate the prognostic significance of SN tumour burden parameters and classification schemes in the largest database on positive SNs to date.
In 1539 SN-positive patients treated between 1993 and 2008 at 11 melanoma treatment centers in Europe and Australia, indices of SN tumour burden (intranodal location, tumour penetrative depth (TPD) and maximum SN tumour size) were evaluated.
Non-subcapsular location, increasing TPD and increasing maximum size were all predictive factors for NSN status and were independently associated with poorer melanoma-specific survival. (Table 1) Patients with subcapsular micrometastases <0.1 mm in maximum dimension had the lowest frequency of NSN metastasis (5.5%). Despite differences in SN biopsy protocols and clinicopathologic features of the patient cohorts

(between centers), most SN parameters remained predictive in individual center populations. Maximum SN tumour size >1 mm separated the 1539 patient cohort into two large groups of similar size and was the most reliable and consistent parameter independently associated with higher NSN positivity, poorer disease-free and poorer melanoma-specific survival. In this large retrospective, multicenter cohort study, several parameters of SN tumour burden including intranodal location, TPD and maximum size provided prognostic information, but their prognostic significance varied considerably between the different centers. This could be due to sample size limitations or to differences in SN detection, removal and examination techniques. Prospective studies employing consistent SN assessment protocols are required to establish a classification system for SN tumour burden that accurately and consistently stratifies patients into prognostic groups.

No conflict of interest.

Table 1. Melanoma specific survival

Characteristic	Univariate analysis		
	HR	95% CI	p-value
Dewar classification			
subcapsular	1		
non-subcapsular	1.75	1.31–2.35	<0.001
Tumour penetrative depth *(mm)*			
continuous	1.19	1.13–1.26	<0.001
S-classification			
SI	1		
SII	1.58	1.09–2.28	0.016
SIII	1.93	1.38–2.70	<0.001
Maximum size *(mm)*			
continuous	1.10	1.08–1.12	<0.001
⩽1	1		
>1	1.96	1.61–2.37	<0.001
Rotterdam classification *(mm)*			
<0.1	1		
0.1−1.0	1.99	1.21–3.28	0.007
>1.0	3.55	2.17–5.80	<0.001

HR = Hazard Ratio; CI = Confidence Interval.

3702 ORAL

A meta-analysis of randomized, controlled trials in metastatic melanoma establishes progression-free survival as a surrogate for overall survival

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Background: Four randomized, phase 3 metastatic melanoma trials have shown a statistically significant overall survival (OS) benefit over the last few years. This provides the first opportunity to investigate progression free survival (PFS) as a potential surrogate for OS, taking into account a large number of recently conducted melanoma trials.

Materials and Methods: A meta-analysis was performed of 10 randomized controlled trials enrolling 4,215 metastatic melanoma patients. From initially 48 published trials identified, those were selected which included DTIC as control arm, reported both PFS and OS, conform to the convention of reporting hazard ratio (HR) demonstrating benefit as <1. Experimental arm therapies included vemurafenib, dabrafenib, trametinib, sorafenib, ipilimumab, intetumumab, bosentan, oblimersen, temozolomide, and nab-paclitaxel. HRs for OS and PFS were correlated using several weighting strategies: by sample size or by precision of the HR estimate assuming fixed and random effects. Sensitivity analysis was performed including or excluding trials with crossover upon progression, phase 3 trials only, large trials, and only those with DTIC 1,000 mg/m^2 dosing.

Results: There was a statistically significant correlation between PFS and OS regardless of weighting strategy. Correlation coefficients (R) ranged from 0.74 (95% CI 0.26–0.93) for random effects assumption to 0.90 (95% CI 0.66–0.97) for sample size weighting. Considering only trials without crossover, R was 0.97 (95% CI 0.82−1.0) and only slightly lower after including 2 additional trials with less than 50% crossover (R = 0.94; 95% CI 0.74–0.99). Similarly, the correlation strength was non-significantly affected by restricting to phase 3, large, or DTIC 1,000 mg/m^2 (0.95, 0.94, and 0.92, respectively). Only inclusion of mature follow-up data after >50% crossover (vemurafenib and dabrafenib phase 3 trials) significantly weakened PFS/OS correlation (R=0.58; 95% CI −0.03–0.88). We considered the inclusion of trials with no or limited crossover using the random effects assumption to yield a conservative and appropriate statement of the PFS/OS correlation: R=0.93 (95% CI 0.70–0.99).

Conclusions: Based on a meta-analysis of all reported randomized trials in melanoma for which DTIC was the control arm therapy, we found a strong correlation between PFS and OS regardless of mechanistic class of therapy. PFS should be considered as a robust surrogate for OS in subsequent randomized trials.

Conflict of interest: *Ownership: None. Advisory board: GSK, Roche/Genentech (KTF), GSK, Roche, Novartis, BMS (RD), Amgen, AZ, BMS, BI, Celgene, Eisai, GSK, IGEA, Lilly, MelaSciences, Merck Serono, MSD, Novartis, Oncosec, Roche Pharma (AH), GSK, Roche, Novartis, Amgen, BMS (GVL), BMS, Celgene, Roche, Novartis, GSK (PL), Roche, BMS, GSK, Amgen, Novartis, BI, Leo Pharma (DS). Board of directors: none. Corporate-sponsored research: Roche, Novartis, BMS (RD), Amgen, AZ, BMS, BI, Celgene, Eisai, GSK, IGEA, Lilly, MelaSciences, Merck Serono, MSD, Novartis, Oncosec, Roche Pharma (AH), AZ (PL), Merck (DS). Other substantive relationships: Amgen, AZ, BMS, BI, Celgene, Eisai, GSK, IGEA, Lilly, MelaSciences, Merck Serono, MSD, Novartis, Oncosec, Roche Pharma (AH), GSK (MH − employee), Roche (GVL − honoraria), GSK, Roche, BMS, Novartis (CR − consultancy)*

3703 ORAL

Vemurafenib (VEM) and MEK inhibitor, cobimetinib (GDC-0973), in advanced BRAFV600-mutated melanoma (BRIM7): dose-escalation and expansion results of a phase IB study

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Background: Combined inhibition of BRAF and MEK delays the emergence of resistance in preclinical models. BRIM7 evaluated safety and efficacy of VEM + cobimetinib. The combination was shown to be tolerable when delivered at the respective single-agent maximum tolerated doses (MTDs; ESMO 2012 LBA28). We report updated safety and efficacy data.

Materials and Methods: Eligible patients (pts) had advanced *BRAF^{V600}*-mutated melanoma and ECOG performance status 0−1 and were BRAF inhibitor (BRAFi)-naive or had disease progression on VEM (VEM-progressor). Pts in the dose-escalation portion received VEM 720 or 960 mg BID continuously and cobimetinib 60, 80, or 100 mg QD 14 days (d) on/14 d off (14/14); 21 d on/7 d off (21/7); or continuously (28/0). Two dose levels were expanded: VEM (720 mg and 960 mg BID) + cobimetinib 60 mg QD 21/7.

Results: Of the 115 pts treated with VEM + cobimetinib as of 25 Jan 2013, 58% were male, median age was 54 y (19−76), 76% were M1c, and 54% were BRAFi-naive. Median no. of cycles to date was 5 (1−20). Dose-limiting toxicities (DLTs) were observed in 4 pts including DLTs of mucositis (1 pt) and arthralgia (1 pt) in 4 pts treated in the VEM 960 mg BID + cobimetinib 60 mg QD 28/0 cohort. The most common treatment-related adverse events (AEs; n = 115) were non-acneiform rash (58%), diarrhea (52%), fatigue (37%), liver laboratory test abnormality (37%), and photosensitivity/sunburn (37%). Most frequent treatment-related grade ⩾3 AEs were liver laboratory test abnormality (10%), non-acneiform rash (7%), arthralgia (5%), diarrhea (4%), and fatigue (4%). Cutaneous squamous cell carcinoma occurred in 3 pts (3%). Dose reduction was required for VEM in 9 pts (8%) and cobimetinib in 7 pts (6%). BRAFi-naive pts attained 73% confirmed response rate (RR); median progression-free survival (PFS) is immature due to the short follow-up time with only 11 pts (19%) having a

PFS event to date. VEM-progressor pts attained 14% confirmed RR, stable disease of 49%, and median PFS of 2.8 months. Updated PFS analysis will be presented.
Conclusions: VEM + cobimetinib can be safely administered at the respective single-agent MTDs of VEM (960 mg BID) and cobimetinib (60 mg 21/7). Preliminary efficacy of the combination is encouraging in BRAFi-naive patients.

Efficacy evaluable pts	VEM-progressor pts (n = 49), n (%)	BRAFi-naive pts (n = 59), n (%)
Confirmed response	7 (14)	43 (73)
Overall response		
CR	0	2 (3)
PR	7 (14)	41 (70)
SD	24 (49)	14 (24)
PD	16 (33)	1 (2)
Unable to assess	1 (2)	1 (2)
Not done	1 (2)	0

Conflict of interest: *Ownership: Kite Pharma. Advisory board: Roche/Genentech. Board of directors: Roche/Genentech. Corporate-sponsored research: Pfizer, Novartis, Millennium, Cylene, Roche/Genentech, BMS, Merck, Novartis. Other substantive relationships: Publicaciones Permanyer, Roche/Genentech, Amgen, GSK*

3704 ORAL

Survival analysis with 5 years of follow-up in a phase III study of ipilimumab and dacarbazine in metastatic melanoma

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Background: Prior to the recent approval of new therapies, patients with metastatic melanoma (MM) had a 5-year survival rate of ~10%. Increasingly, clinical trial data suggest long-term survival (beyond 5 years) for some MM patients who received ipilimumab (Ipi). An analysis of 177 pts from 3 phase I/II Ipi studies conducted at the US National Cancer Institute demonstrated 5-year survival rates of 13−25%. In 4 other phase II trials, the 5-year survival rate was ~20% for previously treated patients who received Ipi monotherapy. In the phase III trial, CA184–024, Ipi plus dacarbazine (DTIC) significantly improved overall survival (OS) versus DTIC alone in treatment-naive patients with MM. Long-term safety data for patients who survived >2 years have been previously reported for this study. In the current survival analysis, we report the 5-year survival rates from study 024.
Methods: Patients with treatment-naive MM were randomized to receive either Ipi (10 mg/kg) plus DTIC (850 mg/m^2) or placebo plus DTIC (850 mg/m^2) given at weeks 1, 4, 7, 10 followed by DTIC every 3 weeks through week 22. Patients with stable disease or better could receive Ipi or placebo as maintenance therapy, every 12 weeks from week 24. This analysis reports survival data captured 5 years beyond the last enrolled patient, current as of March 2013.
Results: The table summarizes median OS, previously reported survival rates up to 4 years, and current analyses for 5-year survival rates by treatment group. Median follow-up for OS in months (range) was 11.0 [0.4–71.9] for Ipi plus DTIC and 8.9 [0.1–73.2] for placebo plus DTIC. Seven patients continued to receive Ipi maintenance therapy at the cut-off date for this survival analysis, and 6 patients currently remain on Ipi maintenance therapy.

Treatment group	Median OS, months	Overall survival rate, % [95% CI]				
	[95% CI]	1-year	2-year	3-year	4-year	5-year
Ipi + DTIC	11.2	47.6%	28.9%	21.3%	19.1%	18.2%
N = 250	[9.5–13.8]	[41.2–53.7]	[23.3–34.7]	[16.3–26.6]	[14.4–24.3]	[13.6–23.4]
Placebo + DTIC	9.1	36.4%	17.8%	12.1%	9.7%	8.8%
N = 252	[7.8–10.5]	[30.4–42.4]	[13.3–22.8]	[8.4–16.5]	[6.4–13.7]	[5.7–12.8]

Conclusions: The results of this landmark survival analysis for phase III study 024, with 5 years of follow up, continue to demonstrate a long-term survival benefit for patients treated with Ipi plus DTIC compared to placebo plus DTIC. Consistent with the results of phase II studies, survival rates appear to plateau beginning at 3 years.
Conflict of interest: *Ownership: Lu: Bristol-Myers Squibb (BMS), Chin: BMS. Advisory board: Maio: BMS, Roche, Robert: BMS, Roche, MSD, Novartis, GlaxoSmithKline (GSK), Garbe: BMS, GSK, MSD, Roche, Philogen, Testori: BMS, Roche, GSK, Amgen, Celgene, Wolchok: BMS. Corporate-sponsored research: Garbe: BMS, GSK, Roche, Chin: BMS Wolchok, BMS. Other substantive relationships: Maio: non-profit research programs, BMS.*

Poster Session (Mon, 30 Sep)
Melanoma and Skin Cancer

3705 POSTER

Specific roles for BRAF and CRAF in NRAS-induced mouse melanoma

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Background: The RAS/RAF/ERK pathway plays a key role in melanoma, with BRAF and NRAS mutations in 50% and 15% of cases, respectively. The development of chemical inhibitors specifically targeting mutated ^{V600E}BRAF represents a major breakthrough in the treatment of metastatic melanoma, although resistance often develops quickly following treatment. Furthermore, such compounds cannot be used to treat half of melanoma patients, especially those mutated on NRAS. In this study, we evaluated the contribution of BRAF and its closely related kinase CRAF downstream of NRAS during tumoral progression in mouse models.
Material and Methods: We developed NRASQ61K-induced mouse melanoma models in which single or compound ablation of BRAF and CRAF genes can be achieved in the melanocyte lineage upon tyrosinase promoter-driven Cre or Cre^{ERT2} expression. These models allowed us investigating the role of both RAF kinases at each step of tumoral progression, from tumor initiation (formation of benign nevi) to metastatic melanoma.
Results: Temporally-controlled concomitant ablation of BRAF and CRAF abolished nevi formation and melanoma progression and maintenance, showing that RAF signaling is absolutely required for NRAS-induced melanoma development. However, we will present data showing that BRAF and CRAF play specific roles during the different steps of melanoma progression. In addition, using primary cultures of melanomas, we show that ablation of RAF kinases often lead to the emergence of resistant cells showing reactivation of ERK in the absence of BRAF and CRAF.
Conclusions: Our results disclose specific and complementary functions for BRAF and CRAF in NRAS-induced mouse melanoma, and pave the road for further studies on treatment and resistance mechanisms.
No conflict of interest.

3706 POSTER

New polymorphisms in the ERP29 and LEF1 genes associated with increased risk for cutaneous melanoma

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Background: Recently, we found that genetic polymorphisms in tumor suppressor *ERP29* c.293A>G (rs7114) gene and in gene of DNA transcription *LEF1* c.1213+480C>T (rs2107028) and g.127267C>T (rs4245926) alter the oropharynx cancer risk. Since the roles of these genetic polymorphisms in the risk and clinical manifestation of cutaneous melanoma (CM) are still unknown, these were the aims of the present study.
Material and Methods: For this case-control study, the genomic DNA from peripheral blood of 179 consecutive CM patients (aged 20−89 years; 90 males, 89 female, 167 Caucasians, 12 non-Caucasians) and 199 healthy subjects matched to patients by gender and race were genotyped using real-time PCR. The differences between groups were analyzed by the logistic regression model. Power analysis (PA) was used to verify the effect of sample size on the results obtained in the study.
Results: The frequencies of the *ERP29* AA and the *LEF1* 127267TT genotypes were higher in patients than in controls (80.4% *vs* 69.3%, $P = 0.03$, PA: 68%) and (76.0% *vs* 65.3%, $P = 0.02$, PA: 74%), respectively. Carriers of these genotypes had a 1.77 (95% CI: 1.05–2.98) and 1.80

(95% CI: 1.09–2.96)-fold increased risks for CM than those with the remaining genotypes, respectively. *LEF1* 127267TT plus *LEF1* 1213+480CC and *ERP29* AA plus *LEF1* 127267TT plus *LEF1* 1213+480CC combined genotypes were also more common in patients than in controls (77.6% *vs* 66.7%, $P = 0.03$, PA: 74%) and (92.8% *vs* 80.0%, $P = 0.02$, PA: 93%). Carriers of these genotypes had a 1.81- (95% CI: 1.05–3.12) and 2.92-fold (95% CI: 1.13–7.54) increased risks for CM than others, respectively. Additionally, the *ERP29* AA genotype was more common in patients with advanced tumours than in those with localized tumours (91.5% *vs* 77.2%, $P = 0.04$, PA: 58%). The frequency of *ERP29* AA in patients with advanced CM was also higher than that found in controls (91.5% *vs* 69.3%, $P = 0.001$, PA 99%). Individuals with the *ERP29* AA genotype had a 4.75 (95% CI: 1.63–13.82)-fold increased risk for aggressive CM than others.

Conclusions: The data suggest, for the first time, that *ERP29* and *LEF1* polymorphisms, alone or in combination, alter consistently the risk for CM, particularly of the advanced form of the disease. We believe that healthy carriers of specific genotypes of the genes should receive additional recommendation to avoid exposition to sunlight and periodic follow-up by dermatologist for CM prevention and early diagnosis.

No conflict of interest.

3707 POSTER

Hyaluronan fragments, a novel modulator of tumor progression in squamous skin carcinomas

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Squamous cell carcinoma (SCC) is the second most common skin cancer and strongly associated with chronic UVB exposure of the skin. UVB induced changes of the extracellular matrix contribute to phenotypic responses of tumour and stroma cells. Hyaluronan (HA), as a main component of the dermal extracellular matrix, is synthesized by HA-synthase isozymes (HAS1−3) and is known to be involved in the regulation of several cellular mechanisms like proliferation and migration. Aim of the present study was to evaluate the contribution of HA on tumour progression of UVB-induced SCCs.

Human skin samples from healthy skin and SCCs were analysed via qRT-PCR. mRNA levels of HAS1 and 2 showed no regulation, whereas HAS3, Hyaluronidases (HYAL) 1 and 2 were clearly upregulated. In vitro comparison of normal human keratinocytes and SCC cells (A431) showed the same expression patterns (HAS3 1.951±0.386; HYAL1 74.28±22.1; HYAL2 4.229±1.680 fold of keratinocytes). The amount of HA in the supernatant of SCC cells was significantly increased in comparison to keratinocytes, however HA size was drastically reduced to HA-fragments (sHA) as shown by size exclusion chromatography. To evaluate the influence of HA on tumour progression in vivo, mice were UVB irradiated (80mJ/cm^2) three times a week for 20 weeks. During the experiment the mice received either chow with an inhibitor of HA synthesis, 4-Methylumbelliferon (4-MU), or control chow. Mice treated with 4-MU developed significantly less tumours compared to non treated animals (18.25±2.22 vs. 33.3±4.1 tumours). In vitro 4-MU reduced the amount of HA in the supernatant of SCC cells (0.567±0.1083 fold of control). [H^3−thymidine] incorporation revealed reduced proliferation of SCC cells in response to 4-MU (0.421±0.216 fold of control). Furthermore, time-lapse microscopy as well as PARP and AnnexinV analysis showed a more apoptotic phenotype after 4-MU treatment. Incubation of SCC cells with external sHA let to no additional phenotype. However, treatment of keratinocytes with sHA resulted in a drastic reduction of IL6 expression. Futhermore it could be shown that IL6 induced cell death in SCC cells.

In conclusion, the present data show that SCC cells extrude more HA, possibly related to increased levels of HAS3, in comparison to keratinocytes. Increased amounts of HA appear to be essential for the UVB induced tumour progression of SCCs in mice. Biological active HA fragments derived from HA degradation by hyaluronidases (Hyal1, 2) are thought to be pro-angiogenetic and pro-inflammatory. Furthermore they might, by a paracrine mechanism, reduce IL6 levels in the microenvironment of the tumour thus possibly also promoting tumour survival and malignancy.

No conflict of interest.

3708 POSTER

MicroRNA-medited loss of ADAR1 enzyme in metastatic melanoma promotes tumor growth

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Background: RNA editing is a post transcriptional modification in which adenosine is deaminated into inosine. Decreased RNA editing was reported several years ago in various cancers, but the significance and underlying mechanisms are still elusive. Here we study the mechanistic significance of loss of ADAR1 in the pathogenesis of melanoma.

Methods: ADAR1 expression was tested with qPCR, western blot and immunohistochemistry. Proliferation was tested with XTT. Tumorigenicity was tested in SCID mice. miRNAs were quantified with qPCR or northern blot. Protein-protein interactions were tested with co-immunoprecipitation. Genomic copies were quantified with qPCR. Methylation and RNA-editing was quantified with sequenome MassArray.

Results: We show that the main RNA-editing enzyme, Adenosine Deaminase Acting on RNA-1 (ADAR1) is silenced in many metastatic melanoma cultures. In-depth studies on melanoma samples and progression tissue microarrays point on substantial ADAR1 downregulation during the metastatic transition. Accordingly, ADAR1 suppresses several cancer features, as its downregulation alters cell morphology, facilitates cell-cycle and proliferation in-vitro, and dramatically enhances the tumorigenicity in-vivo. ADAR1 controls the expression of >100 microRNAs, which regulate hundreds of genes that account for the observed phenotype. Importantly, ADAR1 fundamentally regulates the course of miRNA processing in the cell in an RNA-binding dependent yet RNA-editing-independent manner. ADAR1 regulates the expression of Dicer at the level of translation via let-7. In addition, it creates a complex with DGCR8, which is mutually exclusive with the DGCR8-Drosha complex that processes pri-miRNAs in the nucleus. Cancer cells silence ADAR1 by overexpressing miR-17 and miR-432, both of which directly target ADAR1 and operate additively. Both of their genomic sequences are frequently amplified to increase expression, but uniquely, an aberrant hypomethylation of the imprinted DLK1-DIO3 region in chromosome 14 accounts for the miR-432 overexpression.

Conclusion: ADAR1 loss plays a fundamental role controlling melanoma growth by regulating the biogenesis pathway of microRNAs at several stages. Epigenetic and genetic mechanisms account for this loss. This might pave the way for the development of novel technologies.

No conflict of interest.

3709 POSTER

The effect of in vitro NK cell and K562 tumor cell contact on NK cell subset distribution and changes in activation and inhibitory receptor expression in melanoma patients

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Background: NK cell cytotoxicity against malignant cells is regulated by functionally opposing, activating and inhibitory receptors whose balance determines whether target cells will be lysed. Thus, ligation of activating receptors to stress-induced ligands stimulates, while binding of inhibitory, KIR receptors to MHC class I molecules on tumor cells inhibits NK cell cytotoxicity. Based on CD16 receptor expression, NK cells are divided into two functionally distinct subsets: cytotoxic $CD16^{bright}$ and regulatory $CD16^{dim}$ subset. K562 human erythromyeloid tumor cell line is MHC class I deficient and sensitive to NK cell lysis, and it expresses stress induced protein MICA, a ligand for NKG2D activating NK cell receptor. The aim of this study was to investigate the effect of co-culture of melanoma patients' NK cells with K562 tumor cell line on the expression of several receptors on $CD3^-CD16^+$ NK cells and their subsets.

Material and Methods: PBL obtained from 15 metastatic melanoma patients (MM) were co-cultured with K562 cell line in target to effector ratio 2:3. Samples were incubated for 4 h at 37ºC in a humidified atmosphere in CO_2 incubator. The expression of NK cell receptors was performed by flow cytometry after staining with CD3PerCP, CD16FITC, NKG2DPE, CD161PE, CD158a/bFITC, CD107aPE mAbs and analyzed on $CD3^-CD16^+$ NK cells and on $CD3^-CD16^{bright}$ and $CD3^-CD16^{dim}$ NK subsets.

Results: Contact with K562 target cells increased CD107a expression on NK cells and $CD16^{bright}$ NK cell subset indicating degranulation characteristic of NK cell cytotoxicity, as well as CD16 shedding leading to a

decrease in the percent of $CD3^-CD16^+$ NK cells and subsequent $CD16^{bright}$ to $CD16^{dim}$ NK cell subset transition. Target cell induced NK cell functional activation led to lower post-contact NKG2D receptor expression on NK cells and $CD16^{bright}$ NK cell subset due to ligand-induced NKG2D internalization and degradation. Furthermore, the shown post contact increase in KIR and CD161 inhibitory receptors on $CD16^{dim}$ NK cell subset may be due to target cell induced $CD16^{bright}$ to $CD16^{dim}$ NK cell subsets transition.
Conclusions: Considering the scarce data of the effect of cell-cell contact between NK and tumor cells on NK cell receptor expression, we show in MM patients the dynamics of NK cell subset distribution characterized by a decrease in the cytotoxic $CD3^-CD16^{bright}$ NK cell subset and in NKG2D activating receptor expression, as well as a significant post-activation KIR up regulation on $CD3^-CD16^{dim}$ subset. These results give data for novel therapeutic options in MM patients including cytokines and KIR antibody immunotherapy to potentiate innate NK cell-mediated antitumor activity.
No conflict of interest.

3710 POSTER

Lipid raft adhesion receptors recruitment mediated by major histocompatibility complex (MHC) class II signalling in melanoma cells

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Background: The lipid rafts are enriched in freely diffusing, stable assemblies of sphingolipids and cholesterol that are implicated in the selective protein–protein interactions as well as in the assembly of transient signalling platforms. The lipid raft proteins play important roles in cell–cell interaction and are docking site for the proteins involved in focal adhesion and cancer metastasis such as the adhesion receptors. Indeed, the alteration of adhesion receptors expression is related to metastatic progression of melanoma through the deregulation of adhesive functions, the subsequent detachment of tumour cells from the primary tumour site and the tissue borders. Interestingly, in different tumour cell lines has been reported that the signalling activated by the MHC class II molecules is associated to the lipid raft localization of these molecules but only reduced knowledge are available in this field for melanoma. In the aim to understand the molecular mechanisms used by melanomas for the progression to an invasive-metastatic state, we studied in MHC class II constitutive expressing melanoma cell lines, the membrane localization of adhesion receptors as well as the activated signalling.
Material and Methods: The class II constitutive expressing melanoma cells (A375 and HT144 cell lines) were stimulated with a specific anti-HLA-DR mAb (L243) that mimics the TCR interaction with the class II molecules for 24 h and 48 h or left unstimulated. The lipid rafts of stimulated and unstimulated melanoma cells were isolated and analysed by western blot. Exosomes secreted by stimulated and unstimulated melanoma cells were purified and analysed by western blot.
Results: In the lipid rafts domains of stimulated A375 and HT144 cells we observed an increased localisation of HLA-DRa, Integrin b1, MCAM, ICAM as well as FAK kinase. Therefore, we compared the expression of HLA-DRa, MCAM and ICAM receptors in exosomes secreted by stimulated and unstimulated A375 and HT144 melanoma cells.
Conclusions: Therefore, our results underline the role played in melanoma cells by the MHC class II dependent signalling on motility and exosomes functionality. The signalling activated by class II molecules assembling class II, Integrins and CAMs receptors as well as the FAK kinase in the lipid rafts fraction, could elucidate the mechanisms of melanoma cells metastatic dissemination as well as the role of exosomes on the microenvironment of tumour sites.
No conflict of interest.

3711 POSTER

The tamoxifen active metabolites endoxifen and 4-hydroxytamoxifen present superior antitumor activity over the pro-drug in malignant melanoma

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Background: Tamoxifen (TAM) is a selective estrogen receptor modulator used routinely in the treatment of breast cancer. TAM has also been used in malignant melanoma, particularly in combination with other chemotherapeutic agents. However, the inclusion of TAM in melanoma therapeutic schemes remains controversial, as the studies in humans performed so far provided contradictory results. TAM is a pro-drug that is metabolized by cytochrome P450 (CYP) enzymes, namely CYP3A4 and CYP2D6, generating the two active metabolites, 4-hydroxytamoxifen (OHTAM) and endoxifen (EDX), which are considered responsible for the anticancer activity of TAM in breast cancer. In fact, several studies have demonstrated an association between CYP2D6 phenotype and clinical outcome in women with breast carcinoma taking TAM. Additionally, several drugs that influence the enzymatic activity of CYP2D6 have also been shown to limit the biological activity of TAM. As the levels of EDX and OHTAM achieved *in vivo* seem to be closely related with the treatment efficacy and the utilization of TAM metabolites allows avoiding the variability on TAM metabolism, we investigated the effects of EDX and OHTAM on melanoma cells and compared to those promoted by TAM, in order to clarify whether TAM metabolites are an effective alternative to TAM in malignant melanoma.
Materials and Methods: Cell proliferation was measured by sulforhodamine B and bromodeoxyuridine (BrdU) incorporation assays, and cell death by the lactate dehydrogenase assay and by cell count with trypan blue staining. The effects on cell cycle were evaluated by flow cytometry.
Results: The antiestrogens decreased melanoma cell biomass in a concentration-dependent manner, but the effects of TAM metabolites were much more pronounced than those of TAM. The antiestrogens did not increase cell death, but TAM metabolites significantly decreased BrdU incorporation, whereas the same concentration of TAM did not exert significant effects.
Conclusion: These results suggest that TAM metabolites induce a superior cytostatic activity in melanoma cells relatively to TAM, suggesting that, as observed in breast cancer, the steady-state levels of EDX and OHTAM may also have an impact on the treatment efficacy of TAM in melanoma. Additionally, the individual variability in TAM metabolism can contribute to explain the discrepant outcomes observed in melanoma patients taking TAM. These observations should be taken into consideration in future trials.
This study was supported by a PhD grant (SFRH/BD/65130/2009) attributed to M.P.C. Ribeiro by FCT.
No conflict of interest.

3712 POSTER

Real-time assessment of TORC1 suppression following RAF inhibitor treatment can predict responsiveness in BRAF-mutant melanoma patients

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Background: RAF inhibitors such as vemurafenib have transformed treatment for *BRAF*-mutant melanoma. Still, most responses are partial and short-lived, and many patients still fail to respond. Thus, biomarkers predicting which patients are more or less likely to benefit would have important clinical applications.
Material and Methods: To identify potential biomarkers of response, *BRAF*-mutant melanoma cell lines were characterized before and after treatment with vemurafenib. Potential biomarkers were evaluated in tumor biopsies obtained before and after vemurafenib treatment in *BRAF*-mutant melanoma xenografts. Paired biopsies obtained from *BRAF*-mutant melanoma patients before and ~2wks after initiation of RAF inhibitor were assessed by IHC for a change in phosphorylation of ribosomal protein S6 (P-S6), and suppression of P-S6 following treatment was correlated with progression-free survival (PFS). Using a novel multiplexed quantitiative immunofluorescence approach, serial fine-needle aspiration (FNA) biopsies obtained from patients before and 1−2wks after initiation of RAF inhibitor were assessed for P-S6 suppression, and results were correlated with radiographic tumor response.
Results: Suppression of TORC1 activity in response to RAF inhibitors, as measured by decreased P-S6, effectively predicted sensitivity in *BRAF*-mutant melanoma cells. In resistant melanomas, P-S6 was maintained, in some cases despite robust suppression of MAPK signaling by RAF inhibitors. In xenografts, P-S6 suppression by RAF inhibitors was necessary for induction of apoptosis and tumor response in vivo. In paired biopsies obtained from *BRAF*-mutant melanoma patients before and 1−2wks after initiation of RAF inhibitor, P-S6 suppression predicted significantly improved PFS [HR = 0.19, 95% CI 0.01–0.84; p = 0.03]. A change in P-S6 could be readily monitored in real-time by serial FNA biopsies in patients initiating RAF inhibitor therapy. In this small prospective test cohort, a decrease in P-S6 following initiation of RAF inhibitor therapy correlated with objective tumor response.
Conclusions: P-S6 suppression following initiation of RAF inhibitor therapy is a promising functional biomarker to predict sensitivity of *BRAF*-mutant melanomas, predicting improved PFS. Therapy-related changes in P-S6 can be effectively and quantitatively monitored in real-time in *BRAF*-mutant melanoma patients by serial FNA biopsies, providing an early and minimally-invasive means of evaluating therapeutic efficacy.
No conflict of interest.

3713 POSTER

Synergistic effects of glutamate receptors antagonists combined with antiestrogens on melanoma cells

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Introduction: In the last years the role of glutamate outside the central nervous system has garnered significant attention and the use of glutamate receptors antagonists in the treatment of several malignancies has been evaluated. Previous studies performed in our laboratory have demonstrated that *N*-methyl-D-aspartate receptors (NMDAR) antagonists memantine and MK-801 exert a cytostatic action on melanoma cells. Recently, it has been reported that MK-801 decreases melanoma cell motility and that it can also decrease melanoma growth *in vivo*. The antiestrogen tamoxifen (TAM) has been used routinely in the treatment of breast carcinoma, but it has also been shown to decrease melanoma cells proliferation and invasion. TAM is a pro-drug that is activated by cytochrome P450 (CYP) enzymes to 4-hydroxytamoxifen (OHTAM) and endoxifen.
The metabolites present therapeutic advantages comparing with the use of TAM, as their efficacy is not limited by variable CYP enzymes activity or by co-administration of CYP2D6 inhibiting medication. Therefore, we investigated the effects of a combined therapy of memantine or MK-801 with TAM and its active metabolite OHTAM on melanoma cells proliferation and migration.
Materials and Methods: Cell proliferation was measured by sulforhodamine B (SRB) and bromodeoxyuridine (BrdU) incorporation assays, and cell death by the lactate dehydrogenase (LDH) assay and by cell count with trypan blue staining. The effects on cell migration were monitored by the wound healing assay.
Results and discussion: The combinations of memantine or MK-801 with antiestrogens exhibited synergistic antiproliferative effects on melanoma cells, as shown by SRB assays. The effect on tumor cell proliferation was not due to increased cell death, since the combinations did not enhance LDH release neither trypan blue stained cells. Measurements of BrdU incorporation suggest that the combinations of NMDAR channel blockers and antiestrogens decrease cell division. Additionally, the combinations of memantine or MK-801 with OHTAM significantly decreased melanoma cells migration relatively to control.
Conclusion: Altogether, these findings support a combined therapy of NMDAR channel blockers memantine or MK-801 with antiestrogens as a new strategy for melanoma treatment.
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No conflict of interest.

3714 POSTER

Removing barriers to patient detection of early stage melanoma

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Background: The incidence of and death rate from cutaneous melanoma (CMM) continue to increase. More than half of CMM are detected by patients or their close contacts. Outcome is directly related to stage at presentation. Patient-detected melanomas (PDM) present at higher stage than those found by physicians. We undertook this study to identify strategies to improve timely patient detection of early CMM.
Methods: We reviewed demographic, tumor, and prospective questionnaire data obtained at surgical oncology consultation for 488 CMM in 435 patients. Data were analyzed with SAS statistical software.
Results: 248 CMM (51%) were PDM. As shown in the table, factors associated with patient detection included female sex, younger age, non-Caucasian race, no prior skin cancer, non-truncal site, anterior location, and nodular or acral lentiginous histology, but not with family history or CMM diameter. PDM was associated with greater tumor level and thickness, ulcerated, amelanotic and node-positive CMM (all $p < 0.005$). Mean (median) tumor thickness was 1.66 (0.75) vs 0.72 (0.35) mm for PDM vs physician-detected CMM ($p < 0.001$); 66% of CMM>2 mm thick were PDM. The main symptoms prompting patients to seek care were change in size (32%), color (31%) and bleeding (10%).
Conclusions: We identified modifiable barriers that hinder patient detection of early melanoma. Screening programs, which have decreased mortality from breast and colon cancer, may also lower CMM mortality. Our data suggests that public health efforts and novel educational tools are needed to improve awareness among high-risk patients who are unlikely to detect their own CMM. Skin examinations during routine physician visits for these patients may improve early diagnosis and have a meaningful impact upon melanoma incidence and mortality.
No conflict of interest.

Table: Factors associated with patient detection

Variable	Detection Method		p-value
	Patient	Physician	
Gender			0.0110
Male	111/246 (45%)	135/246 (55%)	
Female	137/242 (57%)	105/242 (43%)	
Age (years)			<0.001
<50	63/89 (71%)	26/89 (29%)	
⩾50	185/399 (46%)	214/399 (54%)	
Race			0.0440
Caucasian	236/472 (50%)	236/472 (50%)	
Non-Caucasian	12/16 (75%)	4/16 (25%)	
Prior non-melanoma skin cancer	37/106 (35%)	69/106 (65%)	0.0005
Family history of melanoma	33/217 (15%)	30/225 (13%)	0.4385
Site			0.0232
Extremity	139/231 (60%)	92/231 (40%)	
Head/Neck	44/80 (55%)	36/80 (45%)	
Trunk	62/172 (36%)	110/172 (64%)	
Location			0.0186
Anterior	102/193 (53%)	91/193 (47%)	
Posterior	68/168 (40%)	100/168 (60%)	
Lesion diameter, mm, mean (median)	13.0 (10)	12.5 (10)	0.5509

3715 POSTER

Intra-arterial hepatic chemoembolization with CPT-11 charged microbeads (TACE) combined with systemic fotemustine in metastatic uveal melanoma

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Background: Uveal melanoma (UM) is the most frequent tumor of the eye (70%), and represents 5% to 6% of all melanoma diagnoses. Approximately 50% of patients with UM will develop metastatic disease within 15 years from the treatment of primary tumor and the liver is the first or prevalent site of metastatic disease in up to 95% of the recurring patients. Without treatment the median survival time is generally poor: larger published case series reported a median life expectancy from 3.6 to 15 months, with rare cases of long-term survivors. Notwithstanding the efforts made to improve the outcome of metastatic UM, no standard therapy is established so far.
Material and Methods: A total of 143 patients (73 women and 70 men) were identified from a prospectively maintained database queried under IRB approval for uveal metastatic melanoma patients undergoing clinical treatments and procedures for their disease from September 1990 to October 2012. Data of patients who were treated with TACE combined with systemic fotemustine as first line treatment for stage IV disease were analyzed and compared with data of patients who didn't.

Table 1. Toxicity data of the combination of the1st TACE concomitant with systemic fotemustine, and duration of hospitalization after 1stTACE.

Toxicity (*N*=32)	No pain	Mild	Moderate	Severe	Very severe	Requiring sedation
Pain	5	10	12	5[a]	0	0
	No toxicity	**G1[b]**	**G2[b]**	**G3[b]**	**G4[b]**	**G5[b]**
Nausea/vomiting	27	3	1	1	0	0
Thrombocytopenia	21	6	1	2	2	0
Duration of hospitalization (nights)	**1 (Day Hospital)**	**2**	**3**	**4**	**5**	**6 or more**
	26	3[c]	2[d]	1[e]	0	0

Results: Out of 143 patients who were treated for metastatic uveal melanoma, 32 received TACE combined with systemic fotemustine as first line therapy. Fotemustine was administrated as outpatient chemotherapy. TACE was performed in day-hospital regimen, patients were usually discharged after an observation of 24 hours. Discharge was delayed after 1st TACE for 6 patients because of infection (*N*=1), and pain (*N*=5). Most frequent adverse event related to the procedure was pain (35 patients experimented pain, any grade), that was mostly epigastric and was eased by ranitidine in patients with mild-moderate pain and needed ranitidine plus morphine solphate (up to 40 mg i.v. per day) administration in 5 patients.

Nausea and vomiting were controlled with dopamine antagonists. Most serious adverse event was protracted G4 thrombocytopenia, that required transfusion of platelets for 2 patients. We observed 1 case of fever (peak 38.7ºC) with normal neutrophil count and augment of C reactive protein, the patient was treated with ceftriaxone and discharged after 3 nights. No life-threatening adverse events or procedure-related deaths were observed. Patients who received the combined treatment of TACE and fotemustine had a survival advantage (18.1 vs 14.6 months, $p = 0.039$).
Conclusions: Combined treatment with TACE and systemic fotemustine improves survival in metastatic melanoma patients and is well tolerated. It could be proposed for further studies, also combined with new drugs.
No conflict of interest.

3717 POSTER

Melanoma risk-takers: "Fathers and sons"

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Background: The fast growing rate of the incidence of skin cancers, especially melanoma, has resulted in the recommendation of sun protection measures. The aim of this survey was to analyse the compliance of the general population with these guidelines.
Methods: This French nationwide observational survey, EDIFICE melanoma, was conducted through phone interviews of a representative sample of 1,502 subjects aged $\geqslant$18 years old, using the quota method. The survey took place shortly after the summer from 28 September 2011 to 20 October 2011. Sun protection behaviours were defined by the frequent or systematic use of clothes or sunscreens. Out of the people who reported exposure to the sun (n = 1,172), the group of risk-takers (n = 442) was compared with those who used sun protection (n = 730).
Results: The risk-takers versus those who used sun protection were significantly more often men than women (62% vs. 44%, $p < 0.01$), had a lower level of education (40% vs. 26%, $p < 0.01$), lower incomes (2587 euros vs. 2948 euros), and smoked more often (42% vs.31%, $p < 0.01$). On the other hand, age, being in a relationship and sunbed use were similar in both groups. Interestingly, risk-takers have less melanoma risk factors (number of naevi and skin phototypes). They have less knowledge about high risk exposure timelines and optimal use of sunscreen protection. Sun protection measures for their children were less stringent in comparison to the group who used sun protection: wearing of sun glasses systematically or often (42% vs. 59%, $p < 0.01$), systematic use of sunscreen (77% vs. 86%, $p < 0.01$), frequency of renewal (69% vs. 82%, $p < 0.01$) high protective factors (46% vs. 56%, $p < 0.01$), using clothing (84% vs 92%, $p < 0.01$) and hats (88% vs. 92%, $p < 0.01$).
Conclusions: The risk-taker population is characterised by a lower level of knowledge of sun protection tools and behaviours. Their children benefit less from protective measures than those of people who use sun protection. If improving knowledge improves behaviours, this will be critically important since it will impact on both their own behaviour and on the use of protection methods for their children.
No conflict of interest.

3718 POSTER

Melanoma risk in a subfertile population: Results from a large Dutch cohort study

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Background: Associations between hormonal factors and melanoma have been suggested based on associations with parity or exogenous hormone use. Therefore, we investigated whether subfertile women have an altered risk of melanoma.
Methods: In 1996, a nationwide cohort study (the OMEGA-cohort) was set-up to examine the risk of cancer in a subfertile population receiving ovarian stimulation for in-vitro fertilization (IVF). The cohort includes 19,119 women who received IVF and 6,911 subfertile women not treated with IVF. Cancer incidence was ascertained through linkage with the Netherlands Cancer Registry. Melanoma risk in the cohort was compared with the general population and between the IVF group and the non-IVF group.
Results: The risk of melanoma was not increased in the IVF group compared with the non-IVF group (hazard ratio (HR) = 1.02; 95% CI: 0.61–1.72). In addition, no increased risk was found for the IVF group compared with the general population. Nulliparous women had a significantly increased risk for melanoma (HR = 1.63; 95% CI: 1.04–2.56).
Conclusion: In a subfertile population with 38% nulliparous women we found that nulliparity was associated with increased melanoma risk, while IVF does not appear to affect melanoma risk.
No conflict of interest.

3719 POSTER

Comparison between two widely used laboratory methods in BRAF V600 mutation detection rate in FFPE clinical samples of stage III cutaneous melanoma metastases to the lymph nodes

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The aim of the study was to compare detection rates of somatic oncogenic *BRAF* mutations in a homogenic group of cutaneous melanoma stage IIIB/C patients by the Cobas® BRAF V600 Mutation Test and direct Sanger sequencing.
Material and Methods: The study group consisted of 236 FFPE melanoma lymph node metastases, collected during regional lymphadenectomy in one cancer center in the period 1994–2012. All samples were re-analysed by a pathologist. The majority had a tumour content of >90% and none <40%. *BRAF* mutational status was verified by 1.) an in-house PCR/Sanger sequencing test, using the BigDye® Terminator v3.1 Cycle Sequencing Kit and a ABI3731 instrument (Applied Biosystems) and 2.) the Cobas® 4800 BRAF V600 Mutation Test (Cobas®) with respective equipment (Roche Diagnostics).
Results: Considered as a gold standard in mutation analysis, Sanger sequencing approach enabled us to obtain results for 230/236 samples. In 140, the mutation in codon 600 of *BRAF* (60.9%) was found, additionally 4 mutations outside codon 600 were identified. The 86 remaining samples were wild type (WT). V600E accounted for 91.4% of all mutated cases (128 samples) followed by V600K substitution (9 samples, 6.4%), V600E2 (double substitution) in two cases and one V600D. Cobas® generated results in all 236 cases, point mutations changing codon V600 were detected in 144 of them (61.0%). Among 6 cases that were not amplifiable by the standard sequencing approach, 5 turned out to be positive and 1 was negative for the V600 mutation. Additionally the Cobas® test detected mutations in 5 samples that were negative by the other method.
Interestingly, sequencing allowed us to detect codon 600 mutations in 6 cases negative as assessed by Cobas®, 2 V600E samples and 4 that were V600K. In total, both tests provided us with the same *BRAF* mutational status in 215 out of 230 cases (93.5%).
Conclusions: Frequency of *BRAF* V600 mutations differed depending on the test applied, with 93.5% conformity. Sequencing was a powerful method to detect mutations other than V600, while Cobas® proved to be less susceptible to poor DNA quality or investigator bias.
The study was supported by the Polish National Science Centre grant no. 2011/03/B/NZ5/04513.
No conflict of interest.

Table 1. Sanger sequencing vs Cobas® test

Mutations as by Sanger sequencing	Cobas® 4800 BRAF V600 Mutation Test	
	mutation detected	mutation not detected
V600E	126	2
V600K	5	4
V600E2	2	0
V600D	1	0
WT	5	81
no result	5	1
other than V600	n.a.	4

n.a., not applicable.

3720 POSTER

A novel companion diagnostic assay for BRAF V600E/K detection in melanoma: High clinical concordance of patient outcomes for trametinib and debrafenib treatment

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Background: THxID™-BRAF Assay was developed to detect BRAF V600E/K in formalin-fixed paraffin-embedded (FFPE) melanoma samples. The clinical performance of this assay has been evaluated in GSK-sponsored Phase III clinical trials MEK114267 (Trametinib) and BRF113683 (Dabrafenib) for subjects with BRAF V600E/K (mut+) melanoma. This study was incorporated in both trials to evaluate clinical concordance between the THxID™-BRAF Assay and the Investigational Use Only (IUO) assay from Response Genetics Inc. (RGI) on mut+ patients treated with Trametinib and Dabrafenib respectively.
Materials and Methods: Samples from subjects enrolled in MEK114267 and BRF113683 were tested retrospectively using THxID™-BRAF Assay and comparisons were made to the results from RGI IUO. Clinical outcomes were evaluated for the subjects randomized for treatment. For Trametinib trial (MEK114267), a total of 288 samples were tested with 282 reported mut+ by both assays and 6 samples with discordant results. For Dabrafenib trial (BRF113683), a total of 229 subjects were reported mut+ by both assays and 8 samples with discordant results. All subjects with mut+ by both assays were included in the clinical concordance analyses.
Results: For both Trametinib and Dabrafenib, the hazard ratio (HR) for progression free survival (PFS) for the subset of THxID™-BRAF mut+ subjects (Trametinib HR = 0.43; Dabrafenib HR = 0.32) was similar to that from the randomized population (Trametinib HR = 0.45; Dabrafenib HR = 0.30) respectively; both analyses were statistically significant. Median PFS was the same regardless of assay (Trametinib: 4.8 months for Trametinib and 1.5 months for Chemotherapy; Dabrafenib: 5.1 months for Dabrafenib and 2.7 months for DTIC). To help establish concordance, a 95% CI around the difference of the point estimates of the natural logarithm of the hazard ratio (ln[HR]) in the randomized and THxID™-BRAF Assay mut+ populations was constructed. There was no significant difference between ln[HR] (difference between ln[HR] estimates was 0.046 from Trametinib and −0.012 from Dabrafenib).
Conclusions: The THxID™-BRAF Assay demonstrated high clinical concordance with the RGI IUO assay for detecting BRAF V600E/K mutations. Similar efficacy results were seen between the randomized population and the subset of THxID™-BRAF mut+ subjects.
Conflict of interest: *Other substantive relationships: All authors are employed by the organization they are associated with. All organizations were involved in completing and/or sponsoring the research.*

3721 POSTER

Metastatic basal cell carcinoma in the U.S. Veterans Affairs population

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Background: Metastatic BCC (mBCC) is rare, occurring in 0.0028% − 0.55% of BCC cases, not well characterized, and less than 400 cases have been reported in medical literature. The objective of this study is to describe the clinical, treatment and survival outcomes of mBCC patients (pts) in the Veterans Health Administration (VHA), the largest integrated healthcare system in the U.S.
Methods: Natural language processing (NLP) was used to identify mBCC pts treated at the VHA between 1999–2011 due to lack of BCC-specific ICD-9 codes. Pts with other primary cancers within 12 months of 1st documentation of BCC were excluded. mBCC was defined as pts with metastases to a distant organ or lymph nodes. All NLP-identified cases were confirmed for mBCC diagnosis (Dx) through chart review. The index date was the 1st documented Dx of mBCC. Baseline demographic, treatment, and survival outcomes were summarized. Due to limitations with NLP, ICD-9 codes occurring post-mBCC index date were used as a proxy to summarize lesion location (173.xx) and sites of metastases (196.xx–198.xx). Date of death was obtained through linkage with the National Death Index.
Results: A total of 475 mBCC pts were identified with median follow-up of 17.5 months, representing 0.13% of BCC cases. Median age was 72.0 yrs, 97.9% male, and 76.4% non-Hispanic white. Prevalent comorbidities were diabetes without complications (14.1%), chronic pulmonary disease (11.4%), congestive heart failure (7.0%), cerebrovascular disease (6.5%), and renal disease (6.5%). The most commonly coded lesion sites were unspecified (64.8% pts), unspecified parts of the face (28.0% pts), ear and external auditory canal (13.1% pts), and scalp and skin of neck (13.1% pts). Based on NLP, 28.8% pts indicated lymph node involvement. ICD-9 codes for site of metastases were reported in only 30% of pts. mBCC pts were treated with chemotherapy (24.2%), radiation (11.4%), and surgical treatment (37.5%). At end of observation, 272 mBCC pts (57.3%) were deceased. Amongst the subgroup of deceased pts, the median interval between mBCC Dx and all-cause death was 11.8 months [range 0–138.1 months].
Conclusions: In this study, demographic and disease characteristics of large cohort of mBCC pts from a U.S. military veteran population are presented. mBCC prevalence and time to death is consistent with reported literature. Additional research is warranted to further characterize this patient population.
Conflict of interest: *Ownership: AWC Kamauu is an owner of Anolinx LLC. Corporate-sponsored research: AWC Kamauu received research funding from Genentech, Inc, F. Hoffman-La Roche Ltd, Mylan Specialty and Shire PLC. Scott DuVall: SL DuVall has received research funding from Anolinx LLC, Genentech Inc, F. Hoffmann-La Roche Ltd, Amgen Inc, Shire PLC, and Mylan Pharma LP. Other substantive relationships: Tyler Forbush: Employee of VA Salt Lake City Health Care System. Olga Patterson: Employee of VA Salt Lake City Health Care System. Yeun Mi Yim and Carolina Reyes are employees and have stock ownership of Roche.*

3722 POSTER

Frequency and characteristics of familial melanoma in Spain: Preliminary results of the FAM-GEM-1 study

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Background: It is estimated that 5−10% of melanoma cases occur in a familial setting. The most known high and intermediate susceptibility genes are CDKN2A and M1CR respectively, but they explain less than 1/3 of the cases. The classic definition for familial melanoma (FM) is the presence of 2 or more first degree relatives with melanoma. Multiple melanoma, early age and family history of pancreatic cancer (PC) are also risk factors for carrying a mutation in CDKN2A. In Spain there are no studies that cover all the territory.
Methods: FAM-GEM-1 is a national, observational, 2 years-registry study (2011–2013), conducted by the Spanish Multidisciplinary Melanoma Group (GEM), whose principal objective is to assess the rate of melanoma patients with family history of melanoma in Spain. Secondary objectives are to analyze whether patients with family history are different from sporadic melanoma in terms of clinical, pathological and molecular features; and to constitute a registry of FM in order to deeper characterise these patients in further studies. We present the exploratory results of the first 274 patients registered.
Results: We did not find any significant differences in clinical or pathological characteristics between patients with family history of melanoma or PC and melanomas without family history. There were higher rate of presence of multiple nevi in patients with family history of PC (41.7%) versus patients without it (19.4%) ($p = 0.07$). BRAF mutation was detected in 4 of 5 (80%) cases analysed in the melanoma with melanoma family history.
Conclusions: In our study, almost 11% of patients have family history of melanoma (63% fulfil classic FM criteria) and 4% of PC. There were no significant differences in clinical or pathological characteristics between groups, although there was a trend for higher rate of history of multiple nevi and the presence of PC in the family. BRAF mutation in melanomas with FM has been detected in a high rate, needing further study.
No conflict of interest.

	Family history of melanoma N (%) 30/274 (10.9) 19/30 (63.3) first degree	Family history of pancreas N (%) 12/274 (4.4)	No family history N (%) 232/274 (84.7)	*p* value (t or Fisher Exact)
Gender (male)	16/30 (53.3)	6/12 (50)	120/232 (51.7)	N.S
Multiple nevi	8/30 (26.7)[a]	5/12 (41.7)[b]	45/232 (19.4)[c]	N.S. b vs c 0.07
Phototype I–II	12/30 (40)	6/12 (50)	124/227 (54.6)	N.S.
Age of diagnosis (median years)	50	53	53	N.S.
Multiple melanoma	1/29 (3.4)	0/12 (0)	14/228 (6.1)	N.S.
Breslow (mm) mean	2.14	1.99	2.18	N.S.
Ulceration	5/29 (17.2)	3/12 (25)	42/225 (18.7)	N.S.
Positive nodes	4/30 (13.3)	1/12 (8.3)	40/232 (17.2)	N.S.
Origin in nevus	8/28 (28.6)	4/10 (40)	58/206 (28.2)	N.S.
Braf mutant	4/5 (80)	0/1 (0)	15/33 (45.5)	N.S.
Metastases	5/30 (16.7)	3/12 (25)	51/229 (22.3)	N.S.
Other tumors	3/30 (10)	1/12 (8.3)	22/232 (9.5)	N.S.

3723 POSTER

Relevance of indoleamine 2,3-dioxygenase as prognostic biomarker in melanoma patients

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Background: Previous studies have suggested the value of indoleamine 2,3-dioxygenase (IDO), a tryptophan-catabolizing enzyme with immune-regulating activities, as prognostic factor in melanoma. In this study, we analyze the lactate dehydrogenase (LDH) and S100B serum levels (the most commonly markers used in melanoma) and the IDO expression in melanoma patients, in order to determine the useful prognostic relevance of IDO in comparison with LDH and S100B.
Material and Methods: For a period of four years, 201 melanoma patients with a median age of 59 years at the time of diagnosis (range: 25−91) were enrolled in this study. Healthy controls were also included (n = 43). The study was approved by the medical ethical committee of Burgos University Hospital. All patients signed written informed consent. We analyzed serum levels of LDH, S100B, and IDO (measured as levels of kynurenine in peripheral blood) at the moment of diagnosis and in the course of the disease (every 3 months). In order to detect relapse and distant metastases, clinical/radiological evaluations were scheduled every 3, 4 or 6 months in first, second and thereafter years, respectively.
Results: At the time of diagnosis, only patients with stage IV presented a significant increase in LDH and S100B serum levels with respect to controls. However, IDO serum levels were increased in a clinical stage-dependent fashion, being the difference statistically significant in patients with stage II, III and IV (1.3-, 1.4- and 1.5-fold increase, respectively, with respect to control values; $p < 0.001$). In relapse patients, the three biomarkers were significantly increased with respect to the values performed at the time of diagnosis. In addition, IDO levels were higher in patients with lymphatic dissemination ($p < 0.001$). In fact, we found that IDO values above 1.45-fold of the controls is correlated with lymphatic dissemination (80% sensitivity; 83% specificity; area under the receiver operating characteristic curve, ROC-AUC 0.85), and with a significant decrease in overall survival ($p = 0.011$).
Conclusions: Our results suggest that IDO could be a good prognostic marker for melanoma and useful to predict recurrences or metastatic disease.
This study has been supported by grants from the University of the Basque Country (UPV/EHU), SACYL, Caja Burgos and Mutua Madrileña.
No conflict of interest.

3724 POSTER

Predictive factors for the development of brain metastases in patients with malignant melanoma: A study by the Anatolian Society of Medical Oncology

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Background: The development of brain metastases (BMs) were associated with poor prognosis in melanoma patients. Patients with BMs have a median survival of <6 months. Solitary BMs are more common in melanoma compared with other solid malignancies. Our aim was to identify factors predicting development of BMs and survival.
Patients and Methods: We performed a retrospective analysis of 520 melanoma patients between 2000 and 2012. After eliminating patients who had BMs at the time of melanoma diagnosis and patients who had dropped out of follow up, 470 remaining patients were analyzed. The logistic regression analysis were used to identify the clinicopathological features of primary melanoma that are predictive of BMs development and survival after a diagnosis of brain metastases. Clinical variables such as the presence of neurological symptoms, and the extracranial disease at the time of BMs diagnosis were also assessed.
Results: There were 52 patients (11.1%) who developed melanoma BMs during the study period. The ages of patients with BMs, ranged from 28 to 82 with a median age of 51, and 73.1% of the patients were male. At the time of BMs diagnosis, 61.5% (n = 32) of patients had evidence of extracranial disease. The majority of patients with BMs had neurological symptoms (89.4%). The median post-BMs survival was 4.1 months (range 2.9−5.1 months). On logistic regression analysis site of the primary tumor on the head and neck ($p = 0.002$), primary tumor thickness (Breslow $\geqslant$4 mm) ($p = 0.008$), ulceration ($p = 0.007$), pathologically N2 and N3 disease ($p = 0.001$), were found to be significantly associated with the development of BMs. In univariate analysis, tumor thickness, mitotic index, AJCC stage, performance status had a significant influence on post-BMs survival. In multivariate analysis, these clinicopathologic factors were not remained as significant predictive factors.
Conclusions: Our results revealed the importance of primary tumor characteristics associated with the development of BMs. Ulceration, primary tumor thickness, anatomic site, and pathologic $\geqslant$N2 disease were found to be significant predictors of BMs development.
No conflict of interest.

3725 POSTER

Increasing number of melanoma in situ in Serbia due to media campaign − experience of melanoma center

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Background: Melanoma is the most serious type of cancer of the skin and is becoming increasingly common, worldwide. The incidence rates in Australia and New Zealand (between 30−40 per 100,000) are about four times higher than those found in North America and the United Kingdom, though in Serbia incidence is about 5 per 100,000. The incidence of melanoma in situ is growing significantly. Detection at the stage provides the highest cure rate for melanoma, but reliable detection with digital epiluminesence microscopy may allow more precise detection of melanoma in situ.
Material and Methods: During the period of five years, from the beginning of opening Melanoma Center, we examined 11,352 patients with the total number of 354,785 evaluated digital images with an integrated system for digital epiluminescence microscopy based on a new concept of illumination.This system combines an easy to use microscope with excellent optical quality and modern computer technology for efficient

data storage and retrieval.Therefore, simultaneous dermatologist/patient on screen observation of potential mole alteration is made possible. The integrated system has capability to recall and display stored images.
Results: In total, 354,785 pigmented lesions from 11,352 selected patients were evaluated using digital epiluminescence microscopy. Comparison with histology was performed on the 1022 surgically excised lesions.Epiluminescence microscopy sensitivity, specificity, positive and negative predictive values as well as agreement for the different risk levels of the lesions were determined. Of the 1022 cutaneous pigmented lesions removed and histological examined, *232 (22.7%)* were non-melanocytic lesions and *790 (77.3%)* were melanocytic lesions. Sensitivity and specificity of digital epiluminscence microscopy in the analysis of melanocytic lesions with a pigment network were both very high (99.8% and 98.7%, respectively). Forty-seven new case of *thin melanoma* (Clark I and II, Breslow I) were identified from one hundred seventy six new cases of all types of melanoma *(26.7%)*. A remarkable proportion of melanoma *in situ* (21 out of 176; *11.9%*) was diagnosed exclusively by digital epuluminescence microscopy.
Conclusions: The prognosis of melanoma can be improved if the tumor is recognized and treated in its early phase.Our study clearly shows that a nationwide public melanoma education campaign significantly reduces the mean Breslow invasion thickness of all melanomas in patients seen in one institution. Although this phenomenon persisted in the post campaign year, the Breslow thickness increased in the years thereafter. Nevertheless, the increased number of patients with earlier stages of the disease during the campaign proves the value of melanoma education campaigns. The immediate worsening of the prognostic features in the post campaign years strongly indicates the need for a permanent education of professionals and the public.
No conflict of interest.

3726 POSTER

Sentinel lymph node biopsy is less frequently performed in melanoma patients with a low socioeconomic status

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Background: Sentinel lymph node biopsy (SLNB) is a widely accepted procedure and is recommended for patients with a cutaneous invasive melanoma with a Breslow thickness larger than 1 mm. However, in the United States this procedure is only performed in approximately half of these patients. Performing a SLNB in the US is associated with patient factors including high socioeconomic status and possession of a private health care insurance. The latter of these factors is not applicable in the Netherlands since every patient is insured for health care. Therefore the aim of the present study was to analyse whether socioeconomic status of melanoma patients had an influence on the frequency of performing SLNB.
Material and Methods: Patients who were diagnosed with a cutaneous invasive melanoma of $\geqslant$1 mm between 2004 and 2011 from the north-eastern part of the Netherlands were selected from the Netherlands Cancer Registry (n = 2428). An estimate of the socioeconomic status was defined by income, employment, and level of education. Patients were equally divided over five groups based on socioeconomic status. The Chi square test was used to analyse the association between socioeconomic status and the use of SLNB, for this association odds ratios were defined using univariate logistic regression. Furthermore, the chi square test was also used to analyse if the frequency of SLNB had significantly increased during the past 8 years.
Results: SLNB was performed in 1014 of the 2428 patients (41.8%) The frequency of performing SLNB increased from 24.9% in 2004 to 55.2% in 2011, which was a significant increase (P<0.01). There was a significant association between socioeconomic status and the frequency of performing SLNB (P = 0.05). The group of patients with the highest socioeconomic status had an odds ratio of 1.4 (95% confidence interval: 1.05–1.75) for undergoing a SLNB compared to the group of patients with the lowest socioeconomic status.
Conclusions: In 2011 SLNB was only performed in 55.2% of the patients with a cutaneous invasive melanoma $\geqslant$1 mm, while it has become a recommended staging procedure for these patients. The frequency of performing SLNB has increased over the last 8 years. SLNB is less frequently performed in melanoma patients with a low socioeconomic status and this will have an impact on their disease free and overall survival.
No conflict of interest.

3727 POSTER

Sentinel lymph node biopsy improves regional disease control for selected patients with thin melanomas

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Background: Recently updated clinical practice guidelines suggest that sentinel lymph node biopsy (SLNB) only be offered to selected patients with thin melanomas as these patients generally have an excellent prognosis and a low incidence of SLN metastasis. Yet, nearly 25% of all melanoma-related deaths result from thin primaries. It is unclear whether SLNB with selective LN dissection (LND) represents an opportunity to cure patients with high-risk thin melanoma or whether LN disease in these patients lacks the clinical significance of nodal metastasis in patients with thicker tumors.
Methods: From our Melanoma Registry, we identified 339 consecutive thin (clinical stage T1 N0) melanoma cases in 301 patients. Data were verified by pathology and record review. Median patient follow up was 61 months.
Results: Thirty-seven patients (12.2%) underwent SLNB. Patients selected for SLNB were younger (median 57 vs 69 years, p = 0.03), with thicker (median 0.68 vs 0.25 mm), more often level IV/V (43.2 vs 5.3%), ulcerated (15.3 vs 0.3%) and mitotically active (67.6 vs 22.3%) melanomas, all p < 0.001. Three patients (8.1%) were SLN-positive: one patient had isolated tumor cells in a solitary SLN, one had several 0.1 mm metastatic foci in one of 2 SLNs, and one had 2.0 and 0.2 mm foci in 2 of 2 SLNs. None had additional positive LNs detected at completion LND. After a median of 32 (IQR 19−82) months, disease recurred in 6/37 patients after SLNB (16.2%) and 20/264 non-SLNB patients (7.5%). Isolated regional recurrence was the site of first relapse in 9/264 non-SLN patients (3.4%, or 45% of recurrences in non-SLN patients) but in none of the SLN biopsy patients, p < 0.001. Melanoma specific survival was governed by tumor thickness.
Conclusions: SLNB with selective LND appears to provide excellent regional disease control for selected patients with thin melanomas. For the few patients with thin melanoma found to harbor SLN metastasis, completion LND is advised although the likelihood of identifying additional nodal metastatic disease is small. Whether some early melanoma patients have even microscopically occult nodal disease which may be cured with SLNB alone is an intriguing hypothesis that warrants further investigation.
No conflict of interest.

3728 POSTER

Residual melanoma after an excisional biopsy is an independent prognostic factor for local relapse and overall survival

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Background: Excisional biopsy with a 1−3 mm margin of normal skin and a cuff of subcutaneous fat is a preferable method of biopsy for any suspicious pigmented skin lesion. After micro staging of a primary melanoma a wide (re)excision with/without a sentinel lymph node biopsy (SLNB) should be performed according to the thickness of the primary melanoma. There is a very few data about the impact of residual melanoma on frequency of a local relapse and on overall survival.
The aim of this study was to evaluate the effect of a residual melanoma after an excisional biopsy on prognosis of patients with cutaneous melanoma.
Material and Methods: Between 2000 and 2007 SLNB with/without wide reexcision of a primary melanoma site was successfully performed in 692 patients (315 male and 377 female; mean age 55.7 years) at the Institute of Oncology Ljubljana, Slovenia. Clinicopathological data of all patients were extracted from a prospective institutional melanoma database and the frequency of local relapses and survival were compared between patients with residual melanoma and those without it. For a statistical analysis univariate and multivariate analyses were used.
Results: Only 25 (3.6%) patients had a residual melanoma. There was no difference in mean tumour thickness (3.91 and 2.79 mm) and ulceration (40% and 34%) of the primary melanoma between patients with and without residual melanoma. However, a number of local relapses (16% versus 2.7%) and a number of metastases in sentinel lymph nodes (44% versus 22%) were significantly higher and a 5-year survival was significantly lower (64% versus 87.5%) in patients with residual melanoma. Breslow thickness, ulceration, positive SLNB and residual melanoma were independent prognostic factor for overall survival.
Conclusions: Residual melanoma is very rare after an excisional biopsy of the primary melanoma. However, when present it indicates a higher probability of local relapse and a worse overall survival.
No conflict of interest.

3729 POSTER

The number of metastatic foci in positive sentinel nodes with a tumor burden <0.1 mm does not affect prognosis of melanoma patients

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Background: Controversies exist in order to perform a routine completion lymph node dissection (CLND) in melanoma patients with Sentinel Lymph-Node (SLN) metastases <0.1 mm, showing they similar survival rates of SLN-negative patients. The aim of the present study was to investigate this population of patients in order to define factors affecting survival.
Material and Methods: A SNL positivity was found in 348 of 2013 stage I/II patients consecutively treated from 2000 to 2006. The analysis categorized topography of SN-metastases, amount of SN tumor burden and number of metastatic foci. Non-SLN positivity and Melanoma Specific Survival (MSS) were evaluated.
Results: Mean Breslow thickness was 2.1 mm; mean FU was 46 months. Cases with SLN metastasis <0.1 mm were 33 (9.5%). Patients were shown to have similar estimated 5-year MSS rates in the subgroup with one metastatic focus as well as in that with more than one (93% and 91%). Similar rates were found in the two subset of patients relatively to non-SLN positivity (6% and 7%). Topography of SLN involvement had impact on MSS whereas patients with sub-micrometastases present in the subcapsular area only did not show non-SLN positivity and had an estimated 5- and 10-year MSS of 98%.
Conclusions: Our data suggest that patients with SLN sub-micrometastases (<0.1 mm) could be judged as those SLN-negative irrespectively from the number of metastatic foci located in the subcapsular area.
No conflict of interest.

3730 POSTER

Isolated limb perfusion in the management of in-transit melanoma metastases: A monoistitutional experience

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Background: The Isolated Limb Perfusion (ILP) is an established treatment for melanoma *in transit* metastases (ITM) but the use of tumour necrosis factor (TNF) α is not uniformly accepted. This study reports on a monoinstitutional experience in performing TNF and melphalan-based ILP.
Patients and Methods: A total of 377 ILP were performed on 343 patients with stage IIIB/IIIC melanoma between 1991 and 2012. Melphalan doses were 10−13 mg/l (leg and arm, respectively); TNF was performed at high doses of (3−4 mg) up to 2004 (n = 199) and at low doses of TNF (1−2 mg) from 2004 to 2012 (n = 144) under mild hyperthermic conditions (38ºC-39.5ºC.).
Results: Median follow up was 92 months. Five-year overall survival (OS) was 40% and median survival was 42 months. Stage IIIB and IIIC patients had a 5-year OS rate of 49% and 27%, respectively. Complete, partial and minor responders had a 55%, 33% and 20% 5-year OS, respectively. A second ILP was performed in 30 patients, a third ILP in 4 patients. Treatment-related mortality was observed in 3 patients (0.9%). Severe or grade V toxicity occurred in 6 patients (1.8%). A second or a third ILP performed in the same patient did not cause increased morbidity and provided improved local control. Stage of disease and the extent of immediate response are two significant prognostic factors.
Conclusions: ILP with Melphalan and TNF was an effective treatment modality for melanoma with ITM, in order to obtain a loco-regional disease control.
No conflict of interest.

3731 POSTER

The UK sentinel lymph node biopsy service in stage 1B cutaneous melanoma

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Introduction: Sentinel Lymph Node Biopsy (SLNB) has been advocated as part of the diagnostic and prognostic process in the 2010 updated guidelines for management of cutaneous melanoma. However, there remains some discrepancy in practice across the UK regarding offering SLNB in patients with 1B melanoma (ulceration or mitotic rate $\geqslant 1/mm^2$).
Materials and Method: Fifty-two plastic surgery units from the UK were identified and contacted via telephone and email. Responses were predominantly obtained from skin cancer specialist nurses and consultants interested in skin cancers.
Results: Of the 52 units surveyed, 40% provide a SLNB service within their trust. Of these, 71% offer the surgery to stage 1B patients with either ulceration or high mitotic rate. Specifically, 57% routinely offer SLNB to patients with stage 1B disease due to ulceration; and 62% to stage 1B disease due to a high mitotic rate.
Conclusions: Despite recommendations from the UK guidelines, variation in management of melanomas remains. The risk of a positive SLNB in <1 mm melanoma is quoted at between 5 and 10%. Further studies are therefore warranted to look at the relationship between SLNB outcomes and Stage 1B disease, to guide us in formulating a more united approach to patient management across the UK.
No conflict of interest.

3732 POSTER

Gastrointestinal melanoma metastases surgery in the age of targeted therapy

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Background: Malignant melanoma is the most common tumour metastatic to the gastrointestinal tract. The aim of this study is to assess in a large series of patients the clinical outcomes following therapeutic or palliative surgery of gastrointestinal tract melanoma metastases. The significance of the prognostic factors who affect the prognosis will be evaluated too.
Material and Methods: From 1985 to date 106 patients affected by Stage IV melanoma underwent surgical resection for gastrointestinal metastases at the Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy. The surgical procedure performed was radical or incomplete resection of intestinal metastases. Post operative outcomes were collected and studied by a multivariate analysis. In a small subgroup of patients recently treated gene BRAF mutational status was also evaluated.
Results: In 62/106 (58.5%) patients who underwent surgical resection for gastrointestinal metastases the primary melanoma was nodular type. All patients usually showed symptoms due to anemia and/or bowel obstruction. The intent of surgery was palliative in 61 (57.5%) and therapeutic in 45 (42.5%). Surgical procedure performed was ileal resection in 57 patients, digiunal resection in 31 patients, large bowel resection in 11 patients and duodenal resection in 7. 37 operations involved multiple small bowel resection and/or another intraabdominal organ. The 5-year survival in the group of patients who received a complete resection was significantly higher than in the incomplete resection group. A multivariate analysis identified as important prognostic factors for survival the complete surgical resection of the recurrence (P = 0.0001) and the single site visceral metastases (P = 0.0001). Preliminary and observational data in 35 patients seem to correlate a higher presence of BRAF mutation to long survivor patients.
Conclusion: In highly selected patients with melanoma metastatic to intra abdominal solid organs an aggressive attempts at complete surgical resection may improve the 5-year and disease free survival. The prognostic value of presence of BRAF V600 mutation will be evaluated in a larger series of patients as possible biomarker for patients management.
No conflict of interest.

3733 POSTER

Secondary endpoints from OPTiM: A multicenter, randomized phase 3 trial of talimogene laherparepvec vs GM-CSF for the treatment of unresected stage IIIB/C and IV melanoma

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Background: Talimogene laherparepvec (T-VEC) is a novel oncolytic immunotherapy derived from herpes simplex virus type-1 designed to selectively replicate within tumors and to produce GM-CSF to enhance locoregional and systemic antitumor immune responses. OPTiM evaluated T-VEC or GM-CSF for the treatment (tx) of unresected regionally or distantly metastatic melanoma (CT #NCT00769704). Key secondary

endpoint results are reported in addition to the primary results previously reported at ASCO 2013.

Materials and Methods: Patients (pts) had age ⩾18 yrs; ECOG PS ⩽1; unresectable melanoma Stage IIIB/C or IV; injectable cutaneous, subcutaneous (SC), or nodal lesions; LDH ⩽1.5X upper limit of normal; ⩽3 non-lung visceral lesions, and no lesion >3 cm. Pts were randomized 2:1 to T-VEC (initially ⩽4 mL $\times 10^6$ pfu/mL then after 3 wks, ⩽4 mL $\times 10^8$ pfu/mL Q2W) intralesionally or GM-CSF (125 $\mu g/m^2$ qd $\times$ 14 days q28d) SC. *BRAF* status at baseline was collected if known. The primary endpoint was durable response rate (DRR): partial or complete response (CR) continuously for ⩾6 mos starting within 12 mos. Responses were per modified WHO by blinded central review. Key secondary endpoints included OS, objective response rate (ORR) by central review, and time to treatment failure and time to and duration of response (DoR) per investigator.

Results: 436 pts are in the ITT set: 295 (68%) T-VEC, 141 (32%) GM-CSF. Male 57%; median age 63 yrs, Stage IIIB/C 30%, IVM1a 27%, IVM1b 21%, and IVM1c 22%. DRR (95% CI) for T-VEC was 16% (12%-21%) and 2% (0%-5%) for GM-CSF, p < 0.0001. ORR (95% CI) was 26% (21%-32%) with 11% CR for T-VEC, and 6% (2%-10%) with 1% CR for GM-CSF. In an interim analysis of OS there was a trend in favor of T-VEC (HR = 0.79 [95% CI: 0.61–1.02]). With T-VEC, the most common adverse events (AEs) were fatigue, chills, and pyrexia. No grade ⩾3 event occurred in ⩾3% of pts; 26% of T-VEC and 13% of GM-CSF pts had serious AEs. Among responders, DoR was longer with T-VEC (HR = 0.30 [95% CI: 0.13–0.68]; p = 0.003). Responses ⩾12 mos were estimated to occur in 53% (95% CI: 42%-63%) of T-VEC responders. Baseline *BRAF* mutation status was known for 31% of pts in the T-VEC arm; DRR was 11% in both wild-type and mutant pts and 19% in the *BRAF* unknown set.

Conclusions: DRR and ORR are significantly improved with T-VEC in pts with unresectable Stage IIIB-IV melanoma. More than half of T-VEC responses lasted ⩾12 mos and T-VEC treatment was tolerable with an interim trend toward improved OS.

Conflict of interest: *Ownership: Robert Coffin is a shareholder of BioVex. Advisory board: Robert Andtbacka, Kevin Harrington, Frances Collichio, and Jason Chesney have all attended Advisory Boards for Amgen Inc. Board of directors: None. Corporate-sponsored research: Jason Chesney receives research funds from Amgen Inc. Howard Kaufmann corporate sponsored reasearch fro Amgen Inc. Other substantive relationships: Frances Collichio receives lecture fees from Amgen Inc. Ari VanderWalde is a full-time, paid employee of Amgen Inc. Robert Coffin is a consultant for Amgen.*

3734 POSTER

Combined nivolumab (anti-PD-1, BMS-936558, ONO-4538) and ipilimumab in the treatment of advanced melanoma (MEL) patients (pts): Safety and clinical activity

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Background: The immune checkpoint receptors PD-1 and CTLA-4 have non-redundant immunologic functions. Antibody blockade of PD-1 with nivolumab or CTLA-4 with ipilimumab demonstrated substantial activity in pts with MEL. Concurrent treatment with anti-PD-1 and anti-CTLA-4 resulted in synergistic antitumor activity in syngeneic murine tumor models. Therefore, we conducted a phase 1 study of nivolumab combined with ipilimumab in MEL pts.

Materials and Methods: Pts received IV nivolumab concurrently with ipilimumab q3 wk $\times$ 4 doses, followed by nivolumab alone q3 wk $\times$ 4 doses (Table). At wk 24, combined treatment was continued q12 wk $\times$ 8 in pts with disease control and no DLTs. In sequenced cohorts, pts with prior ipilimumab therapy received nivolumab q2 wk $\times$ 48.

Results: Fifty-three and 33 pts received concurrent and sequential nivolumab/ipilimumab, respectively. In the concurrent/sequential cohorts, 57%/55% of pts were stage M1c and 38%/100% received prior systemic treatment. In concurrent cohorts 1−3, treatment-related AEs (rAEs) were qualitatively similar to those observed in published monotherapy studies, although some occurred more frequently. Grade 3−4 rAEs occurred in 53% of pts; the most common were lipase, AST, and ALT elevations. AEs were generally reversible and in some pts required immunosuppressants. Cohort 3 exceeded the MTD (3/6 pts with asymptomatic grade 3−4 lipase elevation) and cohort 2 was the MTD. For cohorts 1−3, aggregate clinical activity rate (aCAR; N = 52 evaluable) was 65%, objective response rate (ORR) was 40%, and 31% of all pts had ⩾80% tumor reduction at 12 wk (Table). In cohort 2 (MTD), aCAR was 65%, ORR was 53%, and all 9 responding pts had ⩾80% tumor reduction at their first assessment. ORR was similar among pts with positive vs. negative baseline tumor PD-L1 expression and among pts with normal/high vs. low (<1000/μL) ALC at wk 5−7 with concurrent therapy. With sequenced therapy, 18% had grade 3−4 rAEs; the most common was lipase elevation; aCAR was 43%, ORR was 20%, and 13% of pts had ⩾80% tumor reduction at 8 wk.

Conclusions: Concurrent nivolumab/ipilimumab had a manageable safety profile and produced clinical activity that appears distinct from published monotherapy data. The data also support the potential activity of the combination therapy irrespective of the explored biomarkers. Based on these results, a phase 3 randomized trial in MEL pts of concurrent nivolumab/ipilimumab vs. each monotherapy will be initiated in 2013.

Conflict of interest: *Ownership: Not applicable. Advisory board: Bristol-Myers Squibb for Drs. Sznol, Postow, and Wolchok. Board of directors: Not applicable. Corporate-sponsored research: Bristol-Myers Squibb for Drs. Sznol, Callahan, and Wolchok. Other substantive relationships: Bristol-Myers Squibb, employment and stock ownership, for Drs. Hong, Selby, Korman, and Gupta*

Cohort	Nivolumab (mg/kg) + Ipilimumab (mg/kg)	n[a]	aCAR[b] (%) [95% CI]	ORR (%) [95% CI]	⩾80% tumor reduction at 12 wk (%)
1	0.3 + 3	14	50 [23−77]	21 [5−51]	4/14 (29)
2	1 + 3	17	65 [38−86]	53 [28−77]	7/17 (41)[c]
2a	3 + 1	16	73 [45−92]	40 [16−68]	5/15 (33)
3	3 + 3	6	83 [36−100]	50 [12−88]	0/6
1−3	Concurrent	53	65 [51−78]	40 [27−55]	16/52 (31)
6	1 + prior	17	69 [41−89]	38 [15−65]	4/16 (25)[d]
7	3 + prior	16	14 [2−43]	0	0/14[d]
6−7	Sequenced	33	43 [26−63]	20 [8−39]	4/30 (13)[d]

[a]Total treated. [b][(CR + PR + uCR + uPR + irPR + SD ⩾24 wk + irSD ⩾24 wk)/response-evaluable pts] $\times$ 100. [c]Two other pts had ⩾80% tumor reduction at their first scheduled assessment, which was after wk 12. [d]First assessment at 8 wk.

3735 POSTER

Vemurafenib treatment in patients with BRAF mutated melanoma failing MEK inhibition with trametinib

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Background: Trametinib was shown to improve progression-free and overall survival in patients with metastatic melanoma with a BRAF V600E or V600K mutation as compared with chemotherapy in the METRIC trial. However, the median duration of response was 5.5 months and median progression-free survival was 4.8 months in the Trametinib group. Vemurafenib and Ipilimumab were still investigational when this trial was initiated but were available in clinical trials for post-protocol treatment.

Material and Methods: In this phase III trial 87 patients out of the 322 patients of the intent to treat population who had metastatic melanoma with a V600E or V600K mutation received vemurafenib (960 mg twice daily orally). We present data on 60 patients with complete information on vemurafenib clinical efficacy subsequently to trametinib failure.

Results: The median progression free survival was 3.6 months with 95% CI 2.8−4.3 and a range of 0.5–12.1 months. The 2 months PFS was 76.7%, the 4 months PFS was 43.3% and at 6 months 18.3% of patients remained without disease progression. Data on progression free survival on the total number of patients receiving vemurafenib post trametinib and survival data will presented at the meeting.

Conclusions: Some patients who developed a resistance to MEK inhibitor trametinib in first or second line of therapy for BRAFV600 mutated metastatic melanoma seem to benefit from vemurafenib treatment. Sequencing BRAF inhibitors with MEK inhibitors are currently under investigation.

Conflict of interest: *Ownership: None. Advisory board: Roche BMS GSK Pfizer Bayer Novartis Amgen Boehringer Ingelheim, Leo Pharma Delcath,*

Merck/MSD Bristol-Myers Squibb Genta GlaxoSmithKline Philogen Sobi. Board of directors: None. Corporate-sponsored research: Pfizer Novartis Genta Sobi MSD Bristol-Myers Squibb. Other substantive relationships: None

3736 POSTER

Phase I trial evaluating concurrent vemurafenib and ipilimumab in patients with advanced BRAF-mutant melanoma

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Background: Ipilimumab (Ipi), a fully human monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4 to augment antitumor immune responses, and vemurafenib (Vem), a potent inhibitor of BRAF V600-mutated kinase, are both approved for the treatment of advanced melanoma. The phase I/II trial, CA184–161, was designed to evaluate concurrent Vem and Ipi in patients (pts) with advanced BRAF-mutant melanoma.
Methods: An escalating 3+3 dose design was planned to determine the maximum tolerated dose of the combination. The first cohort received Vem and Ipi at the full approved monotherapy doses: Vem was initially given alone for 28 days at 960 mg (po bid), followed by Vem in combination with Ipi at 3 mg/kg (IV q 3 weeks x 4). Pts who experienced tumor stabilization or regression received Vem (po bid) + Ipi maintenance treatment (q 12 weeks beginning at Week 24). The second cohort was planned with Vem at 960 mg and Ipi increased to 10 mg/kg in the absence of dose-limiting toxicities (DLTs) in less than one-third of pts in the first cohort. If the first dose level was not tolerated, a dose de-escalated cohort was planned with Vem at 720 mg and Ipi at 3 mg/kg.
Results: A total of 12 pts received Vem, and 10 received Ipi concurrently with Vem, until the trial stopped accruing pts following DLTs in the liver. The first cohort was expanded to 6 pts due to liver DLTs, and overall 4 developed DLTs of grade 3 elevations in aminotransferase levels. These occurred within 2 to 5 weeks after the first dose of Ipi in combination with Vem, and resolved in all 4 pts in 4−12 days with temporary interruption of Vem and use of corticosteroids. The dose de-escalated cohort was explored in 3 pts and expanded to 6 pts. Of the 4 pts who received concurrent Ipi and Vem, 3 had DLTs of elevations in aminotransferase levels within 3 weeks of starting Ipi (two of grade 3, one of grade 2). The remaining 2 pts received only Vem (one pt withdrew consent). One pt in each cohort had an elevation of total bilirubin (grade 2−3) with concomitant grade 3 transaminitis.
Conclusions: Concurrent administration of Vem and Ipi at the approved doses, or with a lower dose of Vem, resulted in hepatotoxicity that was greater than expected for either agent alone. These safety analyses demonstrate the risk of using Vem and Ipi concurrently, and these drugs should not be used in combination outside of a clinical trial. Further investigation should focus on the optimal sequencing of these agents.
Conflict of interest: *Ownership: Konto: Bristol-Myers Squibb (BMS), McHenry: BMS, Choong: Roche employee. Advisory board: Ribas: Roche-Genentech, Hodi: Non-paid, BMS, Callahan: GlaxoSmithKline, Chmielowski: BMS, Genentech, CytRx, Merck, Wolchok: BMS. Corporate-sponsored research: Hodi: To institution clinical trial support, BMS, Callahan: research support from BMS, McHenry: BMS employee, Choong: Roche employee, Wolchok: BMS. Other substantive relationships: Chmielowski: speaker bureau: BMS, Genentech, Prometheus, Konto: BMS employee, Choong: Roche employee.*

3737 POSTER

A phase III trial of nab-paclitaxel vs dacarbazine in chemotherapy-naive patients with metastatic melanoma: Analysis of patients with M1c stage disease

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Background: In a phase III trial, *nab*-paclitaxel significantly improved progression free survival (PFS; 4.8 vs 2.5 months; P =. 044) vs DTIC and demonstrated a trend toward prolonged interim overall survival (OS; 12.8 vs 10.7 months; P =. 094) for the treatment of chemotherapy-naive patients with metastatic melanoma. Patients with metastatic M1c stage disease or an elevated lactate dehydrogenase (LDH) level have a particularly poor prognosis. Here we report on the outcomes of M1c patients.
Methods: Chemotherapy-naive patients with stage IV melanoma and ECOG PS 0−1 were randomized to *nab*-paclitaxel 150 mg/m^2 on days 1, 8, and 15 of a 28-day cycle (n = 264) or DTIC 1000 mg/m^2 on day 1 of each 21-day cycle (n = 265). Before randomization, patients were stratified by region, metastatic stage, and LDH levels. The primary endpoint was PFS by independent radiologic review; secondary endpoints included OS and safety.
Results: The majority of patients had a baseline metastatic stage of M1c (9% M1a, 26% M1b, 65% M1c), 28% had elevated LDH, and 26% had $\geqslant$5 lesions (median 4; range, 0−18). As expected, patients with M1c stage disease had the shortest PFS and OS in either treatment arm vs patients with M1a or M1b stage disease (Table). However, *nab*-paclitaxel conferred a significant PFS advantage compared with DTIC in patients with M1c stage disease (3.7 vs 2.0 months; HR, 0.734; P =. 028). At the interim OS analysis, a trend in favor of *nab*-paclitaxel vs DTIC was also observed in patients with M1c stage disease (Table). The estimated 1-year survival for patients with M1c was 46% for *nab*-paclitaxel vs 40% for DTIC. The incidence of treatment-related grade $\geqslant$3 peripheral neuropathy for M1c patients was 26% for *nab*-paclitaxel vs 0% for DTIC, similar to that observed in the intent-to-treat population.
Conclusions: In this trial of *nab*-paclitaxel vs DTIC, patients with advanced disease (M1c) and poor prognosis showed clinically relevant benefits with acceptable toxicity with *nab*-paclitaxel treatment.
Conflict of interest: *Ownership: AK: Stock ownership in Celgene IE: stock ownership in Celgene. Advisory board: CR:BMS,Roche,GSK and Celgene MPB:Celgene AH: Amgen, AstraZenecai, BMS, Boehringer Ingelheim, Celgene, Eisai, GSK, IGEA, Lilly, MelaSciences, Merck Serono, MSDMerck, Novartis, Oncosec, Roche Pharma CL: Celgene AT: BMS, Roche, GSK, Amgen. Corporate-sponsored research: EH:Celgene MDV:Celgene, Novartis, Roche, Glaxo, BMS MPB:Celgene AH: Amgen, AstraZenecai, BMS, Boehringer Ingelheim, Celgene, Eisai, GSK, IGEA, Lilly, MelaSciences, Merck Serono, MSDMerck, Novartis, Oncosec, Roche Pharma. Other substantive relationships: AH: Speakers' Bureaus AH: Amgen, AstraZenecai, BMS, Boehringer Ingelheim, Celgene, Eisai, GSK, IGEA, Lilly, MelaSciences, Merck Serono, MSDMerck, Novartis, Oncosec, Roche Pharma AK: Employee of Celgene IE: Employee at Celgene AT: Honoraria BMS*

Tumor stage	*nab*-Paclitaxel	DTIC	HR (95% CI)	P value
M1a	n = 27	n = 21		
PFS, months	5.5	3.6	0.614 (0.255–1.479)	0.274
OS,[a] months	17.2	18.3	0.773 (0.313–1.913)	0.577
M1b	n = 66	n = 69		
PFS, months	5.4	5.4	1.027 (0.641–1.645)	0.901
OS,[a] months	15.2	14.1	0.867 (0.550–1.368)	0.538
M1c	n = 171	n = 175		
PFS, months	3.7	2.0	0.734 (0.558–0.965)	0.028
OS,[a] months	11.5	9.2	0.818 (0.632–1.059)	0.127

[a] Interim OS analysis.

3738 POSTER

Phase 2 study of nivolumab (Anti-PD-1; ONO-4538/BMS-936558) in patients with advanced melanoma

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Background: A fully human monoclonal IgG4 antibody, nivolumab (ONO-4538/BMS-936558), which blocks human programmed death-1 (PD-1) receptor expressed on activated T cells, is therefore expected to be a new treatment option for several types of cancers. We evaluated the efficacy and safety of nivolumab in this phase 2 study (ONO-4538−02) with Japanese patients (pts) who had previously been treated for advanced melanoma (MEL) as of December 2012. Potential biomarkers (BMs) were also explored in this study.
Methods: Nivolumab (2 mg/kg IV Q3W) was given to pts until observing unacceptable toxicity, confirmed progression or complete response. Clinical responses were assessed by investigators according to RECIST 1.1 and immune-related RECIST, and were preliminarily analyzed for this presentation. Potential predictive BMs associated with the efficacy and/or safety of nivolumab were explored by assessing tumor tissue, serum and peripheral blood mononuclear cells (PBMC).
Results: Nivolumab was given to 35 MEL pts with an average of 2.1 prior therapies whose responses were evaluable at the time of this analysis. Twenty-seven and 8 pts had ECOG PS 0 and 1, respectively. The ORR and immune-related ORR (irORR) were 23% (8/35 pts) and 28.6% (10/35 pts), respectively. Responses were durable with 172 days of median PFS. Median overall survival had not been reached at the time of this report. The incidence of drug-related AEs was 45.7%. Grade (G) 3/4 drug-related AEs were reported for 17.1% of pts. Relatively frequent AEs consisted of an increase in GGT, anemia, decreased Ht, Hb and RBC counts, and decreased appetite. G3 hepatitis and G2 pneumonitis were reported in 2 and 1 pts, respectively. Psoriasis arthropica was reported in 1pt. No G3/4 pneumonitis or drug-related deaths were reported. Flow cytometric analysis of PBMCs revealed that the number of PD-1-positive CD4 and CD8 T cells decreased from the baseline with nivolumab treatment. The pts are still being followed up in order to identify OS and PFS. Biomarker analysis is underway.
Conclusions: Administration of nivolumab was associated with a durable clinical benefit in approximately one fourth of Japanese pts with advanced MEL without serious safety concerns. These results do not considerably differ from the efficacy and safety profile observed in preceding/ongoing nivolumab clinical studies of Caucasian pts. Thus, further clinical development of nivolumab for MEL pts is warranted.
Conflict of interest: *Advisory board: Ono Pharmaceutical Co.,Ltd*

3739 POSTER

Single agent panitumumab in patients with incurable cutaneous squamous cell carcinoma: A single centre phase II study

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Background: The incidence of advanced cutaneous squamous cell carcinoma (CSCC) is increasing. The objective of this study was to investigate the efficacy of single agent panitumumab in the treatment of incurable CSCC.
Material and Methods: Eligibility included ECOG 0−2 patients deemed to have incurable CSCC not suitable for local therapy or chemotherapy. Prior chemotherapy was permitted. Patients received panitumumab at a dose of 6 mg/kg every 14 days for a maximum of nine cycles, with response assessed after every third cycle prior to proceeding to the next 3 cycles. The primary endpoint was the best overall response rate (ORR) as assessed by RECIST version 1.1.
Results: Between May 2010 and May 2012, 16 patients were recruited. Fourteen patients were male and the median age was 69. Fourteen patients had locoregionally recurrent disease with 15 patients receiving previous radiotherapy and 4 patients receiving previous cytotoxic chemotherapy. The best overall response rate (partial or complete response, PR or CR) was 37.5% (4/16 PR, 2/16 CR) with a further 5 of 16 patients achieving stable disease. The duration of overall response was a median of 8 months. Grade 3 or 4 events were observed in 5 patients (all skin toxicity) with 1 patient ceasing due to skin toxicity. With a median follow up of 11 months, 9 patients died due to progressive disease, 7 are alive, 1 patient with no evidence of disease at the time of analysis.
Conclusions: Single agent panitumumab is a safe and effective agent in the management of incurable CSCC.
Conflict of interest: *Corporate-sponsored research: Amgen − provided panitumumab free of charge and provided research support.*

3740 POSTER

The Italian Network for Tumor Biotherapy (NIBIT)-M1 study: 2-years survival update for metastatic melanoma patients treated with ipilimumab in combination with fotemustine

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Background: In spite of limited objective tumor responses, ipilimumab (IPI) significantly improves the survival of metastatic melanoma (MM) patients (pts). The efficacy of IPI, alone or in novel combinations, is being explored also in sub-sets of MM pts, including those with brain metastases (mts). We recently reported the efficacy of IPI in combination with fotemustine (FTM) in MM pts with or w/o brain mts enrolled in the phase II NIBIT-M1 trial. The immune-related Disease Control Rate (ir-DCR) was 46.5%, with a median OS of 13.3 months (mo) (8.9–19.9), and a 1-year survival rate of 52.6% (Di Giacomo, et al. Lancet Oncol, 2012). We now report the up-dated efficacy from the NIBIT-M1 study, with the assessment of *BRAF* mutation status and its correlation with clinical outcome.
Material and Methods: MM patients received an induction therapy with IPI 10 mg/kg every 3 weeks (Q3W) for four doses and FTM 100 mg/m^2 weekly for 3 weeks, as first or second-line treatment. IPI and FTM maintenance therapy was administered Q12W from Week 24 and Q3W from Week 9, respectively. This analysis reports the median OS and PFS (mo, 95% CI), 1- and 2-yrs survival rates, and ir-Duration of Response (DOR) (mo, 95% CI) for the global population, and for the subpopulation of pts with brain disease. The *BRAF* V600E mutation status was retrospectively determined by PCR-based assay.
Results: Eighty-six pts with unresectable Stage III (3 pts) or Stage IV (83 pts) MM were treated in 7 NIBIT Centers; 20 pts had asymptomatic brain mts at baseline. With a median follow-up of 23.7 mo, median OS was 12.7 mo (7.2–18.2), 1- and 2-year survival rates for the whole study population were 51.2% and 30.7%, respectively; in pts with brain mts, median OS was 12.7 mo (2.7–22.7), 1- and 2-year survival rates were 55.0% and 38.9%, respectively. Median PFS was 4.5 mo (3.1−5.9) and 3.4 mo (2.3−4.5) for the whole study population and for pts with brain mts. Median ir-DOR was 23.9 mo (15.5–46.5). The ir-DCR for BRAF mutant melanoma was 46.3% (19/41) compared with 60% (18/30) in pts with *BRAF* wild-type (WT) gene ($p = 0.25$). Median OS for *BRAF* mutant melanoma and WT pts were 10.0 mo (5.5–14.5) and 17.3 mo (10.3–24.3), respectively ($p = 0.23$).
Conclusions: The combination of IPI and FTM explored in the NIBIT-M1 trial continues to demonstrate effective in MM pts with or w/o brain mts. No significant association between *BRAF* V600E mutation status and clinical outcome was detected.
Conflict of interest: *Ownership: No. Advisory board: Bristol-Myers Squibb for Ascierto, Queirolo,Testori,MaioRoche for Ascierto, Queirolo,TestoriGSK for Ascierto, Queirolo,Testori. Board of directors: No. Corporate-sponsored research: No. Other substantive relationships: NO*

3741 POSTER

A prognostic model for metastatic melanoma treated with ipilimumab

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Background: Metastatic melanoma usually has a dismal prognosis, also because its treatment options have been deluding for long time: until recently, systemic therapies were limited, with poor response rates and short survival advantage. Ipilimumab is a monoclonal anticytotoxic T-lymphocyte antigen 4 antibody that was demonstrated to improve survival of metastatic melanoma patients, but may be associated with immunological toxicities and may impact on National Health Service costs. This is an independent pilot study aimed to design a prognostic model of response to therapy with ipilimumab in the metastatic melanoma setting, with the purpose to improve the identification of patients who would benefit most from therapy.
Materials and Methods: Prospectively collected data of 75 consecutive patients with metastatic melanoma, who received therapy with ipilimumab in the Italian expanded access program (3 mg/kg, q3w), were analysed under a Cox regression model to identify prognostic factors and biomarkers. We analyzed clinical data (sex, melanoma localization and stage at diagnosis, patients' age at first diagnosis and metastatic recurrence, relapse-free interval (RFI), site and number of metastases, previous chemotherapies) and baseline biological data (blood levels of LDH, C-reactive protein, beta-2-microgloulin, VEGF, interleukin-2, interleukin-6, S-100, ALP, transaminases, total circulating leucocytes and subpopulations of lymphocytes and granulocytes analyzed with cytofluorometry). The Wald test was used to assess the significance of each variable included in the full Cox model, only variables with $p \leqslant .05$ were maintained in the final Cox model after fast backward variable selection. Validation was performed with bootstrap method.
Results: After a median survival of 9.9 months from first ipilimumab administration, 7 patients were alive. Covariates that resulted associated with prognosis were sex (HR = 5.01 for female, 95% CI 1.52–16.56), RFI (protective effect of long RFI, HR = 0.60, 95% CI 0.37–0.99), M1a metastatization (HR = 0.23, 95% CI 0.07–0.73), total blood leucocytes (worse prognosis for higher levels of leucocytes, HR = 3.02, 95% CI 1.62–5.63). Among the granulocyte and lymphocyte subpopulations, high baseline levels of T-helper/inducer lymphocytes and of T-suppressor/cytotoxic lymphocytes resulted protective (HR = 0.03, 95% CI 0.01–0.36 and HR = 0.04, 95% CI 0.01–0.68, respectively), while a high percentage of total mature T-lymphocyte was associated with worse prognosis (HR = 12.97, 95% CI 1.46–115.21). The model was validated with the bootstrap method (100 replacements). C-index was 0.71.
Conclusions: The covariates that were significant predictors of survival are feasible for every centre and could be proposed for further validation. The identification of patients who would benefit most from therapy with ipilimumab could help clinicians to better allocate resources, avoiding costs and toxicities for patients who are not to benefit.
No conflict of interest.

3742 POSTER

Effectiveness and safety of first-line ipilimumab (IPI) 3 mg/kg therapy for advanced melanoma (AM): Evidence from a U.S. multisite retrospective chart review

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Background: In March 2011, the U.S. FDA approved ipilimumab (Yervoy®) for the treatment (Rx) of Rx-naive or pretreated advanced (unresectable or metastatic) melanoma (AM) based on prolongation of overall survival (OS) in a Phase III randomized, double-blind, multicenter study in previously treated AM patients (pts). Ipilimumab (IPI) at 3 mg/kg every 3 weeks for 4 doses was superior to a melanoma peptide vaccine. This study (CA184338) describes the pt and disease characteristics, patterns of care, safety, and outcomes of the same IPI dose and schedule in Rx-naive AM pts. The cohort (target n = 300) will be observed for 4 years.
Material and Methods: Adult pts with unresectable stage III or IV AM were identified retrospectively from 27 U.S. sites. Pts had received $\geqslant$1 dose of first-line IPI 3 mg/kg during April 2011 − Sept 2012. This interim analysis reports on pts (n = 120) for whom $\geqslant$12 months (mo) had elapsed since IPI initiation. Data were collected from medical records.
Results: The 120 pts were 65.8% male, median age was 63 years (range 26−91). The primary site was cutaneous (86.7%), ocular (4.2%), and mucosal (2.5%). Most pts were stage M1c (55%), 11.7% had unresectable stage III AM and 7.5% had brain metastases at AM diagnosis. Among the 97 pts with known BRAF status, 21.6% had an activating mutation. Prior to IPI, 40.8% and 51.7% of pts had ECOG PS 0 and 1 respectively, and 36.7% had LDH > institutional upper limits of normal. The median number of IPI doses was 4, 75.8% of pts completed 4 doses, and 5% experienced one dose interruption. From IPI initiation, median OS was 14.3 mo (95% CI 12.1, −). The 1-year survival rate was 59.5% (95% CI 50.1–67.8%). Overall median follow-up was 12.0 mo (range 0.5–21.7). One-year OS rates for BRAF-mutated, wild-type, and untested pts were 71.4% (95% CI 47.2–86.0%), 58.9% (95% CI 47.0–69.1%) and 50.5% (95% CI 28.4–69.0%), respectively. The most frequent drug-related adverse events were immune-related adverse events (irAEs) that occurred in 53% of pts; 27.5% of irAEs were cutaneous, 24.2% were gastrointestinal. Grade 3−4 irAE occurred in 13.3% of pts. Fifty-eight (48.3%) pts died. No deaths were attributable to drug-related AEs or irAEs.
Conclusions: This observational data is the largest study of IPI 3 mg/kg monotherapy in Rx-naive AM and provides clinical practice evidence of the OS benefit and safety profile of IPI. While BRAF status did not appear to impact OS in these pts, this finding warrants further investigation.
Conflict of interest: *Ownership: Wong, Penrod, Song, Chang, and Hebden have stock ownership in Bristol-Myers Squibb. Advisory board: McDermott (Bristol-Myers Squibb (compensated advisory board)). Corporate-sponsored research: Margolin (Bristol-Myers Squibb, GlaxoSmithKline, Genetech, Pfizer, Altor, Promethus). Other substantive relationships: Wong, Penrod, Song, Chang, and Hebden are employees of Bristol-Myers Squibb. Clark (Speaker's Bureau)*

3743 POSTER

A phase III trial of nab-paclitaxel (nab-P) vs dacarbazine (DTIC) in chemotherapy-naive patients with metastatic melanoma: Analysis of patient (pt) characteristics and treatment patterns by region

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Background: In a phase III trial, *nab*-P significantly improved progression-free survival (PFS) vs DTIC (4.8 vs 2.5 mo; HR, 0.792; *P* =. 044) and demonstrated a trend toward prolonged interim overall survival (OS; 12.8 vs 10.7 mo; HR, 0.831; *P* =. 094) for the treatment of chemotherapy-naive pts with metastatic melanoma. This analysis examined geographic variations in baseline (BL) demographics, treatment patterns, and outcomes.
Methods: Chemotherapy-naive pts with stage IV melanoma, LDH $\leqslant 2 \times$ ULN, and ECOG PS 0−1 were randomized to *nab-P* 150 mg/m^2 on days 1, 8, and 15 of a 28-day cycle or DTIC 1000 mg/m^2 on day 1 of each 21-day cycle. Before randomization, pts were stratified by region, M stage, and LDH. The primary endpoint was PFS by independent radiologic review; secondary endpoints included OS and safety.
Results: Of the 529 pts in this trial, 231 (44%) were from North America (NA), 228 (43%) were from Western Europe (WE), and 70 (13%) were from Australia/New Zealand (ANZ). Although treatment arms were balanced for BL characteristics, minor differences were noted among regions. The WE cohort had more pts with ECOG PS 0 (85% WE, 62% NA, 56% ANZ); the ANZ cohort had more male pts (76% ANZ, 66% NA, 62% WE), M1c stage disease (73% ANZ, 66% NA, 62% WE), LDH >1.1−2 $\times$ ULN (30% ANZ, 20% WE, 18% NA), and wild type *BRAF* (67% ANZ, 43% NA, 34% WE). PFS was significantly higher with *nab*-P vs DTIC in pts from WE and trended in favor of *nab*-P in pts from NA and ANZ (Table). An exploratory multivariate analysis of PFS adjusting for BL LDH found that HRs for all regions were <1.0, favoring *nab-P*. Interim OS trended in favor of *nab-P* for all regions. The median number of *nab*-P treatment cycles (2 ANZ, 3 NA, 4 WE) and pts with $\geqslant$1 *nab*-P dose reduction (43% NA, 25% WE, 15%

ANZ) varied between regions. More pts in the WE cohort used second-line ipilimumab therapy (25% WE, 13% ANZ, 15% NA) and BRAF inhibitor therapy (11% WE, 7% ANZ, 1% NA).
Conclusions: Regional variations in pt characteristics and treatment patterns were noted in this trial, which may have influenced outcomes. Overall, *nab*-P showed a greater clinical benefit over DTIC among pts with metastatic melanoma irrespective of region.
Conflict of interest: *Ownership: AK: Stock Ownership in Celgene IE: Stock Ownership in Celgene. Advisory board: MPB: Celgene AT: BMS, Roche, GSK, Amgen AH: Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Eisai, GSK, IGEA, Lilly, MelaSciences, Merck Serono, MSD/Merck, Novartis, Oncosec, Roche Pharma MDV: Celgene CR: BMS, Roche, GSk, Celgene CL: Celgene. Corporate-sponsored research: MPB: Celgene AH: Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Eisai, GSK, IGEA, Lilly, MelaSciences, Merck Serono, MSD/Merck, Novartis, Oncosec, Roche Pharma EH: Celgene MDV: Celgene, Novartis, Roche, Glaxo, BMS. Other substantive relationships: AT: Honoraria-BMS AH: Speakers bureau and consultancy for Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Eisai, GSK, IGEA, Lilly, MelaSciences, Merck Serono, MSD/Merck, Novartis, Oncosec, Roche Pharma AK and IE: Employed with Celgene*

Regional cohort	*nab*-P	DTIC	HR (95% CI)	*P* value
NA	n = 115	n = 116		
PFS, mo	5.5	2.0	0.837 (0.591, 1.186)	0.332
OS,[a] mo	11.8	11.0	0.947 (0.687, 1.306)	0.741
WE	n = 114	n = 114		
PFS, mo	4.1	2.6	0.702 (0.499, 0.987)	0.043
OS,[a] mo	13.0	11.1	0.779 (0.553, 1.098)	0.151
ANZ	n = 35	n = 35		
PFS, mo	3.5	3.1	1.039 (0.529, 2.041)	0.911
OS,[a] mo	14.4	8.2	0.649 (0.342, 1.233)	0.184

[a] Interim.

3744 POSTER

Immunotargeting melanoma stem cells with Hyper-IL6 modified whole cell therapeutic vaccine (AGI-101H) in patients with advanced melanoma − a joint analysis of two phase 2 studies

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Background: AGI-101H consists of two human melanoma cell lines modified with molecular adjuvant Hyper-IL-6 (H6) cDNA. Secreted H6 at the site of vaccine injection provides co-stimulatory signals to immune system by inhibiting T regulatory (FoxP3 +) cells formation, activation of maturation and presentation of cryptic antigens by dendritic cells, activation of T CD8+ and NK cells. Moreover, H6 during the culture stimulates vaccine cells via binding gp130 subunit of IL-6-type cytokines receptor complex. It leads to activation of JAK-kinase and chronic phosphorylation of STAT3 and results in altering vaccine cells towards melanoma stem cells (MSCs)-like phenotype. Up to 92% of AGI-101H cells have ALDH activity − a MSCs marker and loose differentiation antigen SSEA-1.
Methods: Non-selected 77 and 35 patients with unresectable stage IIIB, IIIC or IV melanoma were enrolled into trial 2 and 4, respectively. In November 2008 all alive patients were transferred into **E**xtended **T**reatment for **A**dvanced **M**elanoma Transferred from Trials 2−5 (ETAM 2−5) studies (EnduraCT No 2008–003373−40). Among 112 enrolled pts., 22 (19%) received prior chemotherapy. WHO performance status was 0−1/2/3−4 in 45/58/9 pts., respectively. AGI-101H was administered 8 times every 2 weeks (induction) and then every month (maintenance) until patient's death. At progression, maintenance was continued or induction was repeated and followed by maintenance. The primary endpoint was overall survival (OS), with clinical tumor response used as the secondary endpoint.
Results: Median length of follow-up in trial 2 and 4 was equal to 139.3 and 94.9 months, respectively. There were 102 deaths in total. Among the 112 enrolled pts. 6.3% had IIIB, 22.3% IIIC and 71.4% IV. Complete response (CR) and partial response (PR) was observed in 18.7% and 8.9% of pts., respectively. Disease control rate (CR, PR, or SD − stable disease) was noted in 52.6% of pts. The estimated median objective response (CR+PR) duration was equal to 32 months [95% CI 6.5–56.9]. The observed median OS in was equal to 13.3 months [95% CI 11.9–18.1]. The observed median OS in patients with WHO 0−1 was equal to 21.3 months [95% CI 12.9–34.4]. No grade 3/4 adverse events were observed.
Conclusions: Treatment with AGI-101H in patients with advanced melanoma is safe and effective. Phase 3 study is warranted. Long-term survival of high-risk melanoma patients with resected stage IIIB-IV treated with AGI-101H was recently published (Mackiewicz A et al.).
No conflict of interest.

3745 POSTER

Spanish Melanoma Multidisciplinary Group (gem): Long term survivors (LTS) treated with ipilimumab (IPI) in the expanded access programme (EAP)

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Background: Advances in metastatic melanoma treatment have demonstrated improvement in survival. After 5 year follow-up of clinical trials with IPI, LTS have been reported. Current follow-up of patients treated within IPI EAP in Spain is 2 years.
Methods: Retrospective review of LTS included in the IPI-EAP experience in Spain. Patients (pts) were treated with IPI at 3 mg/kg q 3 w x 4. Data was registered using a socio-demographic and therapeutic questionnaire, collecting overall response (RR), OS and toxicity (T). LTS was defined as those patients with ⩾12 months overall survival (OS). Pts characteristics in the LTS were compared with the overall Spanish EAP population.
Results: We collected data of 138 treated pts, resulting in 48 LTS (34.5%). These 138 pts represent 47.9% of all EAP treated pts. 15 pts were alive at 12 months (M), 18 pts between 13−19 m and 9 pts, 20−24m. Median age was: 59.5 (30−81). Gender: Male 54.2%. Female 45.8% Stage: IVa 27.1%, IVb 20.8%, IVc 51.1%. Primary tumor site: skin 60.5%; accral 10.4%; mucosal 8.3%; ocular 10.4%; rest unknown. Metastases (mts): soft tissue 41.7%, lung 31.3%, visceral 25%. Median number of prior treatments: 1 (1−5), 18.8% received more than one chemotherapy (chx) line. 97.9% of total pts population has completed induction phase (4 IPI doses). Response assessment: Complete Response 14.6%; Partial Response 35.4%; Stable Disease 35.4%; Progressive disease 10.4%. Mean duration of response: 13 m. Mean survival: 16.5m. 54.2% received thx after IPI: 31.3% chx; 12.5% radiotherapy; 12.5% B-RAF inhibitor. 18 pts (50%) presented T: 10.5% Grades (G) 3−4 were reported; 18.8% G2; 10.4% G1. The most frequent T was cutaneous (18.8%). When compared with the overall EAP pts LTS have less visceral disease, lower median LDH, more objective responses and completion of the 4 induction ipilimumab doses.
Conclusions: Ipilimumab within Spanish EAP experience in pretreated pts has shown long term survival consistently with clinical trials in pts with advanced melanoma. Further research and analysis are needed to identify which pts are most likely to achieve a long term survival benefit with ipilimumab.
Conflict of interest: *Advisory board: Alfonso Berrocal and Salvador Martin Algarra have been advisors for Bristol Meyers*

3746 POSTER

Results of a phase 1 study of MEK162, an oral MEK inhibitor, in Japanese patients with advanced solid tumors

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Background: MEK162 (ARRY-162), a small molecule MEK1/2 inhibitor, has shown broad antiproliferative activity in preclinical and early clinical studies in advanced solid tumors and melanoma.

Materials and Methods: The primary objective of this multicenter phase 1 trial (NCT01469130; sponsored by Novartis) is to determine the maximum tolerated dose (MTD) and/or the recommended phase 2 dose of MEK162 in Japanese patients. The study consists of a dose-escalation part in patients with advanced solid tumors and an expansion part in patients with *BRAF*/*RAS*-mutant tumors. Adaptive dose escalations, determined by the investigators and the sponsor, were guided by a Bayesian logistic regression model with overdose control.
Results: As of January 7, 2013, 17 patients have been treated, 14 in the dose-escalation and 3 in the expansion part (6 at 30 mg BID; 11 at 45 mg BID). The median age was 59 y (range, 27−77), 11 (65%) were male, and the most common cancers were lung (n = 4), rectal (n = 3), and bile duct (n = 3). No dose-limiting toxicities (DLTs) were observed in the 5 evaluable patients treated at 30 mg BID. Based on safety, PK data, and the Bayesian inference of DLT rate, the dose level (DL) was increased to 45 mg BID. Two DLTs were reported in 6 evaluable patients at the 45-mg DL (both grade 2 central serous retinopathy [CSR]-like events). The most common treatment-related AEs (>30% of patients) of any grade (G) at either DL were CSR-like events (n = 15; 88%), increased creatine phosphokinase (CPK; n = 12; 71%), diarrhea (n = 10; 59%), increased AST (n = 9; 53%), rash (n = 8; 47%), increased lipase (n = 7; 41%), acneiform dermatitis (n = 6; 36%), decreased appetite (n = 6; 36%), and stomatitis (n = 6; 36%). CSR-like events were all G1/2. Increased CPK was the only G3/4 AE reported in >1 patient (n = 5; 29%; 1 had G4). Four patients discontinued treatment, and 16 patients required a dose reduction/interruption due to an AE. Based on these data and the Bayesian inference of DLT rate, 45 mg BID was determined as the MTD and selected as the dose for the ongoing expansion part. Orally administered MEK162 was rapidly absorbed, with a median T_{max} <2 hours. Plasma concentrations of MEK162 increased with dose and were similar to those seen in studies with Caucasians.
Conclusions: In the dose-escalation part of the study, MEK162 administered orally up to 45 mg BID was well tolerated, and the MTD of MEK162 was identified at 45 mg BID for Japanese patients. This DL is being tested in the expansion part.
Conflict of interest: *Corporate-sponsored research: KW, YA: Novartis Pharmaceuticals. Other substantive relationships: SF, KT, AZ, Novartis Pharmaceuticals employment YA, Novartis Pharmaceuticals speaker honoraria*

3747 POSTER

The utility of BRAF inhibitors in metastatic melanoma to brain

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Background: About 40−50% of patients with metastatic melanoma will develop symptomatic brain metastases. Median survival following a diagnosis of brain metastases is less than 6 months. BRAF mutation status has become core to modern treatment of melanoma. We report our experience with BRAF inhibitors in the setting of brain metastases from melanoma.
Materials and Methods: A retrospective analysis of all patients diagnosed with metastatic melanoma, from January 2011 − March 2013, was undertaken. Clinicopathologic data and BRAF status was collected. Our specific focus was on patients with the V600E mutation who had brain metastases prior to any therapy for metastatic disease.
Results: Sixty-one patients with metastatic melanoma had documented BRAF status and 16 of these patients had brain metastases. Overall 22 patients were found to harbour the V600E (V600E+) mutation and 10 (45%) of these patients had brain metastases prior to any therapy for metastatic disease. One V600E+ patient developed brain metastases during primary therapy. Five BRAF- patients developed brain metastases, representing 31% of patients with brain metastases.
Fifty-five percent (n = 6) of V600E+ patients and 40% of BRAF wild type (wt) patients (n = 2) were female. Median age at diagnosis of metastatic disease was 64 years (37−71) and 45 years (30−68) in the BRAF- and BRAF+ groups respectively.
Seventy percent of BRAF+ patients with brain metastases and 55% of BRAF- patients with brain metastases had symptomatic brain metastases at presentation.
All BRAF wt patients had solitary brain metastases, 2 V600E+ patients had solitary brain metastases. The mean number of brain metastases per BRAF+ patient was 3 (range 1−8).
Six patients with brain metastases and who were V600E+ were treated with a BRAF inhibitor (5 patients with dabrafenib). Four patients were treated with WBRT prior to commencing a BRAF inhibitor. All patients had a partial response on MRI after 2 months of drug. Progression of disease was noted in 2 patients after a median of 7.6 months (range 6.7−8.5 months). Four patients continue to respond (1 patient has had a complete response) after a median of 4.4 months, (range 3−9 months) on a BRAF inhibitor.
All patients experienced at least a grade 2 skin toxicity while on a BRAF inhibitor. Two grade 3 toxicities occurred; a grade 3 skin toxicity and a grade 3 temperature and rigors in the absence of infection.
Conclusion: In our retrospective analysis, patients with V600E+ disease were more likely to develop multiple metastatic brain deposits. BRAF inhibitors have reported activity in this setting. Our experience highlights the utility of BRAF inhibitors in brain metastases. Toxicity was minimal and the median OS of our small group was superior to historic survivals prior to the advent of BRAF inhibitors.
No conflict of interest.

3748 POSTER

Oncogenic BRAF mutation in cutaneous melanoma in Argentina

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Background: BRAF is a protein critical in the mitogen-activated protein kinase (MAPK) pathway, and is mutated in approximately 50% of melanoma patients. A single substitution (V600E) account for 80% of BRAF mutations. The aim of this study was to assess the frequency of oncogenic *BRAF* mutations in cutaneous melanoma and to correlate *BRAF* status with clinicopathological features in Argentinian melanoma patients.
Patients and Methods: Tumor tissue from 93 consecutive patients with primary/metastatic cutaneous melanoma, from 12/2011 to 3/2013 was analyzed in 2 referral centers using real time polymerase chain reaction (RT-PCR) assays for *BRAF* mutation (cobas® 4800 System, v2.0). Clinical (age, gender, ethnics, primary tumor location) and pathological (Breslow, ulceration, histopathological subtype, mitotic rate, AJCC stage) features were correlated with BRAF mutation status. Study population was 52% female. Median age 58 ys (35% <50 years). 100% Caucasian. Primary tumor location was 39% trunk, 36% limbs, 12% head and neck, 13% other. 18% were metastatic at diagnosis.
Results: Twenty-nine patients (32%) had BRAF mutation (100% V600E genotype). Other than age at diagnosis (median age, 51 *v* 62 years for *BRAF*-mutant *v BRAF* wild-type patients, respectively; *P* <0.01) there was no significant difference in clinical features by mutation status. Among histopathologic features of the primary melanoma, BRAF wild-type was significantly associated with the presence of ulceration (31% v 21% in for *BRAF*-wild type *v BRAF* mutant patients) (p = 0.05).
Conclusion: This is the first report of BRAF mutation status using RT-PCR COBAS in Argentina. The frequency of BRAF mutation is lower than that reported in medical literature, and only the presence of ulceration and age at diagnosis were significantly different in *BRAF*-mutant and *BRAF* wild-type patients.
No conflict of interest.

3749 POSTER

Desmoplastic small round cell tumor: Multimodal approach with aggressive cytoreductive and hyperthermic intraperitoneal chemotherapy

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Background: Desmoplastic small round cell tumor (DSRCT) is a rare and highly aggressive type of sarcoma, which mainly develops in the intra-abdominal cavity of adolescents, and young adults with a strong male predominance. The prognosis is poor, with median survival from 17 to 25 months.
The management may include, a multimodal approach with polychemotherapy, whole abdominal radiation, and currently radical cytoreductive surgery plus hypertermic intraperitoneal chemotherapy (HIPEC) is being evaluated to improve outcomes.
Material and Methods: We present two cases with peritoneal sarcomatosis (DSRCT), treated with optimal cytoreductive surgery associated with HIPEC, as part of a multimodal treatment.
Results: The patients were young male adults presented very advanced peritoneal disease (PCI: 28 and 39 respectively). The diagnosis was confirmed by FISH technique, showing typical reciprocal translocation (EWRS1−22q12).

The treatment strategy was initially based on a multimodal therapy:First neodjuvant systemic chemotherapy (Kushner's scheme).
Second extensive and radical cytoreductive surgery: Peritonectomies, several organs, hundreds nodules resection and electrovaporization nodules. 1 to 2 high risk anastomosis were performed respectively.
Optimal cytoreduction (CC1), and HIPEC with cisplatin (100 mg/m^2) and adriamycin (15 mg/m^2) for 90 minutes, at a high temperature to 42 degrees centigrade, was achieved.
After overcoming a complicated postoperative with high morbidity, but no mortality, it evaluated in a multidisciplinary committee, adjuvant treatment with systemic chemotherapy and/or whole abdominal radiation (IMRT), similar to some recently published papers.
Conclusions: DSRCT is a very rare and aggressive entity, which is mainly reported, in young male patient with abdominopelvic malignancy. The diagnosis and treatment needs an aggressive and multimodal approach. The extensive cytoreductive surgery is currently accepted to have a primary role in the achievement of long-term survival.
The cases presented show that it is possible to achieve optimal cytoreduction (residual tumor less than 2.5 mm), requiring that the neoadjuvant and adjuvant and chemotherapy could prolong disease-free time.
No conflict of interest.

3750 POSTER

Endocrine toxicities after treatment with ipilimumab

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Background: Ipilimumab (IPL) is a MAB directed against the CTLA-4 which promotes activation of cytotoxic lymphocytes and augments an immune-mediated anti-tumour response. IPL is now licensed for the treatment of unresectable or metastatic malignant melanoma. A host of immune-related adverse events are associated with the anti CTLA-4 therapy. The endocrinologist may be involved in the management of IPL treated patients in whom may arise secondary hypophysitis with hypopituitarism in 1−6 % of patients, followed by hypo-and hyperthyroidism secondary to thyroiditis in 2.7 and 0.3%, respectively and primary adrenal insufficiency in 2.1%.
Patients and Methods: We studied 8 patients (age: 51±7; M/F:6/2) with metastatic melanoma enrolles in different trials with IPL. They presented hypophysitis symptoms after a median time of 11 weeks (range 7−16). All patients presented fatigue and asthenia and 4 also severe headache.
Results: All 8 patients had biochemical evidence of secondary adrenal insufficiency (median random cortisol level 105 ±112 nmol/L with undetectable ACTH levels); four patients presented also low FT3 (mean 2.86 pmol/L) and FT4 levels (mean 11.1 pmol/L) with low TSH in 3 cases (mean 0.245 mU/L) and in normal range in one (2.59 mU/L). 3 male patients also presented with a severe deficiency of testosterone (6±3 nmol/L). Three cases had also very low values of IGF-1 (65±22ug/L). One patient had the MRI which documented diffuse enlargement of the pituitary gland. All patients, as required by trial safety procedures, started with prednison 1 to 2 mg/kg orally once per day with gradual tapering and then substituted with cortison acetate. 3 patients also started thyroxine treatment.1 patient experienced a concomitant autoimmune hyperthyroidism that still requires thyrostatic treatment. Long term follow-up of our patients (11±8 months after IPL discontinuation) showed a persistent need for glucocorticoid replacement, while 2 patients recovered the thyroid axis function after 4 months from hypothyroidism and 2 patients the gonadal axis after 2 months.
Conclusion: The prevalence of IPL induced hypopituitarism may be higher than that previously thought and the effects on adrenal axis may be irreversible. This emphasizes the clinical relevance of endocrine toxicity and the importance of warning for early screening of pituitary insufficiencies in these patients.
No conflict of interest.

3751 POSTER

A community-based, real-world, study of treatment-naive advanced melanoma (AM) patients treated with 3 mg/kg ipilimumab (IPI) in the United States

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Background: In March 2011 the U.S. FDA approved ipilimumab (Yervoy®) at 3 mg/kg monotherapy for the treatment of treatment-naive or pretreated advanced (unresectable or metastatic) melanoma (AM) based on prolongation of overall survival (OS) in a Phase III randomized, double-blind, multicenter study of previously treated AM patients (pts) treated with ipilimumab (IPI) 3 mg/kg every 3 weeks for 4 doses. We have initiated a four year study (CA184332) to describe pt and disease characteristics, patterns of care, and outcomes in treatment-naive AM pts initiating the approved IPI dose and schedule in a U.S. community-based setting. We currently report interim baseline demographics, pt characteristics, and overall survival (OS) for the first 61 pts.
Material and Methods: Adult pts with unresectable stage III or stage IV melanoma who had received ⩾1 dose of first-line IPI 3 mg/kg during April 2011 − September 2012 were identified retrospectively in U.S. Oncology practices utilizing the iKnowMed electronic medical record system. Clinical data were obtained using programmatic queries in iKnowMed and medical chart abstraction. This interim analysis reports on the subset of pts for whom at least 12 months had elapsed since IPI initiation.
Results: The majority of the 61 pts were male (65.6%) with a mean age of 64 years (SD=14) at IPI initiation. Primary sites at initial melanoma diagnosis were cutaneous (95.1%), anorectal (3.3%) and ocular (1.6%). BRAF mutational testing occurred in 63.9% of pts and of those tested, 20.5% were BRAF mutation positive. At AM diagnosis, 32.8%, 37.7%, and 29.5% of pts were stage M1a, M1b, and M1c, respectively; none had unresectable stage III AM. By IPI initiation, brain metastases were identified in 32.8% of pts. At AM diagnosis, 63.9% and 26.2% of pts had ECOG PS 0 and 1, respectively, and 29.5% had LDH > upper normal limit. From IPI initiation, median OS was 11.5 months (95% CI 6.6, −) with a 1-year survival rate of 49.3% (95% CI 35.6–61.6%). Overall median follow-up was 8.5 months (range 0.4–19.0).
Conclusions: This community-based study is one of the largest studies of IPI 3 mg/kg monotherapy in treatment-naive AM and provides 'real world' evidence of the overall survival benefit of IPI in first-line AM pts.
Conflict of interest: *Ownership: Wong, Juday, Penrod, and Hebden have stock ownership in Bristol-Myers Squibb. Advisory board: Patt (ASCO Treatment Guideline Committee Pathways Task Force, McKesson Specialty Health). Other substantive relationships: Wong, Juday, Penrod, and Hebden are employees of Bristol-Myers Squibb*

3752 POSTER

PTEN loss correlates with shorter time to brain metastasis and overall survival in stage IIIB/C melanoma patients

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Background: Patients [pts] with stage IIIB/C melanoma have variable outcomes. Risk assessment in these pts is currently based on clinical and pathological factors. We hypothesized that integrated analysis of prevalent oncogenic drivers (BRAF, NRAS, PTEN) would improve risk assessment.
Materials and Methods: Under an IRB-approved protocol, regional metastases from stage IIIB/C melanoma pts (n = 137) who underwent surgery at MD Anderson Cancer Center were collected. Tumor DNA from FFPE tissue was tested for *BRAF* and *NRAS* mutations by mass-spectroscopy based genotyping. PTEN protein expression was determined by a CLIA-certified immunohistochemical assay. PTEN loss was defined as <10% of cells with (+) staining, based on correlation with increased AKT activation. Molecular features were compared to clinical characteristics and outcomes. Time-to-event measures and overall survival [OS] from stage III diagnosis were assessed using the Kaplan–Meier method and group differences were assessed using the log-rank test.
Results: Both time-to-distant metastasis [TTM; p = 0.047] and OS [p = 0.005] correlated with clinical stage (IIIB vs IIIC), consistent with validated models. Mutation status was 40% BRAF mutant, 9% NRAS mutant, and 50% no mutation in BRAF or NRAS [WT]. PTEN loss (evaluable in 125 pts) occurred in 25% of pts overall: 31% of BRAF, 23% of WT, and 8% of NRAS pts, respectively. Neither mutation status (p=1.00) nor PTEN loss (p=1.00) correlated with clinical stage. Tumor mutation status did not correlate significantly with TTM (p = 0.37) or OS (p = 0.89). In the cohort with evaluable PTEN, pts with PTEN loss had significantly shorter OS (median 1.88 vs 3.05 yrs, p = 0.03) but not TTM (p = 0.34). Evaluation of patterns of metastasis demonstrated that PTEN loss correlated with markedly shorter time-to-brain metastasis [TTBM] (median 1.84 vs 4.87 yrs, p = 0.03), but not to lung (p = 0.92), liver (p = 0.52), or bone (p = 0.10) metastasis. By genetic subgroup analysis, PTEN loss in BRAF pts correlated with significantly shorter TTBM (median 1.15 vs 4.19 yrs, p = 0.001) and OS (median 1.63 vs 3.60 yrs, p = 0.001), but not in WT pts (TTBM, p = 0.59; OS, p = 0.94). In a multivariate Cox

proportional hazards model of the BRAF pts incorporating stage, PTEN, age, vemurafenib treatment [tx], and ipilimumab tx, PTEN loss was the only significant risk factor for TTBM (HR 4.71, p = 0.004) and for OS (HR 2.99, p = 0.003).
Conclusion: PTEN loss in BRAF-mutant stage IIIB/C melanoma pts correlates with shorter TTBM and OS. These data implicate PTEN loss as a novel molecular risk factor for brain metastasis, add to the evidence supporting the clinical significance of PTEN loss in BRAF-mutant melanomas, and have implications for the management of, and clinical trials for, stage IIIB/C melanoma pts.
Conflict of interest: *Advisory board: M.A.D.- Genentech, GlaxoSmithKline, Novartis. R.W.J.- Nektar, Amgen, Merck. Corporate-sponsored research: M.A.D.- Genentech, GlaxoSmithKline, AstraZeneca, Merck, Myriad, Oncothyreon.*

3753 POSTER

Circulating tumor DNA (ctDNA) in metastatic uveal melanoma patients (MUM): Clinical results and correlation with outcome in 87 patients from Institut Curie

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Background: ctDNA can be detected in the plasma of MUM patients using a real-time PCR based on the pyrophosphorolysis-activated polymerization (bi-PAP) able to detect the most frequent GNAQ and GNA11 point mutations (codon 626) which are present in 85% of UM with high specificity and sensitivity (Madic et al., 2012).
Methods: From May 2011 to March 2013, 87 MUM patients were included in 3 prospective studies to assess the bi-PAP assay. We report here the analysis of clinical and outcome correlations using this new molecular tool.
Results: 87 patients (43 M/44 F), median age 57 (range 23−84), primary tumor: median diameter 15 mm (range 5−25), local treatment: enucleation (32), proton beam (52), iodine disk (3). Enucleated eyes showed mostly mixed histotype and genomic high risk tumors by array-CGH (8q gain and/or 3p loss). With a median disease free interval of 39 months, 83 patients developed liver metastases first, with radiological miliary disease in 55; 4 had extra hepatic lesions without liver involvement. The median number of lesions was 5, the median size 20 mm. 35 patients were enrolled at the time of metastasis diagnostic, LDH was in normal range in 61/87 and performance status (WHO) 0/1/2 in 45/36/6 patients respectively. With a median follow-up of 8 months (range 0−22), 28 patients had disease progression and 34 died of metastasis. The median survival was 13 months (range 2 −115). Tumor samples were available in 82 patients, genotyping is ongoing for 8. GNAQ 626A>T, GNAQ 626A>C and GNA11 626A>T mutations were found in 9, 19 and 26 tumors respectively; rare mutations were present in 6 tumors, and 14 were GNAQ/11 wild-type tumors. Finally, ctDNA was quantitatively detected in 51/54 plasma samples (median 30 copies/ml, range 1–11421) and correlated with the metastatic tumor burden as assessed by liver MRI (median 64 cm^3, range 0.2–7384). Correlation with progression-free and overall survival will be presented.
Conclusion: ctDNA is a promising tool to assess the tumor burden and detect the micrometastatic dissemination of uveal melanoma, and a potential biomarker to evaluate the efficacy of targeted therapies in metastatic patients carrying GNA Q/11 mutated tumors.
No conflict of interest.

3754 POSTER

New DNA repair inhibitors Dbait in combination with radiation therapy to treat melanoma: A preclinical study

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Background: Melanoma is the fifth and sixth leading cause of cancer in men and women, respectively. It is characterized by symptomatic locoregional recurrence, distant metastasis, and a poor response to systemic drugs and particularly radioresistance. The cytotoxicity of radiation therapy (RT) is mainly due to DNA double-strand breaks (DSBs). Dbait are innovative molecules that mimic 'false' DSBs that trap DNA repair proteins and prevent their recruitment thereby inhibiting their repair. This inhibitory effect is partly driven through deregulated activation of DNA-PK kinase (key enzyme of DSB repair). Interestingly, DNA-PK is known to be overexpressed in metastatic melanoma. We assessed the efficacy and safety of combining RT with Dbait in a model of human melanoma.
Material and Methods: Initially, the cytotoxic efficacy of Dbait in combination with RT was evaluated *in vitro* by clonal survival. We further assayed the capacity of Dbait to inhibit RT-induced DNA damage repair over time. Subsequently, nude mice subcutaneously engrafted with human melanomas (SK28) were treated with Dbait (n = 10), 'palliative' (10x3 Gy in 2 weeks; n = 18) or 'radical' (20x3 Gy in 4 weeks; n = 12) RT, a combination of Dbait and RT for 2 (n = 12) and 4 (n = 11) weeks or left untreated (n = 21). Tumor growth and survival of untreated and treated animals were monitored for 250 days.
Results: *In vitro*, Dbait enhanced RT-induced cytotoxicity (67% *vs* 51%; $p < 0.05$). In Dbait and RT treated cells, initially the level of DNA damage was not greater than in RT treated cells, however persisted for longer ($p < 0.05$). Mice treated with Dbait and RT combination treatment had significantly better tumor growth control and longer survival compared to RT alone (median survival: 119 vs 67 days for the 'palliative' protocol, $p < 0.001$; 221 vs 109 days for the 'radical' protocol, $p < 0.001$). Interestingly, only animals receiving the combined 'radical' protocol showed complete responses in 7/11 tumors. No toxicity was observed in Dbait-treated groups.
Conclusions: This preclinical study provides encouraging results for a combination of a new DNA repair inhibitor, Dbait, with RT, in the absence of toxicity. A first-in-human phase I study is currently underway in the palliative management of melanoma in-transit metastases (DRIIM trial).
Conflict of interest: *Other substantive relationships: Sun JS is co-funder of DNA Therapeutics, the company holding the pattent of Dbait and Flavien D is employee of DNA Therapeutics*

3755 POSTER

Locoregional disease control in metastatic melanoma: Exploratory analysis from phase 2 testing of intralesional rose bengal

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Background: PV-10 (10% rose bengal disodium) is a small molecule immuno-chemoablative agent that has completed phase 2 testing in 80 AJCC Stage IIIB-IV(M1c) subjects in clinical trial PV-10-MM-02 (ClinicalTrials.gov ID NCT00521053, sponsored by Provectus Pharmaceuticals, Inc.). Upon intralesional injection, PV-10 elicits selective ablation of injected lesions and a tumor-specific, immune-mediated bystander response in untreated lesions in which T cells are implicated.
Materials and Methods: In the phase 2 trial, up to 10 cutaneous or subcutaneous target lesions and up to 10 additional non-target lesions received intralesional PV-10 at day 0 and could be reinjected as necessary at weeks 8, 12 and 16 if tumor tissue remained. Up to 2 additional cutaneous or subcutaneous lesions were left untreated to assess bystander response. The primary endpoint in the single arm trial was best overall objective response rate (BORR) judged by RECIST in each subject's target lesions.
Results: For all subjects, BORR was 51% (26% CR, 25% PR) with the amount of tumor burden accessible to PV-10 injection prognostic for outcome. In the majority of subjects (66%) the lesions treated with PV-10, together with up to 2 untreated bystander lesions, constituted all disease present, and these subjects achieved a BORR of 62%, while when all disease was treated (33% of subjects) BORR further increased to 73%. Locoregional blistering was observed in 40% of subjects, occurring within 7 days of PV-10 injection but with no clear pattern of incidence, and generally resolving without sequelae within 4 weeks. Occurrence of this potentially immune mediated phenomenon was strongly prognostic for outcome, with 66% BORR in subjects with blisters vs. 42% in those not developing blisters. Locoregional disease control correlated stronger still: 90% of subjects with blisters achieved stable disease or better vs. 54% of subjects without blisters.
Conclusions: In this patient population refractive to other local treatments such as surgery and radiation, intralesional PV-10 provided a viable strategy to maintain, with minimal intervention, locoregional control of the disease with the potential to delay, reverse or prevent progression to life-threatening visceral disease.
Conflict of interest: *Ownership: Provectus Pharmaceuticals (Singer, Wachter). Advisory board: Provectus Pharmaceuticals (Agarwala, Thomp-*

son, Ross, Scoggins). Corporate-sponsored research: Provectus Pharmaceuticals (Agarwala, Thompson, Smithers, Ross, Coventry, Minor, Scoggins). Other substantive relationships: Employee, Provectus Pharmaceuticals (Singer, Wachter)

3756 POSTER

Identification of markers prognostic of survival in lymph node metastases from stage III melanoma patients

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Background: The present American Joint Committee on Cancer staging system for Stage III melanoma stratifies patients into heterogeneous groups, with widely varied outcomes and responses to available therapies. Average 5-year survival following surgical lymph node removal is about 30%. Panels of accurate biomarkers prognostic of survival are urgently needed for more personalised melanoma patient management.
Methods: Complementary quantitative proteomics approaches, 2D fluorescence difference in-gel electrophoresis (DIGE) and isobaric tags for relative and absolute quantitation (iTRAQ) coupled with 2D liquid chromatography tandem mass spectrometry (LC-MS/MS), were used to identify differentially abundant proteins in extracts from melanoma lymph node metastases, surgically excised from Stage III patients with poor (n = 14, <1 year survival) and good (n = 19, >4 years) survival outcomes. Potential prognostic markers were verified by selected reaction monitoring (SRM) mass spectrometry (MS).
Results: Overall, 83 proteins were differentially abundant between patients with good and poor survival outcomes ($p < 0.05$). Subsequent SRM analysis verified 21 proteins as potential biomarkers for survival after surgical treatment of lymph node metastasis. The MS-based analyses, iTRAQ 2DLC-MS/MS and SRM, were highly concordant with a median Pearson's correlation value of R = 0.74. Enhanced protein metabolism/folding, nucleic acid metabolism and angiogenesis, deregulation of cellular energetics and methylation processes, and decreased levels of apoptosis and immune response-related proteins were associated with a poor prognosis. Our panel of significant, differentially abundant proteins include biomarkers previously associated with prognosis in metastatic melanoma.
Conclusions: This is the first report of comprehensive quantitative proteomics used to identify proteins predictive of survival in lymph node metastases from Stage III melanoma patients. Collectively, this panel of identified proteins offers insight into important aspects of melanoma biology and next-generation prognostication that may enable better stratification of Stage III patients.
No conflict of interest.

3757 POSTER

Metalloproteinase pregnancy associated plasma protein-A (PAPP-A) promotes melanoma progression in vitro

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Background: Melanoma is a common and highly aggressive form of skin cancer with a high propensity to metastasise. Metastatic melanoma is a fatal disease with poor prognosis. Insulin-like Growth Factor (IGF1) promotes melanoma metastasis and plays an important role in disease progression. Bioavailability of IGF1 is known to be regulated by IGF-binding proteins (IGFBPs). IGFBP4 forms a complex with IGF1 and inhibits release of active IGF1. IGFBP4 is cleaved by metalloproteinase Pregnancy-Associated Plasma Protein-A (PAPP-A) resulting in release of bioactive IGF1.
Methods: PAPP-A mRNA expression was analysed by quantitative RT-PCR in forty-eight metastatic melanoma patient tumour samples, and in thirty-eight melanoma cell lines developed in our institute. PAPP-A secretion was quantified by commercial ELISA in twelve melanoma patient sera and eleven melanoma cell lines. Efficient knockdown of PAPP-A expression and secretion (down to <90%, $p < 0.01$) was achieved with siRNA transfection lasting for 72 hrs. Functional studies at various timelines were performed post PAPP-A siRNA knockdown, which included proliferation (MTS), invasion (matrigel) and migration (wound healing assay). PAPP-A gene expression was analyzed in melanoma cells resistant to BRAF inhibitor (BRAFi) and cytotoxic chemotherapy (cisplatin & paclitaxel).
Results: PAPP-A was noted to be widely and variably expressed in tumour tissue samples and melanoma cell lines,with some melanoma cell lines expressing PAPP-A as high as 900 copies/10^5 copies of Bactin. PAPP-A protein was secreted in varying concentration by melanoma cell lines, with 3/11 melanoma cell lines secreting PAPP-A as high as 17.5ng/ml. Quantification of PAPP-A in metastatic melanoma patient sera did not reveal elevated levels as compared to normal. PAPP-A knockdown resulted in significant decrease in invasive capability of melanoma cells, with a statistically significant 60% reduction in invasion (paired t-test, p value<0.01). Migration was noted to be markedly inhibited in PAPP-A depleted cells. Proliferative ability of melanoma cells did not change with PAPP-A knockdown. A significant increase in PAPP-A expression was noted in melanoma cells resistant to cytotoxic chemotherapy (upto 20 fold). PAPP-A mRNA levels were noted to be up-regulated in BRAFi resistant cells (upto 3 fold), along with up-regulation in expression of IGF1 receptor (IGFR1) and IGF receptor substrates (IRS1 & IRS2), indicating role of PAPP-A in acquired resistance to BRAFi via modulation of IGF signalling.
Conclusion: Our data suggests that PAPP-A proteolytic activity plays an important role in melanoma progression and treatment resistance to BRAF inhibitors. Targeting PAPP-A could be a novel therapeutic strategy to limit disease progression and holds a promise in overcoming resistance to BRAFi in melanoma patients. In addition, PAPP-A has a potential to be an important biomarker for IGF targeted therapy.
No conflict of interest.

3758 POSTER

BRAF V600 mutations and pathological features in Japanese melanoma

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Background: *BRAF* V600 mutations are frequently found in melanomas and result in constitutive activation of BRAF. Recently, the BRAF V600 kinase inhibitor vemurafenib, which has antitumor activity in patients with *BRAF* V600-mutated melanoma, was developed in conjunction with the cobas® 4800 BRAF V600 Mutation Test. The frequency and most common site of melanoma are different among races and it assumed that the *BRAF* mutation rate is also different. In Japan, since the occurrence of melanoma is rare, the frequency and distribution of *BRAF* V600 mutations has not been elucidated. We investigated the frequency of the *BRAF* V600 mutation in Japanese patients with melanoma as a primary end point. A secondary end point demonstrated the relationship between the mutation and clinical or pathologic features.
Material and Methods: Eighty formalin-fixed, paraffin embedded tumors diagnosed with melanoma were collected by the National Cancer Center Hospital from 2006–2012. DNA was extracted with the cobas® DNA preparation kit. The *BRAF* V600 mutations were detected with the cobas®4800 system z480 and the cobas® 4800 BRAF V600 Mutation Test reagents.
Results: *BRAF* V600 mutations were detected in 41.8% of the tested tumors and the invalid rate was found in 1.3%. The mutation rate was found to be over 50% in patients age <60 or with stage III/IV disease without gender differences. Based on tissue subtypes, mutations were detected in 18.8% of acral lentiginous (ALM), 64.7% of superficial spreading (SSM), 50.0% of lentigo maligna (LMM) and 20.0% of nodal melanoma (NM). Although the mutation ratio was low in ALM, 36.4% were mutation positive at stage III/IV.
Conclusions: The frequency of the BRAF mutations is reported to be high in SSM but low in ALM. Therefore we predicted the mutation ratio would be low because ALM was common among Japanese (about 45%) compared with SSM (about 25%). However, this study showed that the patients with SSM had almost the same rate as ALM (43.0% and 40.5%, respectively). Thus the mutation was detected in 41.8% of specimens. Since the 80 specimens were collected for the last 6 years, patients with SSM might be increasing. Interestingly, the frequency of the BRAF mutation in advanced ALM was 36.4% but 9.5% in early stages. As genetic information accumulates relative to molecularly targeted drugs, these genetic insights are expected to provide better treatment predictions for melanoma patients.
No conflict of interest.

3759 POSTER

The dioxin receptor suppresses melanoma growth and metastasis by differentially acting on the tumor cell and the microenvironment

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Background: Melanoma is a highly metastatic and malignant skin cancer having poor rates of patient survival. Since the incidence of melanoma is steadily increasing in the population, finding prognostic and therapeutic targets appears a crucial task in cancer. The dioxin receptor (AhR) is well known for its role in xenobiotic-induced toxicity and carcinogenesis and for its contribution to cell and organ homeostasis. Yet, the mechanisms by which AhR affects tumor growth and dissemination are still largely uncharacterized.
Methods: To address the tumor-intrinsic and the stromal-related AhR functions in melanoma, we have used two approaches. Firstly, we have molecularly engineered B16F10 mouse melanoma cell lines to either down-modulate or to constitutively activate AhR in order to investigate how variations in AhR signaling affect melanoma growth and metastasis. Secondly, we have transplanted those cell lines on *AhR*+/+ or *AhR*−/− immunocompetent mice to explore the contribution of stromal AhR on melanoma tumorigenesis and metastasis. This scheme allowed us to investigate the interaction between intrinsic (melanoma-dependent) and microenvironmental (mouse stromal-dependent) AhR activities in melanoma.
Results: We report here that AhR contributes to the tumor–stroma interaction, inhibiting melanoma growth and metastasis when expressed in the tumor cell but supporting melanoma when present in the stroma. B16F10 cells engineered to lack AhR (sh-AhR) displayed exacerbated melanoma primary tumorigenesis and lung metastasis when introduced in immunocompetent *AhR*+/+ recipient mice but not when injected in *AhR*−/− mice or when co-injected with *AhR*−/− fibroblasts in an *AhR*+/+ microenvironment. Contrary, B16F10 cells having a constitutively active AhR (CA-AhR) had reduced tumorigenicity and invasiveness in either AhR genetic background. The tumor suppressor role of AhR in melanoma cells correlates with reduced migration and invasion, with lower numbers of cancer stem-like cells and with altered levels of β1-integrin and caveolin1. Consistently, human melanoma cell lines with highest AhR expression also had lowest migration and invasion potentials. Moreover, AhR expression was significantly reduced in malignant melanomas from human patients with respect to nevi lesions.
Conclusion: We conclude that AhR knock-down in melanoma cells requires stromal AhR for maximal tumor progression and metastasis. Thus, AhR can be a molecular marker in melanoma and its activity in both tumor and stromal compartments should be considered.
No conflict of interest.

3760 POSTER

Prevalence of BRAF V600E mutation in metastatic melanoma of Mexican Mestizo population

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Background: The BRAF mutation V600E have been described in Caucasian, European and Asian melanomas. However the status and clinical significance of BRAF mutation in Mexican population have not been investigated on large scale.
Methods: Consecutive BRAF-tested Mexican patients with metastatic Melanoma (n = 146) were analyzed for mutations in exon 15 of the BRAF gene in genomic DNA by Real time polymerase chain reaction (RT-PCR, Cobas) amplification. The results were correlated with clinic pathologic features of the patients. All the samples were collected from the whole country, most of the analyzed tissue were from private office.
Results: For the total population 53% were females and the rest males. The age range in males was 28−82 years, meanwhile in women was 26−89 years. Median age, was 56 years in both groups BRAF-mutant and BRAF wild-type patients. The incidence of somatic mutation V600E within the BRAF gene was 30.13% (44/146). Nodular melanoma were the most prevalent subtype in our population, and showed BRAF mutations in 36.3% (16/44). The second subtype was superficial spread were BRAF mutation was 47% (8/17). Other clinic-pathological features were assessed to correlate with the mutation status.
Conclusions: The most prevalent BRAF mutation type in melanoma is V600E. This mutation has been studied in Caucasians, Europeans and Asians. The information reveals than in México Nodular Melanoma is the most prevalent type for metastatic presentation, this could be explained because most of the patients comes with advanced disease, meanwhile, superficial spread melanoma normally is diagnosticated in early stages. In Caucasian population the most frequent type of MM with BRAF mutations is usually superficial spread, and in Asiatic used to be acral. This is the first study in Latin America in a mixed population.
Conflict of interest: *Corporate-sponsored research: Roche*

Proffered Papers Session (Tue, 1 Oct)
Sarcoma: Soft Tissue and Bone

3800 ORAL

Randomized phase II trial of doxorubicin vs. trabectedin plus doxorubicin in first line treatment of patients with advanced non-resectable or metastatic soft tissue sarcomas: a Spanish Group for Sarcoma Research (GEIS) study

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Background: Doxorubicin, 25 years later, is still the standard upfront systemic treatment for metastatic STS patients whereas trabectedin has been recently approved as second line of therapy in STS. The combination of both drugs was hypothesized to be advantageous based on the following rationale: It was found to be synergistic in sarcoma cell lines culture and additive in murine xenograft sarcoma model. In addition, the toxicity profile of both drugs is different so that no serious summative adverse effects were expected as previous phase I trial indicated. The aim of the present study was to compare, in a randomized phase II trial, the efficacy and toxicity of trabectedin plus doxorubicin vs doxorubicin in first line of STS patients.
Methods: Eligible patients were defined as follows: non-resectable locally advanced or metastatic STS, adequate marrow, hepatic, cardiac and renal function and performance 0−2 (most patients were 0−1 after amendment). Patients with HBsAg positive and replicative positive phase as well as CNS metastases were excluded. Trabectedin 1.1 mg/m^2 in 3-h e.v plus doxorubicin 60 mg/m^2 in 20-min perfusion were given through central venous catheter in experimental arm (EA) and doxorubicin 75 mg/m^2 in 20-min perfusion was administered in control arm (CA). Oral dexametasone 4 mg/12 h was given from −1 day in EA. Cycles were given every 21 days for a maximum of 6 in both arms. Main endpoint was progression free survival (PFS) and interim analysis was planned around the occurrence of 62 events of progression. Disease free interval (⩽12 m vs >12m) was used as stratification factor.
Results: From November 2009 to July 2012, 114 patients were enrolled with a median age of 53 y (21−74). There was 33%/67% and 22%/78% of locally advanced/metastatic cases in CA and EA respectively. There were 4 toxic deaths (2 in each arm) mainly in ECOG 2 patients. Most relevant grade 3/4 toxicity was leukopenia 23% in EA vs 9% in CA and febrile neutropenia 11% in EA vs 8% in CA. Grade 3 nausea found in 8% for EA vs 0% for CA and grade 3 asthenia found in 20% for EA vs 7% for CA were significantly different between both arms. Overall, 469 cycles were administered, 242 in CA and 227 in EA. Median of PFS was 5.8 m (3.6−8) in CA and 5.7 m (2.9−8.5) in EA with HR (IC95%) of 1.32 (0.87−2), p = 0.18. The overall survival rate at one year was 53% in CA and 54% in EA. From 107 evaluable patients, RECIST response rate was distributed as follows: partial response 20% in CA vs 13% in EA, stable disease 47% in CA vs 54% in EA and progressive disease 33% in both arms (p = 0.63). The trial was stopped for futility after interim analysis since the results showed a risk reduction for PFS of less than 9.64% for experimental arm.
Conclusions: Combination of trabectedin plus doxorubicin did not show superiority over doxorubicin alone in first line of STS patients failing to demonstrate, at least with the current scheme, the synergistic effect found in preclinical studies.
No conflict of interest.

3801 ORAL

NGR-hTNF given at low dose (LD) or high dose (HD) with or without doxorubicin (D) in soft-tissue sarcomas (STS)

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Background: NGR-hTNF, a tumor-targeted antivascular agent, exhibits a biphasic dose-response curve with activity shown at LD or HD. Vascular effects at LD are driven by early vessel stabilization, which improves intratumor D uptake, and late vessel damage, while at HD by rapid vessel disruption.
Methods: After stratification for prior D dose (> vs $\leqslant$300 mg/m^2), patients (pts) with advanced STS were randomly assigned to receive NGR-hTNF alone at LD (0.8 μg/m^2/d1/q1w) in arm A and at HD (45 μg/m^2/d1/q1w) in arm B, or combined with doxorubicin (60 mg/m^2/d1/q3w/max 6 cycles) at LD in arm C and at HD in arm D. This 4-arm phase II trial had progression-free survival (PFS) as primary endpoint, with tumor response assessed q6w until progressive disease (PD). Using a 2-stage study design, each regimen was rejected if $\leqslant$2/14 and $\leqslant$7/24 pts were PD free at 3 months after 1st and 2nd stage, respectively (β=20%; α=10%; n = 96). Secondary endpoints comprised adverse events (AEs), response rate by RECIST criteria and early metabolic response (MR), as quantified by fractional changes in SUV using FDG-PET according to EORTC criteria.
Results: Globally, 69 pts (median age 55 years; male 38; PS $\geqslant$1 31; leiomyosarcomas 14; median prior lines 2, range 0−7) received 678 weekly cycles (mean 10; range 1−46). Main grade 3/4 treatment-related AEs were neutropenia (18%) and chills (7%). After 1st stage, primary endpoint was met only for arm C (LD NGR-hTNF plus D), with 7/14 pts PD free at 3 months. At the end of 2nd stage (arm C, n = 28), median PFS was 1.3 months (95% CI, 1.1−1.5) for arm A, 1.5 (1.1−1.8) for B, 3.6 (1.1−6.1) for C and 1.6 (0.9−2.3) for D (p = 0.01 for trend). As best response by RECIST, 25/59 evaluable pts (42%) had stable disease (SD), including 1/12 in arm A, 6/12 in B, 14/23 in C and 4/12 in D. Median SD duration in arm C was 4.8 months (range 1.6–22.8). By FDG-PET imaging done at 3 weeks, 7/37 assessable pts (19%) had partial MR (4 SD/3 PD per RECIST), with mean change in SUV of −34% (SD $\pm$ 12), while 23 pts (62%) had stable MR (7 SD/16 PD per RECIST), with mean change in SUV of 2% ($\pm$10). Median PFS was 4.1 months in pts who achieved partial MR and 1.4 months in pts who did not (HR = 0.58).
Conclusion: LD NGR-hTNF can be safely given with D, showing promising activity.
No conflict of interest.

3802 ORAL

PICASSO 3: A phase 3 international, randomized, double-blind, placebo-controlled study of doxorubicin (dox) plus palifosfamide (pali) vs. dox plus placebo for patients (pts) in first-line for metastatic soft tissue sarcoma (mSTS)

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Background: Pali is a potent bi-functional DNA alkylating agent with activity against multiple tumors including mSTS, and as the active metabolite of ifosfamide, bypasses resistance pathways and toxic metabolites associated with prodrug activation.
Materials and Methods: Eligible pts had measurable mSTS and had not received previous chemotherapy for metastatic disease. Disease histology was centrally confirmed by independent pathology review. Pts were stratified by histological type (synovial, leiomyosarcoma, other sarcoma) and age (<65, $\geqslant$65 yrs), then randomly assigned 1:1 to receive dox 75 mg/m^{2}IV (day 1) plus either pali 150 mg/m^2 IV or placebo (days 1, 2, 3) every 21 days for up to 6 cycles. No cross-over was allowed. The primary endpoint of progression-free survival (PFS) per RECIST v1.1 was assessed by independent, blinded radiographic review. Secondary endpoints included overall survival, response rate, quality of life, and safety and tolerability.
Results: Between Sept 2010 and Jul 2012, 447 pts with mSTS at 113 centers worldwide were randomly assigned to receive pali+dox (n = 226) or placebo+dox (n = 221); 6% had synovial, 34% leiomyosarcoma, 60% other sarcomas; and 26% were $\geqslant$65 years. Median PFS was 5.98 months (95% CI 5.31–6.20) for pali+dox compared with 5.23 months (4.13–5.90) for placebo+dox (HR = 0.87, 95% CI 0.70–1.07; p = 0.18). At interim analysis, median overall survival was 15.91 months for pali+dox vs 16.89 months for placebo+dox (HR = 1.05, 95% CI 0.79–1.39; p = 0.74). Subgroup analysis is ongoing. Adverse event (AE) profiles were similar in both treatment arms, with the rate of febrile neutropenia of 17.8% for pali+dox v 9.8% for placebo+dox. Common AEs were nausea, constipation, fatigue, vomiting, diarrhea, and anemia. Grade $\geqslant$3 AEs were neutropenia, febrile neutropenia, nausea, anemia, constipation and dehydration. Pt-reported health-related QoL was maintained with pali+dox.
Conclusion: PICASSO 3 did not meet its primary endpoint, although pali+dox showed 3.1 weeks improvement in median PFS compared with placebo+dox in the first-line setting for mSTS. Pali+dox had a comparable toxicity profile compared with dox alone in this setting.
Conflict of interest: *Advisory board: Robert Maki: ZIOPHARM. Corporate-sponsored research: Jean Yves Blay: Novartis, Pharmamar, Pfizer, Roche, MSD, GSK; Robert Maki: ZIOPHARM; Ian Judson: ZIOPHARM; Scott Schuetze: Threshold; Christopher Ryan: ZIOPHARM. Other substantive relationships: Jean Yves Blay: expert testimony for MSD; Jean Yves Blay: honoraria from:Novartis, Pharmamar, Pfizer, Roche, MSD, GSK; Robert Maki: honoraria from ZIOPHARM; Scott Schuetze: honoraria from Threshold; Ofer Merimsky: expert testimony for Medison Ltd, Israel; Jill Buck: employee of ZIOPHARM with stock holdings.*

3803 ORAL

A comparison of isolated limb perfusion with surgery to surgery with radiotherapy for large high grade soft tissue sarcomas of the lower limb

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Aims: Isolated Limb Perfusion (ILP) with melphalan and TNFα is an effective induction treatment prior to surgery for locally advanced extremity sarcomas. It is used widely in mainland Europe for large tumours that are considered to be not easily compatible with functional limb conserving surgery. However the outcome of patients undergoing this treatment has never been directly compared to patients with equivalent tumours undergoing standard treatment of surgery and radiotherapy. We conducted a retrospective case matched cohort study comparing patients treated by ILP prior to surgery in two German sarcoma centres with patients with similar tumours treated by surgery and radiotherapy at a sarcoma centre in the UK.
Methods: Patients with intermediate or high grade STS of leg, exceeding 10 cm in size were identified from 2 prospectively maintained databases. Three independent sarcoma surgeons from separate sarcoma centres viewed anonymised MRIs of tumours from patients in each cohort and scored the tumours in terms of compatibility with limb preserving surgery on a linear scale (1−10). Primary outcome measures were local recurrence free survival and local failure rate.
Results: The two cohorts comprised 44 (ILP and surgery) and 80 (surgery and radiotherapy) patients. Twelve patients in the ILP cohort received additional postoperative radiotherapy. In the standard therapy cohort, all patients underwent resection and 66 received adjuvant radiotherapy. Tumour size, grade, histological subtype and compatibility with limb preserving surgery as assessed by independent review were identical between cohorts (Table). There were three amputations because of complications post ILP and surgery. No treatment related amputation occurred in the surgery and radiotherapy group. There were less local recurrences in the ILP cohort although this did not achieve significance (4/44 (9%) versus 13/80 (16%), p = 0.16). Local failure rate (local recurrence or amputation due to complications) was identical between cohorts (7/44 (16%) versus 13/80 (16%)). The rate of distant metastasis was also identical. (43/80(54%) vs 24/44(55%).
Conclusions: This case matched cohort analysis showed that ILP prior to surgical resection may have a lower local recurrence rate for large high grade sarcomas of the leg when compared with surgery and radiotherapy alone. However when treatment related complications are included the

overall local failure rate is identical between treatment groups. Therefore ILP and surgery is not superior to surgery and radiotherapy alone for limb preservation.
No conflict of interest.

	Surgery and DXT − no ILP (UK) (N = 80)	Surgery and ILP (+/− DXT) (Germany) (N = 44)	p-value
Total number	80	44	
Age (years), median (range)	63 (18−93)	56 (17−82)	0.02
Size (cm), median (range)	13 (10−30)	13 (10−34)	0.98
Grade			0.84
2	28 (35%)	14 (32%)	
3	52 (65%)	30 (68%)	
Histology			0.94
NOS	39 (49%)	20 (46%)	
Liposarcoma	17 (21%)	10 (23%)	
Other	24 (30%)	14 (31%)	
Resection margin			0.32
R0	65 (81%)	39 (89%)	
R1	15 (19%)	5 (11%)	
Median score of compatibility with limb salvage (1−10)	4.7	5.1	0.31
Follow-up (months)	25 (4–139)	34 (10–132)	

3804 ORAL

Soft tissue sarcoma care in The Netherlands: Epidemiology, patterns of care and outcome data

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Introduction: This report presents the results of a nationwide soft tissue sarcoma (STS) survey conducted on behalf of the Dutch Cancer Society. Insight in the incidence, patterns of care and outcome may function as starting point for further improvement of STS patient care.
Methods: STS data from the national population based Netherlands Cancer Registry (NCR) were used to study STS pts in the period 2006–2011 with respect to epidemiology and treatment, excluding Kaposi sarcoma, GIST, uterine sarcoma and sarcoma of the skin. Descriptive statistics were applied to analyze patterns of care and outcomes on selected indicators measuring quality aspects of soft tissue sarcoma care.
Results: Overall, a total of 2,709 pts were diagnosed with STS, 1,495 men (55%) and 1,214 women (45%). The age-standardized incidence rate (2.7/100,000) did not change over time, and the same is true for the 5-yrs relative survival rate (60%). Median age at diagnosis was 63 (range 18–100) years; 47% were elderly pts (>65 years). Considering anatomical localization, 11% head and neck, 43% trunk or retroperitoneal cavity, 33% lower limbs, and 14% in upper limbs. Most often diagnosed histology: leiomyoarcoma (21%), NOS (20%), liposarcoma (19%), fibrosarcoma (10%) and undifferentiated sarcoma (10%). With respect to pattern of care: 2,215 pts (82%) were surgically treated (excluded those with metastatic disease), 892 of these pts (40%) received additional radiation therapy and overall 133 pts received adjuvant chemotherapy (5%). In pts left with an R1-status following surgery, the proportion receiving adjuvant radiotherapy was 53%. Resection status remained unknown in 25% of surgically treated pts (excluding those with metastasized disease), and in one third of the STS pts the tumor was not graded according to Coindre. Only systemic or radiation treatment was given in 4% and 3% respectively. Surgical treatment was fairly concentrated in a few centers: in 2010, 20% of all Dutch hospitals accounted for 60% of surgical procedures performed as STS treatment, with 7 centers (8% of hospitals) treating more than 10 pts per yr.
Conclusion: The incidence and relative survival of STS did not change in The Netherlands. Our findings suggest that there is room for improvement in Dutch STS diagnosis and care. Central pathology review may improve definitive histopathology, grading and reporting of resection status. Sarcoma treatment in 4−5 sarcoma centers with clinical and translational research, preferably within the EORTC Soft Tissue and Bone Sarcoma group, may improve overall sarcoma care and alter the disease outcome in the next decade.
No conflict of interest.

3805 ORAL

Presentation, treatment, and prognosis of recurrent osteosarcoma: The EUropean RELapsed OsteoSarcoma Registry (EURELOS)

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Background: A significant proportion of osteosarcomas relapse following multimodal treatment, yet prospectively gathered data on relapse presentation and outcomes is scarce. In order to fill this void, three multi-institutional osteosarcoma groups representing 10 European countries joined to form the EUropean RELapsed OsteoSarcoma Registry (EURELOS).
Material and Methods: EURELOS registers Cooperative Osteosarcoma Study Group (COSS), Italian (ISG) and Scandinavian (SSG) Sarcoma Group patients with recurrent osteosarcoma. Details on demographic, tumor, and treatment-related variables are collected according to a predefined common dataset.
Results: As of 03/13, 470 patients registered: 327 COSS, 120 ISG, 23 SSG; 305 male, 165 female; 423 primary extremity tumor, 47 axial; 381 initially localized, 87 metastatic (2?). Median interval diagnostic biopsy to 1st relapse: 1.66 years (range: 0.2–20.4), 432 within 5 years, 34 later (4?). First suspicion of relapse: symptoms 105, routine imaging 301 (64?). 375 recurrences metastatic, 60 local, 34 combined (1?). Metastases: lungs 353, bones 82, other sites 31. Median follow-up from first relapse: 1.26 years (0−9.4) for all 470, 1.69 years (0−9.4) for 229 survivors, 146 patients in 2nd (109) or later (37) CR. Actuarial 2-/5-year overall survival (OS): 48%/30%. 2-year OS isolated local relapse 63%, metastases 49%, combined 24%. 2 year OS with 2nd complete surgical remission (CR) 71%, without 14%. Factors correlating with better OS in univariate analysis: No primary metastases, good histologic response to 1st line chemotherapy, relapse detection by imaging, disease-free interval >median, solitary lesion at recurrence. Overall, neither 2nd line chemotherapy nor the use of immuno- or targeted therapies nor that of radiotherapy predicted for better OS, but all of these were much more likely to be used in patients with brief disease-free intervals and multiple lesions at relapse and particularly in patients not achieving a 2nd CR ($p < 0.001$).
Conclusions: International collaboration in relapsed osteosarcoma is feasible but demanding. Results obtained from the first 470 EURELOS patients confirm those from retrospective analyses and add novel information. Data from EURELOS may be used to help further delineate standards of care.
Support: Deutsche Krebshilfe; AXIS-Forschungsstiftung; H. Frank Memorial Fund; European Union's Seventh Framework Programme (FP7/2007–2013) under the project ENCCA, grant agreement HEALTH-F2–2011–261474
No conflict of interest.

Poster Session (Mon, 30 Sep)
Sarcoma: Soft Tissue and Bone

3806 POSTER

Delay in diagnosis and treatment of soft tissue sarcomas (STS): Causes of late intervention and their role in prognosis − a prospective, multidisciplinary group study

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Background: STS are 1% of malignant tumors in adults. Rarity, heterogeneity in presentation, low expertise in Primary Care Physicians (PCP) or in general hospitals, organisation problems in Specialized Centres may cause a delay in both diagnosis and treatment. Aim of this study is to acknowledge the barriers to optimal care and the consequences of the delay on prognosis.
Material and Methods: Patients with STS of the extremities, trunk, retroperitoneum treated and followed from 1999 to 2011 by the same multidisciplinary group were included.
Time and pattern of symptoms onset, anatomic site, tumor volume, patients' age, gender and home, interval between diagnosis and surgical treatment or neoadjuvant chemotherapy; time to start adjuvant RT or CT were considered in a univariate − multivariate analysis.

Results: 449 adult patient (53% F, 47% M, median age 55 years) were followed for a median time of 116.38 months. 65.7% of STS were at the extremities, 17.6% retroperitoneal, 16.7% at the trunk wall. Median volume at diagnosis was 8 cm for trunk and extremities; 15 cm for retroperitoneum. Commonest histologies: liposarcoma. 18.2%; leiomyo 16.8%; mixofibro 13.6%. Increasing mass, pain and abdominal disconfort were the main revealing signs of diseases. Median time of delay were: from onset of symptom to first medical visit 68 days for trunk and extremities, 82 for retroperitoneum; 104 days from symptoms to histological diagnosis; 129 days from symptoms to start of therapy. Time to surgery after definitive diagnosis was 12 days in extremities and 21 in abdomen. Adjuvant CT started 22 days after surgery for extremities, 25 in trunk, 35 in retroperitoneum. RT initiated after 78 days. Longer delay in treatment lead to worse prognosis: MS 89.95 months if delay was >3 months; 190.40 months if wait was <3 months (p 0.007).
Conclusions: Low self consciousness of the patient; misdiagnosis or inadequate approach in general hospitals; late referral to specialized centres are 75% of the cause of wasted time. Organization problems at the referral Centre concur for 25% of delay. Guidelines implementation and educational programme among general population and PCP are necessary.
No conflict of interest.

3807 POSTER

Hyperthermia-mediated BRCA2-degradation and cytotoxicity of trabectedin in human soft-tissue sarcoma (STS) cells

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Background: Regional hyperthermia combined with chemotherapy improves treatment response and survival of patients with high-risk STS (Issels, Lancet Oncol 2010). Trabectedin (Yondelis®) is approved in Europe for the treatment of advanced STS after failure of anthracyclines and ifosfamide or for patients unsuitable to receive these drugs. Its cytotoxicity is associated with the induction of DNA double-strand breaks (DSB). The rationale to combine trabectedin with hyperthermia is that heat-exposure inhibits the repair of DSBs by degradation of BRCA2 which is crucial for homologous recombination (HR) DNA-repair by Rad51 recombinase (Krawczyk, PNAS 2011).
Methods: Combination of trabectedin and hyperthermia was analyzed in four different human cell lines: osteosarcoma (U2Os), liposarcoma (SW872), synovial sarcoma (SW982) and colorectal cancer (DLD1). For investigation of BRCA2 deficient cells, DLD1 mutant ($^{-/-}$BRCA2) cells and U2Os cells treated with siRNA knock-down were used. Trabectedin (500–4000 pM) was applied for 3 hours with hyperthermia (41.8ºC and 43ºC) for 90 or 150 min either before, during or after trabectedin. Cytotoxicity was assessed by clonogenic survival, expression of BRCA2 by Western Blot (WB). The amount of γH2AX positive DSB-repair-foci and recruitment of Rad51 were analyzed by immunocytochemistry (ICC).
Results: Cell lines showed a dose dependent reduction of clonogenic survival after trabectedin. Treatment with hyperthermia enhanced cytotoxicity of trabectedin with strongest effects when combined simultaneously. According to WB analysis, a heat-dependent reduction of BRCA2 expression was observed. ICC showed a reduced recruitment of Rad 51 to DSBs after 41.8ºC, which was abolished after 43ºC. Combined treatment also significantly increased the amount of cells with DNA damage (>50 γH2AX-foci per nucleus). In cells deficient for BRCA2, heat-dependent enhancement of trabectedin cytotoxicity was nearly abolished.
Conclusions: Concomitant treatment with trabectedin and hyperthermia resulted in enhanced cytotoxicity, which was accompanied by elevated DNA-damage. Heat-mediated BRCA2-degradation and impairment of HR dependent DSB-repair seem to be related mechanisms for the thermosensitization of trabectedin.
Conflict of interest: *Other substantive relationships: R. Issels and L. Lindner: Consultancy for Medtherm*

3808 POSTER

Brain metastases from sarcoma: Identification of prognostic factors and analysis of treatment impact − a retrospective analysis from the French Sarcoma Group (GSF/GETO)

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Background: Brain metastases (BM) from adult soft tissue sarcomas or bone sarcomas are rare and only limited data exist on their prognostic factors and treatment.
Material and Methods: A retrospective study in 16 centers of the French Sarcoma Group was conducted to identify prognostic factors and determine the impact of chemotherapy, radiation therapy and surgery on outcomes. The median number of patients per center was 9.5 (range, 2−74).
Results: Between 1992 and 2012, 246 pts (139 men and 107 women) with a median age of 50 (range, 16−86) were managed for BM. BM included 221 cerebral and cerebellal metastases and/or meningeal sarcomatosis (n = 40) and among them 87 patients with only one. Histological subtypes were leiomyosarcoma (n = 46; 18.7%), Ewing sarcoma/primitive neuroectodermal tumor (n = 30; 12.2%), liposarcoma (n = 19; 7.7%), alveolar soft-part sarcoma (n = 14; 5.7%), osteosarcoma (n = 14; 5.7%), rhabdomyosarcoma (n = 14; 5.7%), angiosarcoma (n = 14; 5.7%), synovialosarcoma (n = 13; 5.3%) and others (n = 82; 33.3%). Pathological grades were low, intermediate and high grade in 4.2%, 24.7% and 71.1% of cases, respectively. Patients developed BM at 18 months (0–215) after diagnosis of primary tumour and 9 months (0–110) after diagnosis of others metastases (pulmonary, hepatic and bone metastases in 72.8%, 12.6% and 23.2% respectively). Surgery of BM was carried out for 38 (15.5%) of patients. Radiotherapy to the whole brain and stereotactic radiotherapy were carried out in 144 (58.5%) and 24 (9.8%), respectively. Chemotherapy (the most frequent protocols were doxuribicin +/− ifosfamid, etoposid alone or in association, trabectedin) was carried out in 91 (37.0%) and palliative care in 46 (18.7%). Whatever the treatment, BM have been controlled in 49 pts (19.9%), including 31 partial (12.6%) & 18 complete (7.3%) response. Stable disease, disease progression and no evaluable status were observed in 64 (26.0%), 120 (48.8%) and 13 (5.3%) patients respectively. One hundred and ninety six patients (79.7%) died with a median overall survival (OS) from diagnosis of brain metastasis of 2.7 months (0.-133). In multivariate analysis, the following parameters influenced OS: chemotherapy (Hazard ratio (HR) = 0.38 [95%-CI: 0.26–0.48]), surgical removal (HR = 0.40 [95%-CI: 0.22–0.72]), stereotactic radiotherapy (HR = 0.41 [95%-CI: 0.19–0.90]), whole brain radiotherapy (HR = 0.51 [95%-CI: 0.35–0.76]) and grade (HR = 0.65 [95%-CI: 0.43–0.98]). In univariate analysis, 2 others clinical factors seemed to influence the OS: age (less or plus 50 years (HR = 0.64 [95%-CI: 0.48–0.85])) and number of BM (alone or multiple (HR = 0.76 [95%-CI: 0.56−1])).
Conclusion: BM of adult sarcomas are rare with poor prognosis. Our results suggest the positive impact of chemotherapy, radiation therapy and surgery on outcomes.
Conflict of interest: *Advisory board: Novartis, Pfizer, Pharmamar, GSK*

3809 POSTER

A novel model of skull osteosarcoma in athymic mice

G.C. De Miguel[1], M. Laranjo[2], A.M. Abrantes[2], M. Gracia[1], K. Santos[2], T. Rocha[1], M. Marques Ferreira[3], M.F. Botelho[2], D.G. Priolli[1]. *[1]São Francisco University, Postgraduate Program in Health Science, Bragança Paulista, Brazil; [2]Biophysics Unit − IBILI − CIMAGO, Faculty of Medicine of University of Coimbra, Coimbra, Portugal; [3]Department of Dentistry, Faculty of Medicine of University of Coimbra, Coimbra, Portugal*

Background: Osteosarcoma (OS), a malignant tumor characterized by direct formation of bones or osteoid, is the second most common primary bone neoplasm. This type of cancer affects both children and adults and it grows predominantly on metaphyseal region in young adults or flat bones on patients over 50 years. It has an unknown etiology, and the clinical symptomatology comprises local pain and in surrounding area, such as adjacent joint, unrelieved by rest or analgesic. Furthermore, it is a tumor with low response to chemotherapy, leading to a variety of tumor cell necrosis, with a better prognosis of surgery for complete removal of the tumor. Frequently, tumors are located on so-called hard to access locations

or in areas impossible to access surgically. Therefore, the development of new therapeutic strategies is mandatory, based on appropriated model assay to pursue the success on OS treatment. Consequently, the aim of this work was to develop an orthotopic animal model of skull OS. This model might be of paramount importance to evaluate new therapy options as well as to study this disease.
Material and Methods: Human OS cell line MNNG/HOS, purchased at American Type Culture Collection (ATCC), was cultured according to manufacturer's procedure. Eight athymic nude mice (Balb/c nu/nu), with 20−24 g weight were split in two groups: control and test. $1x10^6$ cells were inoculated directly onto the surface of the skull of test group, right after a scarification was made with the needle. Nuclear imaging studies with ^{99m}Tc-MIBI were performed in two different timeframes: in the day of tumor implantation and 30 days later before sacrifice of the mice. Nuclear medicine images allowed the drawing of ROIs at the skull and in quadriceps muscle projections leading to the tumor/muscle ratio calculation. After the sacrifice, RX were made using a Genoray PORT-X II, a portable dental X-ray, analyzed with Gx Vin Wix Pro software, and a conventional histopathological study was performed.
Results: All mice recovered well from the procedure without signs of pain or discomfort. Three days after the surgery the animals does not have any signal of tumor, but ate the fifth day it started to show a small taint at the skull. All five animals submitted to the procedure developed a tumor which volume increased slowly till the tenth day, when it achieved volumes of $424.25\pm243.54\ mm^3$. Tumor/muscle ratio was of 3.7 ± 0.4. At day twenty the animals were subjected to RX. In the control group no alterations were found. However, in the test group the animals presented clearly signs of bone aggression with cortical destruction and lytic lesion in both side views, just below the tumor area.
Conclusion: It was possible to successfully develop an orthotopic animal model of skull osteosarcoma. Imaging studies showed that the tumor cells implanted had continuity with bone area and thus modifying bone structure. The orthotopic model of OS is feasible, allows noninvasive monitoring of the tumor growth and is suitable for studying new therapies.
No conflict of interest.

3810 POSTER

Factors related to the early toxicity of hypofractionated preoperative radiotherapy in treatment of localized extremity/trunk wall soft tissue sarcoma (STS)

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Background: The aim of this prospective study is to assess the rate and factors influencing early toxicity in the group of patients localized extremity/trunk wall soft tissue sarcoma (STS) who underwent preoperative hypofractionated radiotherapy.
Methods and Materials: Two hundred and twenty patients with operable STS treated between 2006 and 2010 received preoperative 5×5 Gy short-term irradiation and surgery performed within 5 days. The neoadjuvant chemotherapy was given for the subset of patients with high grade tumors. The potential impact of factors on early toxicity, such as gender, age, addition of chemotherapy, pathological subtype, anatomical site, grade and size of tumor, was analyzed.
Results: The early toxicity after 5×5 Gy was noted in 62/220 (28%) patients: 17.2% had prolonged wound healing >1 month, 12.7% had wound dehiscence, 4% needed prolonged evacuation of lymphatic fluid and 2.7% had grade 3 skin toxicity. Ten patients required reoperation (4%). Only tumor grade, lower limb localization and addition of neoadjuvant chemotherapy were significant risk factors for early toxicity.
Conclusion: The 5×5 Gy regimen in preoperative treatment of STS had acceptable rate of early toxicity. The addition of chemotherapy especially in lower limb sarcomas may increase risk of complications.
No conflict of interest.

3811 POSTER

Early 18F-FDG-PET monitoring during long-term treatment of desmoids (aggressive fibromatosis) with imatinib mesylate

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Background: We used early dynamic 18F-FDG PET (dPET) in patients with unresectable aggressive fibromatosis undergoing treatment with imatinib to analyse whether treatment was affecting tumor perfusion and phosphorylation indicating treatment efficacy. The goal of the study was to evaluate whether parametric imaging could serve as a decision element to continue with the drug and await tumor shrinkage at a later stage.
Methods: Out of 224 patients treated with desmoids since 2004, 32 patients with progressive AF were not amenable to surgical resection without significant functional deficit and received imatinib with a target dose of 800 mg per day. Patients were examined using PET prior to the start of therapy and and 4 weeks after reaching the target dose, typically at week 6 to 10. Patients (25 f, 7 m; median age of 28 yrs, range, 16−48 yrs) were characterized by recurrent disease (n = 20), residual tissue (n = 4), or primary disease (n = 8). Median duration of imatinib therapy was 28 mos. (range, 3−66 months).
Parametric images were calculated based on the dPET data by fitting a linear regression function to the time-activity data and for each voxel. Images of the slope and the intercept of the time-activity data were calculated and the resulting parameters of the FDG kinetics [blood volume (VB), k1-k4] were compared with the volume-of-interest-based slope and intercept data. The evaluation of the parametric images was performed visually and quantitatively.
Results: 27 of 32 tumors could be visualized in the SUV images with a moderate uptake, in locations known from the MR images. 23/32 of the tumors demonstrated a clear enhancement in intercept images, whereas 5 tumors showed an intermediate enhancement and another 4 tumors did not show any enhancement. The comparison of slope revealed the highest correlation to the SUV ($r = 0.56$, $P < 0.05$). In median, a 28% decrease in the average standardized uptake value (SUV) of the sequential PET examinations was demonstrated in all evaluable patients. Patients showing a decrease in SUV of more than 40% (n = 15) subsequently developed at least a PR of their disease (PPV of 72%). No patient showed a substantial increase in SUV during imatinib therapy. Four patients developed a CR, three of them after more than 1 year of treatment, in one case it took 5 years to develop after an initial tumor size of 22 cm. Five patients had to stop imatinib therapy for tumor progression.
Conclusion: Our data indicate that the use of regression-based parametric PET allows to identify responders to imatinib treatment early, thus helping to decide whether therapy should be continued or not.
Conflict of interest: *Advisory board: Novartis. Corporate-sponsored research: Novartis*

3812 POSTER

Evaluation of outcome and prognostic factors in primitive neuroectodermal tumor of adults: A single institutional experience of 112 cases with uniform chemotherapy protocol

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Purpose: To evaluate prognostic factors and treatment outcome in primitive neuroectodermal tumour (PNET) of adults.
Materials and Methods: This is single institutional data review of PNET patients with >18 years of age treated between June 2003 and November 2011 with uniform chemotherapy protocol and evaluated on intent to treat analysis. All patients received neoadjuvant chemotherapy (NACT), surgery and/or radiotherapy as local treatment followed by adjuvant chemotherapy.
Results: Of 374 patients with PNET, 112 (30%) were adult PNETs with median age of 22 years (range: 19−55) and male: female of 80:32. Most common regions included extremity in 50 (45%), thorax in 24 (21%); 44 (39%) had metastatic disease. Thirty-eight patients underwent surgery; 39 patients received radical radiotherapy following NACT. After median follow up of 21.8 months (range: 1.6–108.5), 5-year EFS, OS and local control rate (LCR) were $29.6\pm5.8\%$, $49.6\pm8\%$ and $66.5\pm8.5\%$, respectively for entire cohort, and $40.2.6\pm7.8\%$, $61.6\pm9.6\%$ and $72.3\pm8.7\%$, respectively for localized disease (n = 68). On multivariate analysis, skeletal primary ($p = 0.03$), albumin $\leqslant 3.4$ g/dl ($p = 0.008$) and metastatic disease ($p = 0.006$) predicted inferior EFS. Primary of head and neck, thorax and extremities ($p = 0.02$) and white blood cell count (WBC) $>11\times10^9$/L ($p = 0.04$) predicted inferior OS on multivariate analysis, whereas WBC$>11\times10^9$/L ($p = 0.03$) independently predicted LCR. Adult PNETs had lower systemic symptoms (20% versus 34%, $p = 0.007$), longer symptom (7.9 months versus 5.4 months, $p = 0.004$), lager tumour (10.6 cm versus 9.4 cm, $p = 0.05$), and lower haemoglobin level (12 versus 10.8 g/dl, $p < 0.0001$) as compared to paediatric cohort. In comparison to paediatric PNET (n = 262), adult cohort has superior EFS (21.9% versus 29.7%, $p = 0.11$) and OS (39.5% versus 49.6%, $p = 0.04$).

Conclusions: Adult PNET formed 30% of the all PNETs with 39% patients presenting with metastatic disease. We identified novel prognostic factors including tumour origin, tumour location, WBC count, hypoalbumenia ($\leqslant$3.4 g/dl) and metastatic disease as independent prognostic factor to affect outcome. Patients with localised disease and WBC$\leqslant 11\times 10^9$/L had best prognosis. Those with metastatic disease and high WBC or hypoalbuminemia may merit aggressive therapy. Local treatment modality didn't affected outcome. Adult cohort has marginally superior EFS, but significantly superior OS as compared to paediatric PNET.
No conflict of interest.

3813 POSTER

A non-comparative phase II study of dose intensive chemotherapy with doxorubicin and ifosfamide followed by high dose ICE consolidation with PBSCT in non-resectable, high grade, adult type soft tissue sarcomas (STS)

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Background: To determine the feasibility and effectivity of dose intensive induction chemotherapy (CTh) in patients (pts) with STS that was considered as either unresectable or resectable only with mutilating surgery.
Materials and Methods: Treatment consisted of at least 2 cycles of DOX (75 mg/m^2) on day 1 and IFO (12 g/m^2 as a 72 h infusion). In responding and stable pts, this was followed by one cycle of HD-ICE), ETO 500 mg/m^2, Carbo 500 mg/m^2 and IFO 4 g/m^2 (days −4 to −2, peripheral blood-derived hematopoietic stem-cell support on day 0. Pts with a single distant metastasis deemed resectable were allowed.
Results: 30 out of 631 consecutive pts, age 46 years (range, 21−62), were included, 5 of whom had a single lung (4) or liver (1) metastasis. 29 pts completed at least 2 cycles of DOX/IFO. While 16 pts (55%) remained stable, 7 pts (24%) showed a PR, 1 pt (3%) a CR, and 5 pts (17%) progressed. HD-ICE was withheld because of PD in 5 pts, neurotoxicity in 6, insufficient PBSC mobilization, CR and refusal in 1 pt each. Thus, 16 pts received HD-ICE, which was associated with non-hematological grade III toxicity including emesis, mucositis, fever, neurotoxicity, and transaminase level elevation. Two additional pts attained a PR after HD-ICE. Overall, 24 of 30 (80%) pts underwent surgery, with complete tumor resections in 19 pts (63% of all pts, 79% of the operated subgroup); however, 2 of whom required amputation. After a median follow up period of 50 mos in surviving pts (range, 26–120), 5-yr DFS and OS rates were 39% and 48%, respectively. Pts with shrinking STS becoming resectable after pretreatment had a markedly improved DFS (median, 50 vs. 3.5 mos; HR: 7.22 (95% CI, 1.52–34.29), $p < 0.01$) and survival (median, 73 vs. 9 mos; HR: 9.11 (95% CI 1.82–45.59), $p < 0.007$). Early response to CTh was associated with improved OS. Negative margins and grade III had an impact on DFS. Tumor size was associated with an improved OS (trend only). Extent of necrosis in the resected specimen did not impact survival neither did age, gender and late response to CTh.
Conclusion: Induction chemotherapy plus consolidation HD-ICE is generally feasible, but is associated with significant neurotoxicity. In an intent-to-treat-analysis, complete (R0) resection as the primary end point of the study was achieved in approx. 60% of pts initially considered as not R0 resectable. The advantage of HD-ICE over conventional dose CTh plus EBRT in non-resectable disease remains unproven.
No conflict of interest.

3814 POSTER

Poor clinical outcome in patients with retroperitoneal/intra-abdominal Ewing sarcoma

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Background: Ewing sarcoma can arise in either bone or soft tissue locations. Extraskeletal Ewing sarcoma, especially in the origin of retroperitoneal/*intra-abdominal*, is rare in the form of soft tissue sarcoma. We sought to investigate if patients characteristics, treatment strategies, and prognosis differ between skeletal Ewing sarcoma and retroperitoneal/ intra-abdominal Ewing sarcoma (R/I-ES).
Material and Methods: Clinicopathological features and patient outcomes were reviewed retrospectively for Ewing sarcoma patients receiving treatment in our institution between September 1978 and August 2012. We evaluated based on retroperitoneal/intra-abdominal vs skeletal site of origin. Patients characteristics were compared using Fisher exact tests. Overall survival was estimated by Kaplan–Meier methods and compared using log-rank tests and Cox models.
Results: Of the 134 patients identified, primary site of retroperitoneal/ intra-abdominal were 19 (14.1%), skeletal were 95 (70.9%), and the others were 20 (15%). The site of origin of R/I-ES were retroperitoneal 8, kidney 4, small intestine 2, and omentum, peri-anal, pelvis, uterus that were one case each. Patients with R/I-ES had a higher median age (32 vs 19 years; $P<0.001$). At the first visit, 10 patients with R/I-ES had metastatic or invasive lesions and 10 patients with skeletal site of origin (52.3% vs 10.5%; $P<0.001$), mean tumor size was 104 mm and 88.6 mm (n.s.). Radical surgery were performed 15 patients with R/I-ES, and 59 patients with skeletal site of origin and recurrence were confirmed 12 patients with R/I-ES and 25 patients with skeletal site of origin (recurrence rate: 85% vs 42%; $P<0.001$). 15 patients with R/I-ES had received chemotherapy (7: adjuvant settings, 8: after recurrence). Patients with R/I-ES had poor prognosis significantly compared with skeletal site of origin (MST: 2.6 vs 7.8 years: $P<0.004$).
Conclusions: R/I-ES patients had poor prognosis compared with skeletal site of origin. The reason why regardless of tumor size, tumor was diagnosed progression state, and that made it difficult to curative resection, but it was not clear resection rate in this study. It is necessary to increase the cure rate, carrying out multimodality treatment effectively, also cases that curative resection was not performed.
No conflict of interest.

3815 POSTER

Long survivors with brain metastases from sarcomas: A retrospective analysis from the French Sarcoma Group (GSF/GETO)

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Background: Brain metastases (BM) from adult soft tissue or bone sarcomas are rare with poor prognosis. The aim of this retrospective study was to describe the characteristics of long survivors (overall survival (OS) greater than 2 years).
Material and Methods: Data of 246 patients (pts) with BM of sarcomas from 16 centers of the French Sarcoma Group were collected from 1992 to 2012.
Results: Among the 246 pts, 17 (6.9%) − 11 men and 7 women − with a median age of 31 years (range: 17−65) had an OS greater than 2 years. BM included 14 cerebral and cerebellal metastases and/or meningeal sarcomatosis (n = 4) and among them 9 (53%) patients with only one metastasis. Histological subtypes included leiomyosarcoma (n = 4), Ewing sarcoma/primitive neuroectodermal tumor (n = 3), alveolar soft-part sarcoma (n = 3), rhabdomyosarcoma (n = 1), synovialosarcoma (n = 1) and others (n = 4). Pathological grades were low, intermediate, high grade and unknown in 2, 4, 4 and 7 pts, respectively. Interval between diagnosis of sarcoma and BM, and between diagnosis of others metastases and BM were 73 months (range: 0–204) and 10 months (range: 0−88) respectively. Surgery of BM was carried out for 7 patients. Radiotherapy to the whole brain and stereotactic radiotherapy were carried out in 10 and 3 cases,

respectively. Eleven patients received cytotoxic chemotherapy. The most frequent protocols were doxuribicin +/− ifosfamid, etoposid alone or in association, trabectedin. Whatever the treatment, BM have been controlled in 12 pts, including 3 partial & 9 complete response. Stable disease was observed in 5 patients. Nine patients died with a median overall survival (OS) from diagnosis of brain metastasis of 47 months (range, 24–133).
Conclusion: Long survivals with BM of adult sarcomas are rare. Half of these patients had a single metastasis. Our results suggest the positive impact of chemotherapy, radiation therapy and surgery on outcomes.
Conflict of interest: *Advisory board: Novartis, Pfizer, Pharmamar, GSK*

3816 POSTER

Biological features, prognostic factors and outcome of 114 patients with GISTs: A single institution experience

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Background: To retrospectively analyse the distribution of biological features and their impact on clinical outcome in a cohort of 114 patients with gastrointestinal stromal tumour (GIST) treated at the GIST Unit of Palermo University between 2000 and 2012.
Methods: We retrospectively analysed 114 patients with GIST treated at the GIST Unit of Palermo University during the past 12 years. Patients with localised disease were stratified according to Fletcher and Miettinen criteria. Patients were treated according to NCCN guidelines. Biological features on tumour specimens, treatment and clinical outcome were recorded and compared with published data.
Results: Among 114 patients, 88 had resectable disease, 26 had metastasis at diagnosis. Ninety GISTs were examined for mutational analysis of KIT or PDGFRα, resulting KIT exon 11 mutation in 59%, KIT exon 9 mutation in 16%, PDGFRα mutation in 11% while 14% were wild type. Median 5-years recurrence-free survival of 88 patients with localised disease undergoing radical resection was 60 months. Adjuvant imatinib 400 mg daily was delivered in 21 cases; 5 patients recurred and received standard treatment for advanced disease while 16 are still free of disease. Clinical outcomes were significantly poorer for 19 patients with exon11 deletion. Miettinen criteria better predicted the risk of recurrence than Fletcher criteria ($p = 0.0046$ vs $p = 0.1$). In patients with metastatic disease undergoing standard I and II line therapy with imatinib and sunitinib ($n = 29$ and $n = 18$) median progression-free survival was respectively 36 and 6 months. Six patients progressing prior treatment with TKI were enrolled in a randomized multicenter phase III trial of regorafenib, experiencing 7 months mPFS. This result was comparable to data from the phase II trial of regorafenib (mPFS=10 months).
Conclusions: All data from our retrospective analysis reproduced those from published literature. Mutational analysis allows risk stratification, predicts response to TKI and should be routinely performed at diagnosis. Our experience demonstrates that GIST Unit guarantees a high standard for diagnosis, biological assessment for risk stratification, staging and treatment delivery, providing clinical outcomes that are comparable to published data. Therefore is essential for patients with rare tumours to be addressed to highly specialised multidisciplinary centers.
No conflict of interest.

3817 POSTER

Guidelines for time-to-event endpoint definitions in randomized cancer trials for sarcomas and GIST: Results of the DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials)

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Background: With the necessity of reducing randomized clinical trial (RCT) duration, cost and number of patients, potential surrogate endpoints of overall survival (OS) are increasingly being used as replacements for OS in cancer RCT. However, most of these endpoints lack standardized definitions enabling comparison between RCT. Some recommendations have been proposed for specific cancer sites but they do not rely on formal consensus methodologies. The objective of the **DATECAN** initiative (**D**efinition for the **A**ssessment of **T**ime-to-event **E**ndpoints in **CAN**cer trials) is to provide guidelines to standardize definitions of time-to-event (TTE) endpoints in RCT for different cancer sites. We present results for sarcoma and GIST (similar abstract submitted for breast cancer).
Methods: We relied on the modified Delphi consensus method, a validated formalized consensus process for the development of practice guidelines. International experts with various backgrounds and expertise were involved. First, the coordinating committee, a group of statisticians and epidemiologists involved in the design and conduct of RCT, led a comprehensive literature review to identify TTE endpoints and clinical events of interest. The steering committee, which included additional medical experts, prepared the questionnaire sent for rating to international experts from the rating committee.
Results: The consensus process involved two rounds of rating (28 international experts) and one in-person meeting (Chicago 2012). Each expert had to rate on a 1−9 scale if s/he agreed to include clinical events (e.g. toxicity) in the definition of TTE endpoints. Consensus was reached for 73% of the events after the rounds of rating and was finalized at the meeting for the remaining events. Guidelines for the definitions of 13 TTE endpoints were established (e.g. progression-free survival, disease-free-survival, time-to-treatment failure, etc.) across different settings (adjuvant, metastatic, both).
Conclusions: The DATECAN guidelines should help standardize definitions of commonly used TTE endpoints. They should (i) facilitate the comparison of RCT, (ii) improve the quality of trial reporting and (iii) improve the quality of future RCT. We acknowledge that these guidelines will be presented at ASCO 2013. However, communicating about these recommendations at ESMO/ECCO is also a key step towards wide scale dissemination and implementation of these guidelines.
No conflict of interest.

3818 POSTER

Regional variation and challenges in studying the epidemiology of giant cell tumour of the bone (GCTB)

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Introduction: Population-based sources of data on the epidemiology of benign bone tumours are limited. The relative frequency of such tumors, including GCTB, can be estimated from published case series of bone cancers and extrapolated to broader populations, a method recommended by the US Bone and Joint Initiative (BMUS 2011). The primary goal of this study was to compare approaches to estimate incidence of GCTB in the US, France, Germany, Italy, Spain, UK, Sweden, Australia, Canada, and Japan in 2013.
Methods: GCTB incidence was calculated using 3 different scenarios consistent with the BMUS method using the relative index (RI) of GCTB to osteosarcoma from case series. The low scenario represents the literature where GCTB accounts for 5−7% of primary bone tumors. The base scenario reflects the Dahlin-Unni series RI of GCTB to osteosarcoma of 32%, and the high scenario corresponds to the Ward series RI of 84%. Differences between the 2 series reflect center of excellence (Mayo clinic) vs. community referral, respectively. To validate the approaches, we compared estimates to the latest incidence of benign GCTB reported by registries in Sweden (1993–2011), Australia (1972–1996), and Japan (2008). United Nations population estimates were used to project to 2013.

Table: Incidence in 2013.

	Bone cancer	GCTB					
		By scenario			Per registry		
		Low	Base	High	Australia	Japan	Sweden
US	2659	133	332	873	424	357	358
France	704	35	77	203	83	70	70
Germany	1213	61	133	351	107	90	90
Italy	841	42	92	243	81	69	69
Spain	426	21	47	123	62	52	52
UK	604	30	66	174	83	70	70
Japan	850	43	93	245	164	138	138
Australia	249	12	27	72	31	26	26
Canada	338	17	38	99	46	39	39
Sweden	88	4	10	25	12	11	11

Results: Three estimation scenarios were compared relative to latest bone cancer incidence (Table). Because osteosarcoma represented 39% of bone cancer incidence in the US in 2013, the base scenario thus reflects a 12% RI (39% x 32%) of GCTB to bone cancer incidence. Similarly, the high scenario corresponds to 33% RI relative to bone cancer. Registry data reflected an incidence rate of GCTB as 1.33 per million in Western Australia, 1.12 per million in Japan, and 1.12 per million in Sweden. If survival is assumed to resemble life expectancy in the general population, 5-year prevalence is the cumulative incidence over 5 years.
Conclusions: The findings highlight challenges in estimating the incidence of GCTB, resulting in a wide variance in the point estimates under different scenarios. Nonetheless, all scenarios reflect that GCTB is a rare disease. Estimates derived from registries in Australia, Japan, and Sweden represent GCTB incidence consistent with the base scenario (which equates to 1.04 new cases per million in the US in 2013).
Conflict of interest: *Corporate-sponsored research: Study sponsored by Amgen Inc. Other substantive relationships: Authors employed by Amgen Inc. (including stock ownership), Pygargus AB, and Plan A Inc. respectively.*

3819 POSTER

Perceptions of participants and professionals in bone sarcoma clinical trials: Implications for study design and conduct

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Background: Under-representation of teenagers and young adults (TYA) in cancer trials is internationally recognised. Compared to children and older adults, this cohort have gained the least improvements in survival from cancer: this is particularly so for bone sarcomas?. Reasons for low trial entry for young people have so far focussed on structural and organisational barriers. There is little understanding of TYA's perceptions of trial entry and those of healthcare professionals caring for them. The aim of this study was to understand the perceptions of TYA who were approached about participation in bone sarcoma trials and health professionals involved in their recruitment and associated care.
Methods: Semi-structured interviews using narrative inquiry were undertaken at a supra regional sarcoma centre between November 2011 and February 2012. Twenty-one young people between 15 to 24 years at diagnosis who were eligible for two bone cancer trials and eighteen associated healthcare professionals were recruited.The transcripts were read and reread; using memoing, coding and constant comparison, categories and themes were developed. Analytical frameworks developed for both data sets were then integrated into a combined framework.
Results: Emergent themes are: the perceptions of clinical trials; the contrasting experience of being asked to register and later consent to randomised treatment on a clinical trial; weighing up burdens and benefits in decision making; the role of communication with, and support from, professionals, family and peers, together with the centrality of autonomy in decision making; and lastly the importance of a culture of expert care.
Conclusion: This study provides new understandings about the experience of young people invited to participate in bone cancer clinical trials, and the factors that influence decision-making. The intensity and longevity of treatment, and the impact of cancer during TYA years, commonly negatively influenced decisions made. The professionals had a good understanding of what it meant to young people to participate in a trial.
The findings have the potential to contribute to interventions to facilitate decision-making and to inform education and training of health professionals. Our study reinforces the need for patient involvement in the design of clinical trials. This is essential to positively influence recruitment of TYA to clinical trials and ultimately improve the outcomes of disease such as bone sarcoma.
No conflict of interest.

3820 POSTER

What is the price of cure for the treatment of pelvic Ewing Sarcoma?

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Objective: Substantial progress has been made in the management of childhood bone tumors over the last 25 years. However, survivors of childhood pelvic tumors are at risk of developing long-term functional restrictions and late sequelaes. So far no data are available concerning the effect of multimodal therapy on the level and quality of physical activity. The aim of this study was to objectively quantify the level of activity in 80 long-term survivors of pelvic Ewing-Sarcoma using a continuous measurement device. All patients were treated according to the Ewing sarcoma trial guidlines, set by the German Society of Pediatric Hematology and Oncology (GPOH).
Methods: The frequency and intensity of physical activity were objectively assessed for 7 consecutive days by means of a uniaxial accelerometer, the Step Activity Monitor (SAM). In addition, function was assessed using the TESS (Toronto Extremity Salvage Score) questionnaire. All patients were asked about long-term late-effects by questionnaire. The median age at diagnosis was 15.4 years (range 0.7−45), median age at time of assessment was 32.8 years (range 10.6–57.1). Initial local therapy was surgery in only 10/78 patients (12.8%), surgery and irradiation in 50 patients (64.1%) and radiotherapy alone in 28 patients (23.1%).
Results: Participants with initial pelvic Ewing-Sarcoma averaged 4650 gait cycles/ per day (SD=1897gait cycles; median: 4443; range: 1887–10738) which had to be considered as somewhat active. (7,500–10,000 steps/day) 30/80 patients reached an active lifestyle (>10,000 steps/day) however 9/80 patients were sedentary (<5000 steps/day). The TESS score (0–100) for tumors located in the pelvis was 90.7 SD = 11.8), suggesting the achievement of moderate to good function following multimodal tumor treatment.
Conclusions: Data indicate that patients can achieve good step activity following pelvic tumor treatment. However, most patients limit themselves to low intensity activity. SAM can be used to capture activity levels in long-term Ewing-sarcoma survivors. It may be advantageous to consider the use of a combination of outcome measures, including SAM, for objective functional mobility assessment. Parallel recording of physical activity (SAM) and TESS provides a better measure reflecting the complex situation of the patients by combining objective and subjective parameters.
Further investigations must identify discriminating factors that influence the degree of recovery following intensive treatment of disease.
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No conflict of interest.

3821 POSTER

Population study of the gastrointestinal stromal tumors based on the data from the clinical registry − Czech and Slovak Republic

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Background: Gastrointestinal stromal tumors (GIST) are quite rare mesenchymal tumors mostly presenting typical expression of thyrosinkinase receptor c-Kit (CD117). In the past years, especially before 2001, there have been problems with identification and understanding of GIST and therefore a lack of significant population data and clinical studies focusing on patients with these uncommon malignancies.
Material and Methods: The online registry called 'reGISTer' has been compiled and maintained since December 2006. It involves relevant epidemiological data, pathology results and molecular analysis, clinical information and treatment results on patients with GIST from the Czech and Slovak Republic. Until November 2012 there have been included adequate dataset on 845 patients.
Results: Most of the tumors belong to the high-risk group (50.4%, n = 426), most common location is jejunum and stomach. More than 70% of the tumors are resectable at the time of diagnosis. Median overall survival is 9.2 years. In cases of inoperable and metastatic disease targeted therapy is used, ie. imatinib mesylate in the first line, sunitinib in the second line or regorafenib in the third line.

Table: Results of treatment with imatinib in the palliative setting (n = 399 patients)

Overall survival	
All	65.2 months
Non-metastatic/non-resectable at beginning of treatment	80.3 months
Metastatic at the beginning of treatment	63.3 months
Progression free survival	
All	32.3 months
Non-metastatic/non-resectable at beginning of treatment	43.0 months
Metastatic at beginning of treatment	28.1 months
2-year survival − all	82.2%
Median treatment length	20.1 months
Best treatment response (CR+PR+SD*)	82.6%

*CR: complete response; PR: partial response; SD: stable disease.

Conclusions: The poster comprises up-to-date analysis of the register. Presented data are generally similar to those from the world-wide clinical studies published recently.
Acknowledgments: Authors thank all centers participating in the reGISTer project both in the Czech and Slovak Republic.
No conflict of interest.

3822 POSTER

Carbon ion radiotherapy for unresectable sacral chordomas

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Background: Clinical trials on carbon ion radiotherapy for intractable malignancies have been conducted since 1994 at National Institute of Radiological Sciences in Chiba, Japan. As of March 2013, over 7000 patients had been enrolled into studies to analyze toxicity and local tumor response. Since a clinical study for unresectable sarcomas started in June 1996, over 1000 sarcomas have been treated with carbon ion radiotherapy. In this study we evaluated the effectiveness and safety of carbon ion radiotherapy in patients with unresectable sacral chordomas.
Material and Methods: The standard protocol for the treatment consists of 16 irradiation sessions for 4 weeks. The basic eligibility was as follows; 1) unresectable tumors judged by their orthopedic surgeons, 2) pathological confirmation, 3)15 cm in maximum size, 4) no metal instrumentation, 5) no urgent systemic metastasis. We performed a retrospective analysis on 175 patients with unresectable sacral chordomas treated with carbon ion radiotherapy between June 1996 and February 2012. All of the patients in this analysis presented without prior treatment. All patients were observed for at least 12 months from the initial date of radiotherapy. The applied carbon ion dose ranged from 64.0 GyE to 73.6 GyE (Gray equivalent, median 70.4 GyE) in a total of 16 fixed fractions over four weeks.
Results: The median age of the patients was 67 ranging from 26 to 87. The study group consisted of 55 females and 120 males. The cranial extension of tumor was at S2 or higher level in 70% of the patients. The median clinical target volume was 340 cm^3 ranging from 42.4 to 1497. The median follow up period was 58 months. Five-year overall survival and 5-year local control rates were 81% and 79%, respectively. Of the tumors 30 % showed local recurrences over 5 years later after the treatment. The ambulatory in 97% of the patients remained with or without supportive devices. Two patients experienced severe late skin/soft tissue complications requiring skin grafts.
Conclusion: Carbon ion radiotherapy appears effective and safe in the management of patients with unresectable sacral chordomas and offers a promising alternative to surgery.
No conflict of interest.

3823 POSTER

Role of radiation therapy in the conservative management of sarcoma within irradiated field

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Background: Sarcoma within irradiated field (SIF) is a rare but severe complication of radiation therapy (RT). Complete tumoral resection remains the cornerstone of localised SIF management, but clear margin surgery is often difficult to obtain in previously irradiated tissues. Residual disease enhances the risk of local failure and SIF mortality, partly explaining their poor prognosis. Thus, in our institution, we perform adjuvant or exclusive RT when unresectable, gross or microscopically positive-margin SIF. We hereby report on the long-term outcomes and toxicity profile of this combinative approach.
Patients and Methods: Individual clinical data from all consecutive patients diagnosed and treated for a localized SIF between January 2000 and October 2011 at the Institut Claudius Regaud, Toulouse, France, were retrospectively reviewed.
Results: Twenty-seven patients were eligible for this study. Twenty-four patients underwent surgery. Adjuvant or definitive RT was performed in 10 patients. The median follow-up was 3.8 years. Interestingly, there is a trend toward longer survival and better local control in the subgroup of patients who received adjuvant or definitive RT compared to the rest of the cohort with a 4-year overall survival and relapse free survival estimated to 66%, 53% vs 40% and 27% (ns) respectively, whereas the rate of unresectable, gross or microscopically positive-margin disease among this subgroup is significantly higher than the rest of the cohort ($p < 0.001$). The long-term moderate and severe complication's rates were 30% and 40% respectively but allowed a conservative management.
Conclusion: Re-irradiation might improve local control of unresectable localised SIF or after suboptimal surgery. Its non-negligible toxicity has to be balanced with the worse prognosis of SIF particularly when ineligible to surgery or if residual tumour left. RT should be discussed in some cases, as part of intensified local management with a curative intent.
No conflict of interest.

3824 POSTER

Surgery for recurrent gastrointestinal stromal tumors (GIST): A retrospective study of patients in a tertiary institution

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Background: Surgical resection of primary gastrointestinal stromal tumours (GIST) is associated with recurrence rates of up to 50% at 2 years. The mitotic activity, size and location of the tumor are known risk factors for postoperative recurrence. At recurrence, tyrosine kinase inhibitor (TKI) therapy is recommended, and has been shown to confer survival of up to 55 months. Several studies have also shown that patients with TKI-responsive recurrent GIST benefit from surgery, compared to patients who do not respond to TKI. However, there are no studies which compare surgery plus imatinib therapy vs. imatinib alone. Hence, the role of surgery in recurrent GIST still remains unclear. We review our institutional experience with the management of recurrent GIST and evaluate the overall and disease-free survival rates in this group of patients.
Materials and Methods: Data was retrospectively collected from patients with recurrent GIST treated at the Department of General Surgery at the Singapore General Hospital during a 12 year period. The patients were divided into 2 groups: patients who had underwent a second surgical resection vs. patients who did not have surgery. A comparison of prognostic factors was made between the two groups. Our primary end points were disease-free and overall survival.
Results: A total of 187 patients underwent curative surgery between Jan 2000 and June 2012. Of the 187 patients, 58 (31%) had recurrent disease of which 31 (16.5%) underwent a second surgery; The surgical intent was curative in 28 patients, and palliative in 3 patients. Of the remaining 27 recurrent GIST patients, 20 received palliative TKI therapy, while 7 patients were managed conservatively. In the group of patients who underwent a second surgery, the median disease free survival (DFS) was 2.33 years (95% CI 1.44-undefined). The overall survival (OS) for all recurrent GIST patients was 6.98 years, with 1-, 2- and 3-year OS of 88%, 77% and 62% respectively. The median OS for patients who underwent a second surgery was 8.36 years, with 1-,2- and 3-year OS of 96%, 81% and 71% respectively vs. 3.87 years, with 1-, 2- and 3-year OS of 76%, 70% and 49% respectively for patients who had palliative TKI and conservative management. Patients who underwent a 2nd surgery were more likely to have a primary tumor arising from the small intestine with a lower mitotic rate & of a smaller size than patients who were not subjected to a 2nd surgery.
Conclusion: Our study shows that in a select group of patients with recurrent GIST, curative surgery confers acceptable DFS and OS.
No conflict of interest.

3825 POSTER

The off-label use of targeted therapies in rare disease as sarcomas: The OUTC'S program

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Background: Few targeted therapies (TTs) are registered for sarcoma treatment, despite numerous phase II studies, but they are potential treatment options for patients after standard treatment escape. The French Sarcoma Group − Bone Tumor Study Group created a national registry to evaluate the outcome of patients treated with off-label TTs.

Table 1 (abstract 3825).

Targeted therapy	N	%	Histotype 1	n (%)	Histotype 2	n (%)	Histotype 3	n (%)	Histotype 4	n (%)	Histotype 5	n (%)
Sorafenib (1)	125	45	GIST	31 (25)	LMS	22 (18)	AS	14 (11)	uterine LMS	8 (6)	liposarcoma	8 (6)
Sunitinib (2)	67	24	LMS	9 (13)	Ewing	8 (12)	SS	8 (12)	unclassified S	8 (12)	uterine LMS	4 (6)
Imatinib	23	8	chordoma	8 (35)	AF	4 (17)	DFSP	4 (17)	epithelioidS	2 (9)	–	–
Sirolimus-cyclophosphamide	18	6	osteoS	8 (44)	chondroS	5 (27)	AS/chordoma/lipoS/ Ewing/SFT	1 each (6)	–	–	–	–
Everolimus (3)	10	4	GIST	3 (30)	LMS	3(30)	KS/MPNST/SS	1 each (10)	other	1(10)	–	–
Bevacizumab (4)	9	3	other	5 (56)	SFT	2 (22)	AS	1 (11)	epithelioidS	1 (11)	–	–
Sirolimus alone	5	2	osteoS	2 (40)	PEComa	1 (20)	other	1 (20)	–	–	–	–

AF: aggressive fibromatosis; AS: angiosarcoma; DFSP: dermatofibrosarcoma protuberans; epithelioidS: epithelioid sarcoma; GIST: gastro-intestinal stromal tumor; KS: kaposi sarcoma; LMS: leiomyosarcoma; MPNST: malignant peripheral nerve sheath tumor; OsteoS: osteosarcoma; SFT: solitary fibrous tumor; SS: synovial sarcoma.

Patients and Methods: Every consecutive sarcoma-patient receiving off-label TT outside a clinical trial was included. The objective was to describe these patients' efficacy and safety data in routine practice.
Results: From October 2008 to October 2011, 249 patients in 24 centers received 278 treatment lines with TTs. Decision of treatment was made under control of multidisciplinary tumor board in 76%. Twenty-five histological subtypes were included: most frequent were leiomyosarcoma (n=48, receiving sorafenib in 63%, sunitinib in 27%), GIST (n=39, receiving sorafenib in 79%), and angiosarcoma (n=18, receiving sorafenib in 78%). The overall response rate to TTs was 15% (95% CI [10.6–20.2]), the disease control rate was 65.4% (95% CI [58.9–71.5]). The median progression-free survival was 4.1 months (95% CI [3.2−4.8]). Three complete responses (CRs) were observed: for a PEComa with temsirolimus, for a Ewing sarcoma with sunitinib, and for a Dermatofibrosarcoma with imatinib. No toxic death occurred, grade 3 and 4 toxicities were reported in 74 (27%) and 14 (5%) patients respectively.
Conclusion: Off-label TTs can be used for sarcoma-patients in routine practice with an acceptable toxicity profile and efficacy similar to that reported in uncontrolled clinical trials. With 3 CRs in rare subtypes, this approach is interesting to identify therapeutic niches.

Table 2. Targeted therapy by histotypes

Histotype	Targeted therapy
1	Alone in 120 cases, combination in 5 cases
2	Alone in 66 cases, combination in 1 case
3	Alone in 7 cases, combination in 3 cases
4	Alone in 3 cases, combination in 6 cases

Targeted therapies with less than 5 patients are not listed in this table.

Conflict of interest: *Ownership: Dr Axel Le Cesne. Advisory board: Pharmamar, Novartis*

3826 POSTER

Final results of sequential phase 2 studies of palbociclib (PD0332991) in CDK4-amplified liposarcoma

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Background: The oncogene cyclin-dependent kinase 4 (CDK4) is amplified in >90% of well-differentiated/de-differentiated liposarcomas (WD/DDLS). Palbociclib is a selective CDK4/CDK6 inhibitor that inhibits growth and induces senescence in liposarcoma cell lines and xenografts.
Methods: We performed two sequential phase 2 studies of palbociclib in patients with advanced WD/DDLS, evaluating two dosing schedules: 2/1 schedule (200 mg PO daily x 14d, every 21d) and 3/1 schedule (125 mg PO daily x 21d, every 28d). Participants were adults with advanced WD/DDLS, measurable disease by RECIST 1.1 and progression on $\geqslant$1 systemic therapy. All had CDK4 amplification by fluorescence in situ hybridization and retinoblastoma protein expression by immunohistochemistry ($\geqslant$1+). The primary endpoint was progression-free survival (PFS) at 12 weeks. Based on historical data, a promising result was defined as a 12-week PFS of $\geqslant$40% and not promising as $\leqslant$20%. The study was approved by the Institutional Review Board of Memorial Sloan-Kettering Cancer Center and all patients provided written informed consent. The study was registered at Clinicaltrials.gov (NCT01209598) and was sponsored by Pfizer.
Results: 29 evaluable patients were treated on 2/1 schedule and 25 on 3/1 schedule. PFS at 12 weeks was 66% (90% CI 51–100%) on 2/1 schedule and 56% (90% CI 41–100%) on 3/1 schedule. Median progression-free survival was 18 weeks on 2/1 schedule and 24 weeks on 3/1 schedule. There was one partial response on each schedule. Grade 3−4 toxicity on 2/1 schedule: neutropenia 50%; thrombocytopenia 30%; anemia 17%. On 3/1 schedule: neutropenia 34%, thrombocytopenia 10%, anemia 21%.
Conclusions: In patients with WD/DDLS with CDK4 amplification, palbociclib treatment was associated with a favorable PFS and objective tumor responses. Both dosing schedules are active but the 3/1 schedule is associated with less hematologic toxicity. Updated survival and response data will be presented. The 3/1 schedule has been selected for a randomized phase 3 study.
Conflict of interest: *Advisory board: MA Dickson, S Singer, and GK Schwartz served on an advisory board for Pfizer in 2011.*

3827 POSTER

Time course of adverse events in the phase III GRID study of regorafenib in patients with metastatic gastrointestinal stromal tumors (GIST)

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Background: Regorafenib (REG), a unique oral multikinase inhibitor, has demonstrated significant improvement in progression-free survival *vs* placebo (P; HR 0.27, p < 0.0001) in the international phase III GRID study (NCT01271712, sponsored by Bayer HealthCare). To better characterize the safety profile of REG in GRID, we investigated adverse events (AEs) and the dose intensity tolerated over time.
Materials and Methods: Adults with metastatic GIST after treatment with imatinib and sunitinib were randomized 2:1 to receive oral REG 160 mg or matching P once daily for the first 3 weeks of each 4-week cycle. Treatment-emergent AEs and biochemical abnormalities were assessed at each cycle.
Results: The safety population comprised 198 patients (pts): REG n = 132; P n = 66. The median treatment duration was 22.9 weeks (range: 9.3–50.9) in the REG group and 7.0 weeks (5.1–25.9) in the P group.
Treatment-emergent AEs of any grade occurred in all of the REG pts and 92% of P pts, at grade 1/2 in 24% and 53%, respectively, at grade 3 in 64% and 29%, respectively, and at grade 4 in 7% and 6%, respectively. AE-related deaths occurred in seven REG and four P pts. The most frequent AEs occurring in REG pts were hypertension (59%), hand–foot skin reaction (HFSR) (57%), fatigue (50%), diarrhea (47%), and oral mucositis (41%). The frequency of these AEs over time is shown in the Table. The incidence of all of these AEs peaked in cycle 1 and tapered to relatively stable lower incidence rates over later cycles.
AEs led to dose modification in 72% of REG pts and in 26% of P recipients. The proportion of planned REG dose actually administered decreased between cycles 1 and 4 (89% of planned dose received in cycle 1 and 77% of planned dose received in cycle 4), and dose intensity was relatively stable in subsequent cycles (planned dose received remained above 72%).
Conclusion: In the GRID trial, the incidence of the most common AEs in the REG group peaked early during treatment, and was manageable with

dose modification so that lower levels of AEs occurred in later treatment cycles, with no evidence of cumulative toxicity. Few pts (6% REG, 8% P) required discontinuation from study due to AEs.

Conflict of interest: *Ownership: (stock ownership) Bayer, Kolltan Pharmaceuticals, Blueprint Medicines. Advisory board: Novartis, Pharmamar, Pfizer, Roche, MSD, GSK, BMS, Sanofi-Aventis, Ariad, Kolltan Pharmaceuticals, Blueprint Medicines. Board of directors: n/a. Corporate-sponsored research: Novartis, Pharmamar, Pfizer, Roche, MSD, GSK, Bayer, Sanofi-Aventis. Other substantive relationships: (honoraria) Novartis, Pharmamar, Pfizer, Roche, MSD, GSK, BMS, (employment) Bayer, (expert testimony) Bayer, GSK, MSD*

Table: Frequency (%) of most common treatment-emergent AEs over time in REG pts

	Cycle							
	1	2	3	4	5	6	7	8
n at risk	*132*	*125*	*111*	*101*	*96*	*90*	*82*	*58*
Hypertension	42	23	17	23	10	11	15	12
HFSR	46	32	27	20	19	16	13	9
Fatigue	29	17	11	10	3	6	4	7
Diarrhea	19	18	14	17	10	10	12	5
Oral mucositis	28	13	11	4	4	6	4	3
Total AEs (all grades)	99	89	80	76	66	56	52	52

3828 POSTER

Safety of trabectedin versus doxorubicin-based chemotherapy (DXCT) as first-line therapy in patients with translocation-related sarcoma (TRS)

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Background: The safety profiles of trabectedin and DXCT, given as 1st therapy in a randomised phase III trial in patients with locally advanced, or metastatic TRS, were analysed.

Methods: Patients were randomised (1:1) to receive trabectedin (1.5 mg/m^2 in 24 h iv infusion q3wk) vs doxorubicin alone (75 mg/m^2 q3wk), or doxorubicin (60 mg/m$^{2)}$ plus ifosfamide (6−9 g/m^2 q3wk). Descriptive statistics were used to evaluate safety, including adverse events (AEs), serious AEs (SAEs), deaths, and laboratory data.

Results: 121 patients were randomised, 61 were treated with trabectedin and 57 with DXCT (36 with doxorubicin single-agent, and 21 with doxorubicin plus ifosfamide). The safety profile observed was expected for both trabectedin and DXCT. Safety is summarised in the tables.

Table 1. Adverse events

Most common AEs	Trabectedin (%)		DXCT (%)	
	G1−2	G3−4	G1−2	G3−4
Nausea	68.9	1.6	64.9	–
Fatigue	57.4	6.6	61.4	1.8
Vomiting	42.6	1.6	26.3	–
Anorexia	23.0	1.6	21.1	–
Alopecia	1.6	–	43.9	–
Mucositis	4.9	1.6	26.3	8.8

Table 2. Laboratory disorders

Laboratory disorder	Trabectedin (%)	DXCT (%)
Neutropenia grade 3−4	55	75
Febrile neutropenia	1.6	12.3
Thrombocytopenia grade 3−4	16.4	14.3
ALT increase grade 3−4	53.3	1.9

General and gastrointestinal disorders were balanced between both treatments. Severe neutropenia was more frequent in the DXCT arm. However, it was generally controlled with G-CSF (61.4% of patients), while in the trabectedin arm it was more frequently managed with dose delay until recovery (49.2% of patients received G-CSF). Drug related discontinuations were slightly higher in the trabectedin arm: 16.4% vs. 10.5%. Nevertheless, patients receiving trabectedin were able to be treated for prolonged periods of time due to lack of cumulative toxicities: 25% of patients received ⩾10 cycles of trabectedin (max. 8 cycles of DXCT, per protocol). Transient transaminases increase occurred more frequently in the trabectedin arm. SAEs incidence was similar (18.0% with trabectedin; 19.3% with DXCT); most frequent SAEs were extravasation (4.9%) in trabectedin arm and febrile neutropenia (12.3%) in DXCT. One drug related death occurred in each arm: rhabdomyolysis in trabectedin arm and pneumonia in DXCT.

Conclusion: Trabectedin and DXCT were generally well tolerated with limited incidence of severe side effects. No new safety signals have emerged from this trial.

No conflict of interest.

3829 POSTER

Results of a multivariate analysis for potential factors affecting outcome in translocation related sarcomas (TRS) treated with trabectedin or doxorubicin-based chemotherapy (DXCT) as first-line therapy

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Background: A Phase III randomized clinical study was conducted to evaluate trabectedin (1.5 mg/m^2 in 24 h iv infusion q3wk) *versus* doxorubicin, either single agent 75 mg/m^2 q3wk, or 60 mg/m^2 combined with ifosfamide (6−9 g/m^2 q3wk) as first line treatment in locally advanced or metastatic TRS. Primary efficacy endpoint was progression free survival (PFS). A pre-planned multivariate analysis was conducted to analyze the potential factors which may influence the PFS, assessed by independent review, in both arms.

Methods: A Cox proportional hazard model was performed including the variables: treatment arm (trabectedin *vs* DXCT), gender, age, age at diagnosis, race, baseline ECOG, BMI, height, weight, BSA, histology: myxoid/round cell liposarcoma (MRCL) *vs* other TRS, time from diagnosis and from last progression to study entry, primary site (limbs *vs* other), locally advanced/metastatic, prior surgery, prior radiotherapy, number of sites involved, liver metastases, LVEF, presence of bulky lesions (<50 mm *vs* ⩾50 mm), sum of all target lesion diameters, and region (Europe *vs.* other). In the stepwise analysis, the significance level chosen to enter an explanatory variable was 0.05 (for all variables not included, the one with the smallest p-value was entered if the p-value was less than or equal to the specified significance level). The significance level to remove a variable was 0.05 (for all variables included, the one with the largest p-value was removed if the p-value exceeded the significance level).

Results: 88 patients integrated the efficacy population. The only significant covariate found to influence the PFS was the histological type: MRCL *vs* other TRS subtypes.

Analysis of maximum likelihood estimates

Parameter	DF	Parameter estimate	Standard error	χ^2	PR > χ^2	HR (95% confidence limits)
MRCL *vs.* other TRS	1	2.23478	0.62750	12.6837	0.0004	9.344 (2.732, 31.965)

DF, degrees of freedom; HR, hazard ratio.

PFS at 12 months for MRCL was 84.9% (trabectedin) *vs* 79.6% (DXCT). For other TRS it was 28.8% *vs* ~20%.

Conclusions: Of all the covariates included, only histological subtype showed up as prognostic factor for PFS with significant difference in favour of MRCL patients. In addition, according this analysis, no significant difference between the two treatment arms was detected.

Conflict of interest: *Advisory board: Novartis, GSK, J&J, PharmaMar*

3830 POSTER

Health-related quality of life (HRQoL) of patients with advanced gastrointestinal stromal tumors (GIST) treated with regorafenib (REG) vs placebo (P) in the phase III GRID trial

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Background: The GRID trial (NCT01271712, sponsored by Bayer HealthCare) demonstrated significant improvement in progression-free survival (PFS) for REG *vs* P in patients with metastatic GIST after progression on at least imatinib and sunitinib. Exploratory analyses were conducted to assess the effect of treatment on HRQoL.
Materials and Methods: The HRQoL analyses were selected *a priori* based on clinical relevance; the global health status/QoL (QL) and the physical functioning (PF) scales of the EORTC QLQ-C30 questionnaire were used during the double-blind treatment period. Patients who completed a baseline and at least one post-baseline HRQoL assessment were included. A linear mixed-effects model was used to examine the treatment effect on HRQoL and trends over time, assuming that missing data were missing at random. Pattern-mixture models were applied to assess the treatment effect while accounting for potentially informative missing data. Time-to-deterioration (TTD) of HRQoL and responder analyses were conducted to determine the treatment effect based on timing and proportion of patients reaching a minimal important difference (MID) change in QL/PF ($\geqslant$10 points).
Results: The QL and PF changes over time were numerically similar between REG and P based on the linear mixed-effects model. The pattern-mixture models grouped patients based on timing of last HRQoL assessment (<4 or $\geqslant$4 cycles) and suggest that the missing data (presumably due to disease progression/death) might not be missing at random and are therefore informative, especially for the P group. As such, the results from the linear mixed-effects model should be interpreted with caution and alongside the results from the TTD analysis, where disease progression/death was considered as a deterioration in HRQoL. For the TTD analysis, when an event was defined as the earliest MID decrease in QL/PF, disease progression or death, REG showed significantly longer median TTD than P (QL: 6.5 *vs* 4.0; PF 8.0 *vs* 4.0 weeks, respectively). Median TTD was comparable between treatments after removing disease progression from the definition. The responder analyses showed that a similar proportion of patients achieved an improvement in MID in REG *vs* P (QL: 26.2% *vs* 25.4%; PF: 18.0% *vs* 15.3%, respectively).
Conclusion: The findings of this exploratory analysis demonstrate that HRQoL is similar for REG and P groups, indicating that REG prolongs PFS *vs* P while maintaining at least comparable HRQoL.
Conflict of interest: *Ownership: (stock ownership) Bayer, Kolltan Pharmaceuticals, Blueprint Medicines. Advisory board: Novartis, Pfizer, Bayer, Pharmamar, Roche, MSD, GSK, Sanofi-Aventis, Ariad, Kolltan Pharmaceuticals, Blueprint Medicines. Board of directors: n/a. Corporate-sponsored research: Bayer, Novartis, Pfizer, Sanofi-Aventis, GSK, Pharmamar, Roche, MSD, GSK. Other substantive relationships: (employment) Bayer Pharma AG, (honoraria) Novartis, Pfizer, Bayer, Pharmamar, Roche, MSD, GSK, (expert testimony) Bayer, GSK, MSD, (consultant) Bayer*

3831 POSTER

Exposure-efficacy analysis of regorafenib (REG) and its metabolites M-2 and M-5 in the phase III GRID study in patients (pts) with metastatic gastrointestinal stromal tumor (GIST)

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Background: REG, an oral multikinase inhibitor, demonstrated significant progression-free survival (PFS) improvement *vs* placebo (HR 0.27, $p < 0.0001$) in the phase III GRID study. We examined the relation between drug levels (i.e. exposure) and efficacy outcomes in GRID by correlating individual exposure estimates to the study efficacy endpoints (PFS, disease control rate (DCR), and overall survival (OS)) and tumor dynamics (size/time).
Materials and Methods: Plasma concentrations of REG parent and two pharmacologically active metabolites M2 and M5 were evaluable in 80 of 133 GRID pts on REG. The exposure estimates were derived from a previously developed population pharmacokinetic (PK) model (Jirakova Trnkova *et al*, ESMO WCGI 2013). Exposure parameters: 1. nominal average concentration over a 24 h dosing interval after 21 daily doses of 160 mg REG (Cav_{md}; primary) and 2. average concentration over the treatment period ($Cav(t1\text{-}t2)_{md}$; secondary). Covariates included age, gender, BMI, ECOG, country, duration of prior imatinib Rx, *KIT* mutation (Exon 9 or 11), and baseline total target lesion size (TTL). For tumor dynamics analysis, TTL measured 414 target lesions from 80 pts with available exposure data. Stepwise Cox proportional hazard or logistical regression methods were used. Sensitivity analyses were performed on tumor dynamics.
Results: Three exposures were defined: REG parent (R*p*), aggregate (R*p* +M2+M5 corrected for unbound fraction), and total (bound and unbound R*p* +M2+M5), resulting in six exposure parameters tested. There was no significant association between any exposure parameter or covariates and PFS, DCR or tumor dynamics. OS data are immature, but the preliminary analysis of only 13 uncensored events indicated longer OS for patients with higher total Cav_{md} and smaller baseline TTL. Tumor dynamics analysis showed that REG caused initial tumor shrinkage, decreasing after 9.2 weeks in a typical pt. Drug exposure was not significantly different between pts who discontinued REG within the first 2 cycles vs later.
Conclusions: Exposure-efficacy analysis in GIST pts treated with REG in the GRID study did not reveal any significant relationship between drug exposure and PFS, DCR or tumor dynamics. REG dosing induced tumor shrinkage, with less continuing decrease after 9 weeks. Early preliminary analysis revealed longer OS for patients with higher REG exposure and smaller total target lesion size.
Conflict of interest: *Ownership: (stock ownership) Kolltan Pharmaceuticals, Blueprint Medicines, Bayer. Advisory board: Bayer, Novartis, Pfizer, Sanofi-Aventis, GSK, Ariad, Kolltan Pharmaceuticals, Blueprint Medicines, BMS, Pharmamar, Roche, MSD. Board of directors: n/a. Corporate-sponsored research: Bayer, Novartis, Pfizer, Sanofi-Aventis, GSK, Pharmamar, Pfizer, Roche, MSD. Other substantive relationships: (expert testimony) Bayer, GSK, MSD, (honoraria) Novartis, Pfizer, Bayer, BMS, Pharmamar*

3832 POSTER

Hypertension (HTN) as a biomarker of efficacy in pazopanib-treated patients (pts) with advanced non-adipocytic soft tissue sarcoma (STS)

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Background: Reliable biomarkers of pazopanib's efficacy in STS pts are lacking. HTN is an on-target effect of vascular endothelial growth factor pathway inhibitors such as pazopanib. We evaluated the association of pazopanib-induced HTN with antitumor efficacy in pts with advanced/metastatic non-adipocytic STS.
Methods: Associations between pazopanib-induced HTN and survival (PFS and OS) were retrospectively assessed across 2 studies (EORTC study 62043 and 62072) in pts with metastatic STS who received oral pazopanib starting at 800 mg daily. Only eligible pts with baseline blood pressure (BP) <150/90 mmHg, were considered in this analysis. Anti-hypertensive medication (AHM) to control baseline BP was allowed. BP was measured at monthly clinic visits (in 62072 study bi-monthly after first 3 months). HTN was reported according to NCI-CTC AE grading (v3.0) and assessed as absolute differences compared to baseline.
We first compared the outcome of pts with medically controlled BP at baseline vs. those without baseline AHM in a multivariate Cox model. The cumulative incidence of HTN in pts without baseline AHM was assessed subsequently.
The effect of HTN was assessed on PFS and OS using a landmark analysis stratified by study; univariately using the Kaplan–Meier method and a log-rank test, and in a multivariate Cox regression model after adjustment for important prognostic factors.
Results: Of the 337 eligible pts eligible for this study, 21.7% received AHM at baseline. PFS and OS did not differ significantly between pts using baseline AHM vs. those who did not. In pts without baseline AHM, 38.6% developed HTN. As the vast majority of pts developing HTN did so within 5 weeks (wks) after initiation of pazopanib (68.6%), this time point was used as landmark. Univariately, there was no effect on PFS or OS from occurrence of HTN within 5 wks of treatment expressed either in NCI-CTC AE criteria or as maximal differences from baseline in systolic and diastolic BP. Also in multivariate analysis, after adjusting for important prognostic factors, the occurrence of HTN expressed in the different parameters was not associated with PFS and OS.
Conclusions: In this retrospective analysis, pazopanib-induced HTN did not correlate with outcome in pazopanib-treated non-adipocytic STS pts. The occurrence of HTN cannot serve as an early biomarker in this setting.
No conflict of interest.

3833 POSTER

Trabectedin in patients with advanced soft tissue sarcoma (STS): importance of maintenance therapy in responding patients after 6 cycles of trabectedin

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Background: Trabectedin (Yondelis®) is the first marine-derived antineoplastic drug approved in EU for the treatment of patients with recurrent advanced STS (ASTS) or for patients unsuited to receive anthracyclines and ifosfamide. We retrospectively analyzed the RetrospectYon database with patients' data treated with trabectedin between Jan 2008-Dec 2011.
Material and Methods: Trabectedin was given at the approved dose of 1.5 mg/m^2 as a 24-h infusion every 3 weeks. Patients who achieved partial response (PR) or stable disease (SD) after 6 cycles could receive maintaining trabectedin treatment. Uni- and multivariate analyses of prognostic factors were performed.
Results: A total of 885 patients with ASTS (486 women) from 26 French centers with a median age of 54 years (range 12−84) were included. Most patients had leiomyosarcoma (36%), liposarcoma (18%) or synovial STS (11%). At baseline, performance status (PS) was 0 in 26%, 1 in 47% and >1 in 27% of patients. A median of 4 cycles of trabectedin (range 1−28) was administrated as a 2nd (41%), 3rd (39%) or $\geqslant$4th (20% of patients) treatment line. Toxic death and unscheduled re-hospitalization occurred in 0.5% and 8% of patients, respectively. The objective response rate was 15% (6 complete and 127 PR), and SD was 45.5% (n = 403). After a median follow-up of 22.6 months (range 0.03–51.0), the patients who received trabectedin as 2nd, 3rd or $\geqslant$4th line had the median PFS of 4.3, 4.2 and 3.4 months, and the median OS of 12.9, 12.3 and 9.5 months respectively,. Multivariate analysis identified liposarcoma, leiomyosarcoma, angiosarcoma, undifferentiated pleomorphic sarcoma (UPS) and trabectedin line as independent prognostic factors for PFS, and UPS, angiosarcoma, rhabdomyosarcoma, gender, PS and trabectedin line for OS. After 6 cycles, 205 of the 273 (75.1%) patients with non-progressive disease received trabectedin as maintenance treatment and obtained a superior PFS (median 11.0 *vs.* 7.2 months, $p = 0.0001$) and OS (median 25.1 *vs.* 16.9 months, $p<0.0001$) compared to patients who stopped trabectedin after 6 cycles.
Conclusions: The results of this real-life study have demonstrated that patients with ASTS treated with trabectedin had PFS and OS comparable or better to those observed in clinical trials. Trabectedin maintenance beyond 6 cycles is associated with improved PFS and OS and warrants further exploration.
No conflict of interest.

3834 POSTER

LMS-02: A Phase II single-arm multicenter study to determine the efficacy of doxorubicin in combination with trabectedin as a 1st line treatment of metastatic and/or locally advanced leiomyosarcoma of uterine (U-LMS) or soft tissue (ST-LMS) origin: results of the soft tissue group

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Background: U-LMS and ST-LMS are rare tumours with poor prognosis when metastatic or locally advanced, presenting moderate chemosensitivity mainly to doxorubicin (doxo), ifosfamide (ifo), cisplatin, gemcitabine (gem) and trabectedin (trab). Overall response rates (ORR) in combination therapies (1st line) does not exceed 50% for U-LMS and 35% for ST-LMS. The most active are doxo combinations (mostly with ifo or dacarbazine) and gem plus docetaxel (in particular in U-LMS) with mean response durations of 3−6 months. Trab demonstrated a definite activity on pre-treated LMS with an ORR of ~20%. In view of these encouraging results in LMS, a study combining trab with doxo seems to be of interest. Herein, we present the results in patients (pts) with ST-LMS.
Material and Methods: The primary objective was to determine the disease control rate (DCR) (ORR+SD). Secondary objectives included: PFS at 12 wks, ORR by RECIST, duration of response, overall survival (OS) and safety. Stratification by U-LMS/ST-LMS was carried out, 107 patients planned (45 U-LMS and 62 STS). Treatment: at d1 doxo 60 mg/m^2 followed by trab 1.1 mg/m^2 3-h and pegfilgrastim 6 mg d2 q3wks, 6 cycles. Surgery for residual disease was permitted.
Results: A total of 61 pts (40 women) were included until January 2013, with a median age of 60. Among 42 pts with data for at least 1 cycle, 35 had metastatic disease (mostly lung 26/35); 27 pts had received 6 cycles. For 36 pts with at least 1 evaluation (2 cycles), there were 1 CR, 13 PR, 20 SD for a DCR of 94%, and 2 PD. Progression free survival at 12 weeks is currently 95% [95%IC:84−99]. Common grade 3/4 toxicities in 208 cycles were neutropenia (40.7%), febrile neutropenia (4.3%), thrombopenia (19.7%), anemia (9%), fatigue (6.3%) vomiting (3.8%), and ALAT elevation (9%). One patient died after the second cycle due to a pulmonary oedemia associated to a prolonged febrile aplasia.
Conclusions: Despite expected toxicity observed, doxorubicin in combination with trabectedin seems to be an effective first line treatment in ST-LMS. Final data of the overall population will be available in September 2013.
No conflict of interest.

3835 POSTER

Multicenter phase II study of everolimus in patients with metastatic or recurrent bone and soft tissue sarcomas after failure of anthracycline and ifosfamide

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Background: This multicenter, phase II trial evaluated the efficacy and safety of everolimus, mTOR inhibitor, in patients with metastatic or recurrent bone and soft tissue sarcoma after failure of antracycline- and ifosfamide-containing regimens.
Materials and Methods: Everolimus was given orally as 10 mg once daily. The primary endpoint was progression-free survival (PFS) at 16 weeks, assessed by computed tomography scan according to RECIST 1.0.
Results: Between July, 2010, and May, 2011, 41 patients were enrolled in this study. Among them, 83% received two or more lines of chemotherapy prior to study entry. In 38 patients who the primary endpoint was evaluable, 11 patients reached 16 Week progression-free (one with partial response and 10 with stable disease), indicating PFS at 16 weeks of 27% (95% confidence interval [CI], 16−42%). The PFS rate at 16 weeks was highest in patients with angiosarcoma (2 of 3, 67%). There was a patient with metastatic hemangiopericytoma that everolimus induced prolonged disease stabilization for approximately 18 months with 20 cycles of study treatment after progression on anthracycline/ifosfamide-combination and gemcitabine/docetaxel-combination regimens. With a median follow-up of 10.9 months (range, 2.3–23.9 months) in living patients, the median PFS was 1.9 months (95% CI, 1.3−2.4 months) and median OS was 5.8 months (95% CI, 3.6−8.0 months). Most adverse events were generally mild and tolerable. Grade 3/4 toxicities included hyperglycemia (15%), stomatitis (7%), pain (5%), and asthenia (5%). Grade 3/4 hematologic toxicities were not observed.
Conclusions: Everolimus showed substantial antitumor activity with manageable toxicities in heavily pretreated patients with bone and soft tissue sarcoma.
No conflict of interest.

3836 POSTER

Very late relapse in osteosarcoma: Experience of the Cooperative Osteosarcoma Study COSS

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Background: If osteosarcoma (OS) recurs following multimodal treatment, it most frequently does so within the first three years after diagnosis. Most follow-up programs end after 5 to 10 years. We searched the Cooperative Osteosarcoma Study Group COSS database for recurrences detected after more than 10 years.
Material and Methods: Prior to 01.01.03, 2.405 patients with a diagnosis of a non-pretreated OS of the extremity or trunk (excl. craniofacial and extraskeletal variants) were registered with COSS, of whom 789 (752 high grade (HG), 37 low grade (LG)) were followed for 10 years without recurrence. These were searched for OS manifestations arising thereafter. Data of affected patients was analyzed for demographic, tumor, and treatment-related variables and outcomes.
Results: As of 03/13, 14 very late 1st recurrences >10 years from initial diagnostic biopsy were detected (median: 14.2 years; range: 10.1–22.7; 6 x >15). Median patient age: 17.8 years (3.8–44.8) at initial diagnosis, 33.0 (18.1–60.8) at recurrence; 8 males, 6 females; initial site: limb 13, pelvis 1; all 14 without primary distant metastases. Initial histology: HG central OS 10, HG surface OS 1, LG central OS with areas of HG dedifferentiation 1, dedifferentiated HG parosteal OS 1, LG parosteal OS 1. All had received 1st line chemotherapy (4 good, 8 poor responders, 1 primary surgery, 1?). Recurrences first detected by symptoms (8), lab (1), (?5); histology available for 13/14. Recurrences local (2, both LG above), metastatic (11) or combined (1); 1 lesion 8, >1 6. Metastases: lung (8, only: 3, all 3 involving the pleura), bone (4, only: 2); other sites (5, only: 1). Treatment of late relapse (data: 13/14): surgery 9, chemotherapy 10, radiation 2. Median follow-up from late relapse: 1.8 years (0.3–14.2) for all 14, 2.6 years (same range) for 10 survivors; 6/10 in 2nd (5) or later (1) CR, 4 with disease. 4 fatalities (2 osteosarcoma, 1 cardiomyopathy, 1 unknown cause with progressive disease).
Conclusions: OS can recur after >10 years in 1st CR. This is often detected only through symptoms and at an advanced stage. Some (bone) lesions may represent 2nd primary tumors, but other manifestations are true recurrences. Tumor directed follow-up should not be terminated prematurely.
No conflict of interest.

3837 POSTER

Doxorubicin plus dacarbazine (DD) in advanced leiomyosarcoma: A retrospective review of Gustave Roussy Institute

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Background: Advanced leiomyosarcomas represent a group of rare malignant chemo-resistant tumors with dismal survival. Single agent Doxorubicin remains the gold standard first line treatment in palliative setting.
Methods: Patients (Pts) with recurrent/advanced leiomyosarcoma with no prior chemotherapy were included in this retrospective review. Pts received Doxorubicin /Dacarbazine (60 mg/m^2 Day 1/450 mg/m^2 Day 1, 2 Q 3 weeks) for up to 7 cycles.
Results: Between March 2006 and January 2012, twenty two chemo-therapy naive pts (M=6, F=16), with a median age of 47 years (range 28−70) were treated with DD. Tumor grades being G1−2 (n = 10), G3 (n = 9), Gx (n = 3). Primary tumor sites included extremities (n = 4), abdomen/retroperitoneum (n = 12), uterine (n = 4), and others (n = 2).
Sixteen pts had metastases, 8 pts with more than one site. A total of 105 cycles were administered with a median number of 6 cycles (range 3−7) per pt. Best response according to RECIST criteria were PR (n = 6, 27%) with a median duration of response of 17 months (range: 8−42), disease stabilisation (SD) was achieved in further 15 subjects, resulting in a clinical benefit rate (CBR) of 95%.
Only 1 pt progressed while on chemotherapy. 4 pts underwent surgery of residual tumor after DD, 3 of those achieving anR0 resections. Major toxicities (grade 3−4) included, febrile neutropenia (n = 5), anemia (n = 2), asthenia (n = 2), and thrombocytopenia (n = 1).
The median PFS and OS for the whole population were 15.1(95% CI:10.1–16.5) and 33.9 (CI:25.3–50.1) months, respectively.
Second line therapy (Gemcitabine or Trabectedin or clinical trials) was offered to 17 pts, third line to 13, a fourth line and beyond to 12 pts.
Conclusion: DD seems to be one of the best front-line out-patient chemotherapy regimen in advanced leiomyosarcoma, with a CBR of 95% after 3 cycles with tolerable side effects. Patients achieving at least SD had a significantly prolonged PFS and OS.
Conflict of interest: *Corporate-sponsored research: honoraria: Pfizer, Novartis, Pharmamar, GSK*

3838 POSTER

Phase I and pharmacokinetic study of trabectedin in Japanese patients with soft tissue sarcoma

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Background: Trabectedin is a novel anticancer agent isolated from the ascidian *Ecteinascidia turbinata*. This phase I dose-escalation study of trabectedin administered as a 24-hour continuous infusion every 21 days was performed to define the phase II recommended dose (RD) and pharmacokinetic profile in soft tissue sarcoma (STS) patients in Japan.
Materials and Methods: Patient inclusion criteria were the following: pathologically proven STS, no history of receiving more than 4 anticancer regimens, unresponsiveness or intolerability to anthracycline-containing chemotherapy regimens, age⩾18, and ECOG PS 0−1.
Patients received trabectedin as a 24-hour continuous infusion repeated every 21 days. The starting dose was 0.9 mg/m^2 with escalation to

1.2 mg/m^2 and then to 1.5 mg/m^2 using a '3 + 3' cohort expansion design. Plasma samples were collected in the first cycle from all patients for pharmacokinetic analysis.
Results: Fifteen patients received one of three dose levels of trabectedin: 0.9, 1.2 and 1.5 mg/m^2. DLTs were not observed up to 1.2 mg/m^2; however 2 out of 3 patients experienced DLT at 1.5 mg/m^2. Observed DLT toxicities were Grade 4 CPK increased, Grade 3 anorexia and Grade 4 thrombocytopenia. Grade 3/4 adverse events (AEs) that occurred with high incidence included ALT increased, AST increased, and neutropenia. Frequency and severity of AEs were clearly higher at 1.5 mg/m^2 than at lower doses. With the pharmacokinetic analysis of trabectedin in Japanese patients, it was expected that the area under the concentration-time curve at 1.2 mg/m^2 was sufficient to show antitumor activity. Partial response (PR) to trabectedin was observed in 3 out of 9 patients at 1.2 mg/m^2 by RECIST. These 3 PR patients (1 Myxoid liposarcoma, 1 Synovial sarcoma, 1 Extraskeletal Ewing sarcoma) were diagnosed as translocation-related sarcomas (TRS). Progression-free rate 12 weeks was 80.0% (12 of 15 patients).
Conclusions: In Japanese STS patients, 1.5 mg/m^2 was the maximum tolerated dose and 1.2 mg/m^2 the RD. In consideration of the pharmacokinetic and efficacy results promising efficacy and tolerability was expected especially in TRS patients.
A randomized, controlled phase II study of trabectedin versus best supportive care (BSC) in TRS patients is ongoing to evaluate the Progression free survival benefit of trabectedin.
Conflict of interest: *Corporate-sponsored research: This phase I clinical study is sponsored by TAIHO Pharmaceutical Co.,LTD.*

3839 POSTER

Soft tissue sarcoma treatment: Results from the drug shortage era

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Background: Soft tissue sarcomas are mesodermal malignancies affecting trunk, extremities and abdomen. As a group, it is treated by surgery whenever it is possible; otherwise, chemotherapy is applied using a combination of ifosfamide and anthracyclines.
Objective: The objective of this study was to evaluate the impact of drug shortage (anthracyclines in our study) on response rate especially in locally advanced and metastatic disease.
Material and Methods: The study was done at Al Bairouni University Hospital in Damascus (SYRIA). In 2012, there was a shortage of doxorubicine, therefore the former agent was replaced by cisplatin in combination with ifosfamide. The new combination was: ifosfamide 2gr/m^2 $\times$ 3 days + cisplatin 35 mg/m^2 X 3 days with G-csf support given for 3 cycles every 21 days. The former combination was employed for both neoadjuvant setting and metastatic disease. Patients were evaluated by means of CT-Scan, MRI and physical exam.
Results and discussion: 236 patients were included in the study, 87 patients of which presented with metastatic disease (pulmonary, osseous and abdominal). Evaluation after 3 cycles revealed a complete response in 62 out of 87 (71%) with a P.value of 0.72, while only 34 out of 149 (22%) became resectable after neoadjuvant chemotherapy with a P.value of 0.87.
Conclusions: Results showed that the new combination of ifosfamide and cisplatin seems to be a good choice in metastatic soft tissue sarcomas even a larger number of patients is needed to confirm such results. However, the same combination showed to have a poor efficacy on locally advanced soft tissue sarcomas raising the issue of drug shortage as a negative factor on such disease. Furthermore, this study should alert health professional worldwide to the risk lying behind drug shortage in developing countries and to some extent in developed ones and its negative impact on cancer treatment.
No conflict of interest.

	Patients	Responders	P-value
Neoadjuvant	149	34	0.87
Metastatic	87	62	0.72

3840 POSTER

LOGIST − A Local Observational GIST registry: First interim analysis after a mean observation time of 14.3 months. A non-interventional registry to observe patients with gastrointestinal stroma tumours (GIST) after R0/R1 resection − with or without adjuvant therapy with imatinib (CSTI571BDE77)

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Background: Management of GIST is complex and quickly evolving. The SSG XVIII/AIO Phase-III-study on adjuvant therapy of GIST showed significant benefit for patients after a treatment phase of 36 months compared to 12 months (Joensuu et al., 2011). The objective of the LOGIST registry is the long-term evaluation of trends regarding approaches in diagnosis, therapy and outcome of GIST patients.
Methods: Up to 400 non-metastatic GIST patients after R0/R1 resection with or without adjuvant imatinib therapy are followed up for a duration of 60 months or until progression. Documentation is based on local routine. Patient- and center specific data are summarized descriptively and analyzed epidemiologically.
Results: 215 patients with a median follow up of 14.3 months were included in the first interim analysis. For 199 patients GIST was the primary diagnosis. Most GIST were localized in the stomach (64%) or small intestine (23%). In 12.6% of the patients the tumour size was <2 cm, 39.5% had a tumour size >2 cm and $\leqslant$5 cm, 33.5% >5 cm and $\leqslant$10 cm, in 14.4% a tumour >10 cm was found. R0 resection was achieved in 94.4% of the patients. Based on Fletcher and/or Miettinen, 5.1% of all patients had no risk of relapse, 47.2% of patients had a very low or low risk, while 47.1% had an intermediate or high risk. Mutation analysis was obtained for 61.4% of patients. In most cases, c-Kit and PDGFRa mutations (68.2 and 18.2%) were detected.
Of 98 patients with a follow up of $\geqslant$1 year, a mutation analysis was obtained for 71 and 50 were treated with imatinib. Presence of a c-Kit mutation resulted in an imatinib treatment more frequently compared to no therapy (78.4% vs. 52.9%). A risk classification was performed for 90 patients. Of those patients who received imatinib 37.0% had intermediate and 52.0% had high risk of relapse. 2 high risk patients (4.5%) did not receive imatinib, while 5 low or very low risk patients were treated with imatinib.
Dose modifications or treatment interruptions occurred predominantly due to toxicities in 14 cases. Severe adverse events (SAEs) ocurred in 10.6% of patients, however, the number of SAEs was reduced to 1.5% by case-based analysis. A causality between imatinib intake and an SAE (grade 1−2) was found only in one 1 case.
Conclusion: This first interim analysis shows that patients with an intermediate or high risk of relapse according to Fletcher/Miettinen method and a c-Kit mutation are treated with imatinib in accordance with current guidelines.
Conflict of interest: *Advisory board: Novartis. Corporate-sponsored research: Novartis*

3841 POSTER

Symptoms and health related Quality of Life in patients receiving first line palliative chemotherapy for advanced Soft tissue sarcoma: a longitudinal study

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Background: The main aims of systemic chemotherapy in advanced soft tissue sarcoma (STS) are to increase overall survival and palliate i.e. control symptoms and maintain or improve health related quality of life (HRQoL). There is little evidence demonstrating survival benefit.
Aim: To examine HRQoL and symptom change over time among people living with advanced STS in receipt of first line palliative chemotherapy.
Methods: Forty-one consecutive patients were recruited and followed up at baseline, 2, 6, 12, and 18 weeks post chemotherapy using the

EORTC-QLQ-C30 questionnaire. The 6-week (post 2 cycle) primary end point was considered the earliest time a patient may derive benefit: questionnaires were completed prior to the scheduled 6-week CT scan. Patients not reaching the primary end point had their 2-week results carried forward. The proportion of patients with a clinically significant change (+/− 10 /100 point scale) in overall HRQoL score was calculated. The changes in mean functional and symptom scores were also calculated. An exploratory analysis comparing radiological responders (stable disease or partial response by RECIST) at 6 weeks to those who progressed was also conducted.
Results: 30/41 (73%) patients reached the 6-week primary end point with 11 progressing on CT performed early due to clinical deterioration. 8 patients (19%: 95% CI: 10−34%) experienced a 6-week clinically significant improvement in overall HRQoL,13 (32%: CI: 19−47) experienced no change and 20 (49%: CI: 34−64) a significant reduction.
The mean overall HRQoL score (n = 41) declined at 6 weeks with both clinical and statistical significance (mean ±SD reduction: 10.2±24.1 points, p = 0.01).
Symptomatically fatigue worsened (11.1±28.3, p = 0.02)?? Sleep disturbance improved (14.6±30.8, p = 0.004) possibly related to an improvement in pain (9.4±29.1, p = 0.046). There were no changes in functional scales. At 6-weeks, there was a clinical improvement in pain and sleep disturbance in the radiological responders (n = 25) but a deterioration in fatigue. In the non-responders (n = 16) overall HRQoL and diarrhoea clinically worsened. Only sleep disturbance showed statistical difference between the groups. There was no correlation with scan result and overall HRQoL change.
Conclusion: At 6-weeks after 2 cycles of palliative chemotherapy, HRQoL and fatigue deteriorate. However, pain and sleep disturbance improve enhancing the patient experience.
No conflict of interest.

3842 POSTER

Treatment of synovial sarcoma with high dose ifosfamide: A retrospective single center analysis

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Background: Synovial sarcoma is a rare neoplasm, accounting for 5−10% of all adult soft-tissue sarcomas. Previous studies have shown this histology to be especially sensitive to ifosfamide in a dose-dependent manner. We sought to analyse the outcome of patients with synovial sarcoma treated with high dose ifosfamide (HDIFO) at our institution.
Material and Methods: Between 2008 and 2013, 17 patients were identified in our database as been treated with HDIFO for synovial sarcoma. Information regarding clinical features, efficacy and toxicity could be retrieved from charts of 13 of those patients. They were treated in both neoadjuvant and metastatic setting with doses ranging from 12 to 15.2 g/m^2/cycle every 3 weeks.
Results: Median age was 32 years (range: 21−59). Seven patients were males and 6 were females. All of them had a diagnosis of synovial sarcoma established by a pathologist with sarcoma expertise. Seven patients had primary extremity tumors. Ten patients had metastatic disease at onset of cycle one of high dose ifosfamide. The remaining three patients were treated in the neoadjuvant setting. All patients with metastatic disease had already been exposed to a combination of anthracycline and standard dose ifosfamide. A median of 3 cycles (range: 2−8) were administered. Chemotherapy cycle delays were observed for a median of 1 cycle per patient.
Chemotherapy dose reduction was necessary in 6 patients. Seven patients received HDIFO through continuous infusion regimens and 6 patients through a bolus infusion regimen. All were treated with prophylactic G-CSF. Nine patients were treated with methylene blue starting prophylactically on the first cycle. Grade 3−4 hematological toxicity was observed in 11 out of 13 of patients, mostly anemia and leukopenia. Ten patients experienced febrile neutropenia (only one case of life-threatening febrile neutropenia). Fanconi syndrome, G3−4 acute renal failure and persistent G2−4 renal function loss were observed, each one of them, in 3 patients. Three patients experienced G3−4 non-hematological non-renal toxicity (2 cases of G3 encephalopathy). There were no treatment related deaths. After a median of 2 cycles, a radiological response rate of 53% (all partial responses) was recorded. Subjective clinical benefit was observed in 84% of patients. Median duration of response for the 9 (one still on treatment) patients with metastatic disease who had completed treatment with HDIFO was 143 days (range: 0–255 days). Median progression free survival for the same patients was 193 days (range: 56–287 days). Median overall survival among patients treated for metastatic disease was 450 days (range: 137–717 days). All 3 patients treated with neoadjuvant HDIFO with curative intent remain disease free at 733, 819 and 906 days of follow up.
Conclusions: HDIFO seems to be a highly active regimen in patients with synovial sarcoma. However it must be emphasized the relevant toxicity attributed to this regimen, with an elevated incidence of grade 3 or higher adverse events.
No conflict of interest.

3843 POSTER

Neutrophil to Lymphocyte Ratio (NLR) as predictive factor in patients with metastatic soft tissue sarcoma (STS) treated with trabectedin (T)

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Background: Recent data indicate that tumour microenvironment, which is influenced by inflammatory cells and mediators, has a crucial role in cancer progression and clinical outcome of patients with several cancer type (i.e., STS, colorectal and breast neoplasms). In the present study, we investigated the predictive value of basal NLR in metastatic STS patients treated with T.
Material and Methods: Since March 2008 through April 2013, 51 pts with advanced anthracycline-pretreated STS received T at a dose of 1.5 mg/m^2 every 3 weeks by continuous 24 h infusion. Best response rate was evaluated according to RECIST criteria and basal NLR (before the first trabectedin cycle) as well as demographics, clinical and histopathological data were analyzed. Patients were divided in two subgroups according to a NLR cut-off $\geqslant$3. Clinical results were considered positive if patient had disease control, ie complete response (CR), partial response (PR) or stable disease (SD) vs. negative in the presence of progressive disease (PD). Fisher's test was used to compare relative frequency of positive vs. negative results in the two subgroups.
Results: Median age was 46 years (range, 20−61) with a median ECOG PS of 0. The median number of previous chemotherapy regimens was 1 (range, 0−5). Median number of T cycles was 2 (range 1−6). 44/51 (86%) pts were evaluable for response: positive results were achieved in 22 pts (6 pts (13%) PR and 16 (36%)SD) while negative results were obtained in 22 pts. Basal NLR $\geqslant$3 was significantly associated to a double risk of progressive disease ($p < 0.03$), while the association between NLR inferior to 3 and objective responses is not clearly defined.
Conclusions: Our findings suggest that an elevated NLR ratio may serve as a cost-effective, negative predictive factor in metastatic STS patients undergoing trabectedin.
No conflict of interest.

3844 POSTER

A retrospective analysis of trabectidin infusion in an outpatient setting by peripherally inserted central venous catheters (PICC): a multicentric Italian experience

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Background: Trabectidin (T) is approved as a 24-h intravenous infusion for patients (pts) with advanced sarcomas and, in association with pegilated doxorubicin, for pts with ovarian partially-sensitive cancer. A central venous line is highly recommended for T administration. Central venous catheters (CVC) provide many benefits for pts, but they also put them at risk of catheter-related complication and have a significant budget impact for oncology department. The most frequently used CVC are subcutaneously implanted PORT-chamber catheters (PORT), while peripherally inserted central venous catheters (PICC) are relatively new. PICC are of special interest in the outpatient setting, mainly when a poor survival is expected. In recent years, oncology departments all over Italy have been supporting the development of a nurses' team for PICC management.
Methods: Between November 2009 and March 2013, T became available in Italy. We reviewed the data of T treated pts to evaluate the cost efficient ratio between the use of PORT and PICC in 6 italian centers.
Results: 102 pts received T, 20 for advanced sarcoma, 2 for cervical cancer and 80 for ovarian cancer. Median age was 55 years (range,

31−78). In 45 pts T was infused by a PICC, inserted by trained nurses with an ultrasound-guided technique at the bed-side, while in 57 pts a PORT, requiring a day surgery procedure in the hospital by a surgeon, was used. Device's dislocations and infections were reported in 4 pts, equally distribute between pts with PORT or PICC. Thrombosis occurred only in a single pt with a PORT. Complications requiring devices removal were not reported during any of the 509 cycles of therapy (median 5, range 1−20). Nor PICC misplacement nor early malfunctions were experienced during T infusion. These data are in line with Azienda Sanitaria Firenze-oncology department experience with nearly 500 PICC inserted since 2009, with misplacement occurring in 5% of pts with only 0.5% needing removal, and rare major complications (8%). Based on budget data, cost efficient ratio favor PORT over PICC but only when the device is used for more than 1 years. Pts showed a good acceptance of PICC, but data on quality of life have not been specifically collected.
Conclusions: Our data suggest that T infusion by PICC in an outpatient setting is safe and well accepted. PICC showed a preferable cost efficient ratio than PORT in pts requiring a short standing of the device.
No conflict of interest.

3845 POSTER

Systemic palliative treatment of patients with inoperable/metastatic L-sarcomas (liposarcoma and leiomyosarcoma)

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Background: The current outcomes of systemic palliative therapy in metastatic soft tissue sarcomas (STS) are still poor with median overall survival (OS) about 12 months. We conducted a retrospective analysis of inoperable/metastatic L-sarcoma patients treated in one tertiary center.
Material and Methods: One hundred twelve patients (48 women, 58 men; median age 50 years) with diagnosis of inoperable/metastatic leiomyosarcoma LMS (67 patients), liposarcoma LPS (45 patients) were treated between 1997 and 2010. The most common primary localization of the tumor were extremities. 28 patients at the time of the first visit in our center had a diagnosis of metastatic disease.
Results: The most common site of metastatic disease were lungs. 56 patients had three or more lines of chemotherapy. 71 patients had the first line of chemotherapy based on doxorubicin. 29 patients (26%) underwent a metastasectomy. At the time of the analysis 85 patients (75%) died because of the disease. The median OS from the time of the diagnosis of inoperable/metastatic disease was 23 months (26 months for LMS, 18 for LPS, $p = 0.7$). For the patients who underwent metastasectomy OS was 30 months. Approximately 67% and 45% of patients lived more than one and two years, respectively. Progression-free survival on the 1st line chemotherapy was 6 months, and on the 2nd line 3 months. The clinical benefit of the 1st line chemotherapy (complete, partial regression or stable disease >3 months) was observed in 58 patients (51%).
Conclusions: The patients with advanced L-sarcomas have still poor prognosis, although the use of chemotherapy demonstrated clinical benefit in substantial group of patients. Surgical resection of the metastases is related to prolonged survival but is feasible in a small percentage of them.
No conflict of interest.

3846 POSTER

Efficacy of trabectedin for advanced soft tissue sarcoma: A retrospective single center analysis

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Background: Trabectedin (Yondelis®) is the first marine-derived anti-neoplastic drug approved in Europe for the treatment of patients with recurrent advanced soft tissue sarcoma (ASTS) or for patients unsuited to receive anthracyclines and ifosfamide. In this study the patients with ASTS treated with trabectedin from Nov. 2006 to April 2012 were retrospectively analyzed.
Methods: Trabectedin was given at the approved dose of 1.5 mg/m^2 as a 24-h infusion every 3 weeks. An analysis of response rate, time to progression (TTP) and overall survival (OS) and univariate analyses of prognostic factors were performed.
Results: Overall, 39 patients (24 men) with mostly high-grade ($n = 29$) ASTS with a median age of 57 years (range 20−81) were included in the analysis. Most had L-type sarcoma (leiomyosarcoma $n = 10$; liposarcoma $n = 3$), undifferentiated pleomorphic sarcoma ($n = 11$), sarcoma not otherwise specified ($n = 5$), or synovial sarcoma ($n = 2$). Eight had one of 6 very rare sarcomas. At baseline patients had metastatic ($n = 21$), bulky ($n = 4$) or metastatic/bulky ($n = 14$) disease and were pretreated with a median of 2 prior chemotherapy lines (range: 0−3; 4 patients received adjuvant chemotherapy only), including anthracycline-based chemotherapy ($n = 30$), gemcitabine plus dacarbazine (GEM-DTIC; $n = 18$), other ($n = 20$). Patients received a median of 4 trabectedin cycles (range 1−34). Among 37 evaluable patients best responses as per RECIST were partial response (PR, $n = 7$), stable disease (SD >3 months, $n = 9$, 5 had SD >6 months) and disease progression ($n = 19$), while 5 patients had a decrease in tumor density. Responses to trabectedin and GEM-DTIC did not exclude responses to the other regimen suggesting the feasibility of sequential treatment. After a median follow-up of 9.37 months, median TTP and OS were 4.4 months (95% CI: 3.5−5.4) and 9.7 months (95% CI: 4.5–14.9), respectively. Univariate analyses identified low/medium-grade STS and growth modulation index >1.13 as independent favorable prognostic factors for TTP, and retroperitoneal/visceral localization, L-type and rare STS and low/medium-grade STS for OS.
Conclusions: The results of this real-life retrospective analysis confirmed the findings of previous trials showing that trabectedin is active drug for ASTS.
No conflict of interest.

3847 POSTER

The value of high-dose chemotherapy with autologous stem cell transplantation in relapsed Ewing sarcoma patients

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Background: The prognosis of patients (pts) with relapsed Ewing sarcoma (ES) is poor with a 5-year overall survival (OS) of 13%. We analyzed the value of high-dose chemotherapy (HDtx) with autologous stem cell transplantation and conventional chemotherapy (CHtx) in relapsed ES.
Material and Methods: Data from 239 pts with first relapse of ES registered during 2000–2011 in the ES relapse registry of the Cooperative Ewing Sarcoma Study Group (CESS) were analyzed. Patients were treated first line according to cooperative Ewing sarcoma phase III protocols.
Results: 200 of 239 pts received various non-HDtx second-line CHtx regimens, 73 pts had HDtx followed by autologous stem cell rescue. Among those 73 pts, 15 received busulfan–melphalan (bu-mel), 38, treosulfan-melphalan (treo-mel) and 20, other regimens. The 2-year event-free survival (EFS) was 10% in pts treated without HDtx, 47% in pts treated with bu-mel, and 44% in pts treated with treo-mel HDtx. In a second step, we focused on those pts with partial or complete remission (PR/CR) after 4−6 cycles of second-line CHtx ($n = 68$). In this cohort, the 2-year EFS were 44% with HDtx compared to 31% without HDtx ($p = 0.093$). The multivariate analysis revealed HDtx treatment, with a risk ratio (RR) of 0.35 (95% CI 0.17–0.71), and early relapse, with a RR of 4.76 (95% CI 2.31–9.78), as independent prognostic factors for EFS.
Conclusions: Patients with relapse Ewing sarcoma responded to second line chemotherapy appear to benefit from consolidation with high-dose chemotherapy and autologous stem cell transplantation.
No conflict of interest.

3848 POSTER

A new therapeutic combination in sarcomas: RG7112, a small-molecule inhibitor of MDM2, enhances trabectedin response

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Background: The objective of this study was to evaluate the antitumor efficacy of Trabectedin in combination with MDM2 inhibitors in several sarcoma cell lines, representing two different histologic subtypes of sarcomas, both aggressive and chemoresistant. MDM2 is a critical negative regulator of the p53 tumor suppressor protein. Nutlin-3A and the novel compound from the Nutlin series, RG7112, are small-molecule MDM2 inhibitors that fill the p53-binding pocket on MDM2. RG7112 is now under phase I trials in patients with hematologic neoplasms and advanced solid tumors.
Materials and Methods: Using 6 human sarcoma cell lines (2 fibrosarcomas and 4 liposarcomas), the antitumor effects of Trabectedin, Nutlin-3A and RG7112 as single agents or in combination were examined *in vitro*. Cell viability (Cell Titer Cell Proliferation Assay) and cell cycle analysis (FACS) were performed. Changes in cell growth and viability were Real Time monitored using the xCELLigence System. Apoptosis induction as means of Caspase 3 and 7 activity was also measured (Caspaser-Glo 3/7 Assay).
Results: Trabectedin (0.01−5 nM) showed significant antitumor activity in all sarcoma cell lines studied. We used two different MDM2 inhibitors,

Nutlin-3A and RG7112 (0.01−50 μM), to treat cells in combination with the standard therapeutic agent in sarcomas, Trabectedin. When comparing Nutlin-3A and RG7112, the novel drug RG7112 was more potent in inhibiting cell proliferation and inducing cell cycle changes than Nutlin-3A, especially in those cell lines harbouring wild type p53. We therefore studied the combination of RG7112 with Trabectedin in a well-differentiated liposarcoma (WDLS) cell line that has amplified MDM2 and wild type p53 (93T449), which was the scenario with a better potential response. The results were compared to those obtained with a liposarcoma cell line with mutated p53 (SW872). Using drug concentrations that did not have a great *in vitro* effect in both liposarcoma cell lines when used alone, RG7112 (2.5 μM) in combination with (0.01−5 nM) significantly increased the antitumor response compared to Trabectedin alone in liposarcoma 93T449 cells, exhibiting a moderate effect in liposarcoma SW872 cells.
Conclusion: Our results demonstrated that Trabectedin in combination with the novel MDM2 inhibitor, RG7112, represents a promising new therapeutic strategy for the treatment of sarcomas with amplified MDM2.
No conflict of interest.

3849 POSTER

Inhibitory effect of Yangzheng Xiaoji on the ARK/Aurora pathways and in vivo tumour growth of human osteosarcoma

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Background: *Yangzheng Xiaoji* (*YZXJ*) is a traditional Chinese medicinal formula and in the past few years has been used for treating patients with certain solid tumours including primary liver cancer, gastric and lung cancer. The treatment has survival benefit and improve the quality of life of the patients. In a recent study, we have identified that osteosarcoma is one of the tumour types that are highly sensitive to *Yangzheng Xiaoji.* In the present study, we tested the potential effects of *YZXJ* on cellular functions including migration, adhesion and *in vivo* growth on human osteosarcoma and explored the impact on the ARK/Aurora signalling pathway.
Materials and Methods: Human osteosarcoma cell line, MG63 was used. A *YZXJ* extract, named DME25 was prepared from *Yangzheng Xiaoji.* Cell migration, cell adhesion and cell growth was tested *in vitro* respective cellular models. The effect of DME25 on the *in vivo* growth was evaluated using a tumour xenograft model. ARK1 (Aurora-A) and ARK2 (Aurora-B) were evaluated in cells and tumours by immunofluorescent methods.
Results: Using a traditional cell-matrix assay and electric cell-substrate impedance sensing assay (ECIS), it was found that DME25 had a significant effect on the cell-matrix adhesion and cellular migration of MG63 cells. This effect was further strengthened when an ARK2/Aurora-B inhibitor was used together with DME25 in the system. DME25 had little effects on the *in vitro* growth of MG63 cells. Using an athymic mouse tumour model, it was demonstrated that DME25, given orally and intraperitoneally, significantly inhibited the tumour growth of osteosarcoma. It is noteworthy that DME25 also increased the sensitivity of the tumours to ARK2/Aurora-B inhibitor. Treatment of MG63 and tumour bearing mice markedly inhibited the phosphorylation of the ARK proteins.
Conclusions: *Yangzheng Xiaoji* has a profound effect on the adhesion and migration of osteosarcoma cells. It also has an anti-tumour growth effect. The ARK/Aurora pathway is a key pathway targeted by *Yangzheng Xiaoji*.
No conflict of interest.

Author index

Page numbers are followed by abstract numbers in parentheses; I, invited; O, oral; Pd, Poster discussion; Po, Poster. Abstract number in bold type indicates presenter.

A

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Y

Z

Subject index

Numbers following entries are abstract numbers.